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Cost-effectiveness of implantable ventricular assist devices in older children with stable, inotrope-dependent dilated cardiomyopathy

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Abstract

Background: In a stable, inotrope-dependent pediatric patient with dilated cardiomyopathy, we evaluated the cost-effectiveness of continuous-flow VAD implantation compared to a watchful waiting approach using chronic inotropic therapy.

Methods: We used a state-transition model to estimate the costs and outcomes of 14-year-old (INTERMACS profile 3) patients receiving either VAD or watchful waiting. We measured benefits in terms of lifetime QALYs gained. Model inputs were taken from the literature. We calculated the ICER, or the cost per additional QALY gained, of VADs and performed multiple sensitivity analyses to test how our assumptions influenced the results.

Results: Compared to watchful waiting, VADs produce 0.97 more QALYs for an additional $156 639, leading to an ICER of $162 123 per QALY gained from a healthcare perspective. VADs have 17% chance of being cost-effective given a cost-effectiveness threshold of $100 000 per QALY gained. Sensitivity analyses suggest that VADs can be cost-effective if the costs of implantation decrease or if hospitalization costs or mortality among watchful waiting patients is higher.

Conclusions: As a bridge to transplant, VADs provide a health benefit to children who develop stable, inotrope-dependent heart failure, but immediate implantation is not yet a cost-effective strategy compared to watchful waiting based on commonly used cost-effectiveness thresholds. Early VAD support can be cost-effective in sicker patients and if device implantation is cheaper. In complex conditions such as pediatric heart failure, cost-effectiveness should be just one of many factors that inform clinical decision-making.

KEYWORDS
bridge to transplantation, cost-effectiveness analysis, dilated cardiomyopathy, end-stage heart failure, ventricular assist device

Abbreviations: ACC, American College of Cardiology; ACTION, Advanced Cardiac Therapies Improving Outcomes Network; AHA, American Heart Association; CCR, cost-to-charge ratios; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; ISHLT, International Society of Heart and Lung Transplantation; PA, probabilistic analysis; PHIS, Pediatric Health Information System; QALY, quality-adjusted life year; VAD, ventricular assist device.

1 | INTRODUCTION

The use of VADs to support children with heart failure as a bridge to heart transplantation is increasing.[1,2] As the utilization of VADs has grown, pediatric heart transplant waitlist mortality has significantly decreased in the most recent era.[3] However, pediatric VADs are associated with exceptionally high resource costs. For children who received a VAD, median hospital costs including implantation were estimated to be $750 000, and the median length of stay was 81 days.[4,5]

In children with end-stage heart failure, VAD implantation before the patient reaches a state of critical cardiogenic shock is associated with improved outcomes.[6] Beyond this, however, there is very little evidence to further guide the timing of implantation and patient selection in pediatrics. More specifically, in a pediatric patient considered to be inotrope-dependent but relatively stable (INTERMACS patient profile 3), the use and timing of VAD are not clear. Thus, we performed a CEA comparing continuous-flow VAD implantation to a watchful waiting approach in older children with stable inotrope-dependent heart failure due to dilated cardiomyopathy.

CEA is a widely used economic evaluation method that compares the costs and benefits of health interventions and therapies.[7] One of CEA's advantages is its ability to quantify changes in an intervention's efficiency when different assumptions about its effectiveness and costs are made. CEA is therefore well-suited to explore the efficiency of VADs because of uncertainties around their effectiveness and costs.[2,8]

2 | MATERIALS AND METHODS

2.1 | Overview

We used a Markov model to simulate a cohort of children with dilated cardiomyopathy and stable, inotrope-dependent heart failure to estimate the costs and health benefits of immediate VAD implantation compared to watchful waiting approach with chronic inotropic therapy as a bridge to heart transplantation.

We projected health benefits in terms of QALYs gained over the lifetime of the hypothetical patient cohort. A QALY represents a year that a person is alive weighted by that person's health-related quality of life.[9] Health utilities—estimated using various elicitation techniques consistent with expected utility theory—are used to calculate QALYs for health states between perfect health and death, which typically have values of 1 and 0 respectively.[10,11] QALYs, which also have their limitations, are the preferred measure of health in economic evaluations because they combine quantity and quality of life in one metric and provide a common metric that can be used to compare different treatments.[9]

We considered societal and healthcare perspectives in the analysis. In the societal perspective, which is the recommended perspective for economic evaluations in healthcare,[7] all costs and benefits are valued and included, regardless of the payer or beneficiary. In the healthcare perspective, only healthcare costs borne by payers and patients are included. The Impact Inventory (Table S1) lists the health and non-health costs and effects that were included in each perspective.[7]

2.2 | Markov model

A Markov cohort model is a type of state-transition model where an identical group of individuals transition between mutually exclusive and collectively exhaustive health states over time. A condensed schematic of the Markov cohort model is presented in Figure 1, and a full model structure can be found in Figure S1 in the Appendix S1.

The model simulates a cohort of 14-year-old patients with dilated cardiomyopathy and stable, inotrope-dependent heart failure who are awaiting heart transplantation (INTERMACS profile 3). The age and diagnosis were specifically chosen as they represent the median age and most common diagnosis for children receiving implantable continuous-flow VADs.[12] The model does not specify the exact device, but the data are representative of the most commonly used devices in this population—Medtronic HeartWare™ HVAD™ and Abbott HeartMate 3™.[13]

These patients would be classified as pediatric status 1B patients based on current Organ Procurement and Transplantation Network heart allocation policy. In the watchful waiting scenario, all patients are initially treated with intravenous inotropic drugs and may move in and out of the hospital; may require a VAD (and become pediatric status 1A); and/or may undergo heart transplant based on probabilities taken from the literature (Figure 1). In the VAD scenario, all patients are immediately implanted with a VAD and transition between home and hospital states before experiencing heart transplantation, death or hospitalization. The model uses a monthly cycle and is programmed in TreeAge Pro 2019 (TreeAge Software Inc, Williamstown, MA).

2.3 | Data and sources

2.3.1 | Transition probabilities

Monthly transition probabilities were estimated based on peer-reviewed articles (Table 1 and Appendix S1). We conducted several literature searches between January and March 2019 using MEDLINE.

The probability of death and treatment outcomes among watchful waiting patients at home is based on retrospective cohort studies of patients on heart transplant waitlists.[14-16] For patients on VAD, we relied on findings from the Pediatric Interagency Registry for Mechanical Circulatory Support for the probability of death and various treatment outcomes.[6,12]

We obtained several probabilities associated with the rate of transplantation and VAD implantation and post-transplant survival from the 2019 annual report of the ISHLT and other studies.[1,17,18] Because outpatient management of patients on inotropic

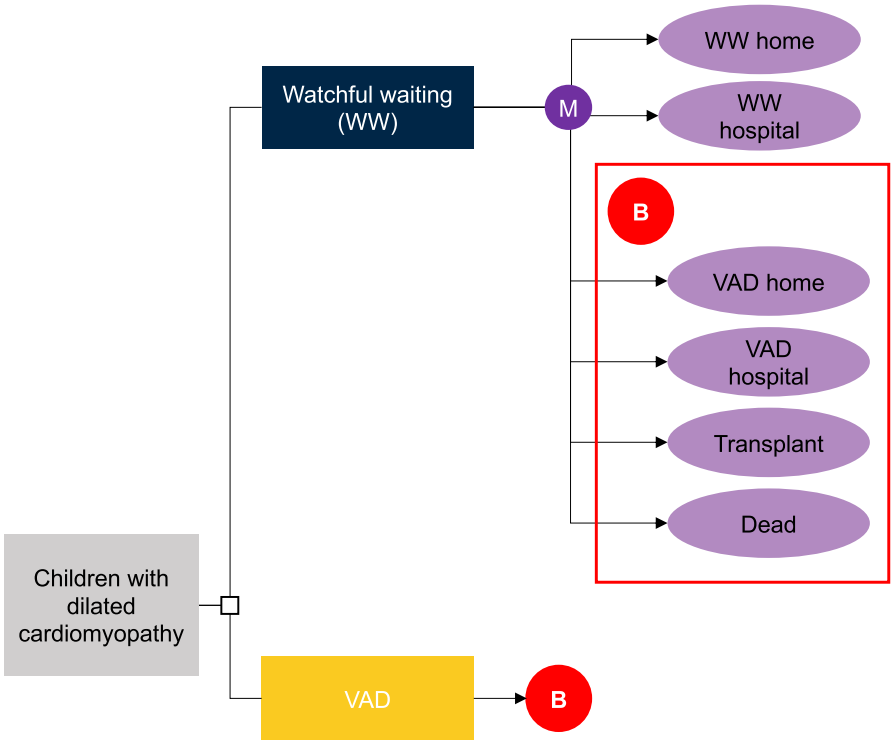

FIGURE 1 Markov cohort model schematic. Root of the schematic shows the two decision alternatives, optimal watchful waiting and early VAD implantation. The purple circle denotes the common Markov node, and the purple ovals are the health states the simulated cohort moves through or between. Branches have been grouped (denoted by the red circle), truncated, and labeled appropriately for simplicity. See Figure S1 in Supplementary Material for full model structure. WW, watchful waiting

therapy or VADs is feasible and is increasing in frequency,[15,19] we assumed that patients who are temporarily in the hospital in the watchful waiting and VAD arms of the decision model (Figure 1) do not transition to permanent hospitalization in the base case analysis, though we vary this assumption in the sensitivity analysis. It is important to note that many of the probabilities (and health utilities) for the at-home and hospital states are similar; however, we decided to separate these states because of the significant cost difference incurred by hospitalized versus ambulatory heart failure patients.

Our final set of inputs (Table 1) show that patients on VAD have a higher probability of survival and a higher probability of transplantation than patients on watchful waiting, which are the main sources of health benefit from immediate VAD implantation in our model.

2.3.2 | Costs

Healthcare costs were estimated using published literature. The costs of heart transplantation were taken from a retrospective analysis of a linked dataset containing PHIS and Scientific Registry of Transplant Recipients data which used CCRs to estimate actual service costs from hospital charge data.[20] Similarly, the costs of implantable continuous-flow VADs were taken from a retrospective analysis of PHIS data which also used CCRs.[4] These one-time costs were valued separately from costs of routine healthcare services, check-ups, and other treatments (eg, hospitalizations) borne by pediatric heart failure patients which were derived from previous cost-effectiveness analyses.[21-23] Healthcare costs include healthcare service delivery (eg, physician and facility fees), medical device, and drug costs.

For the societal perspective, we included lifetime productivity and consumption costs. We used productivity and consumption data from the general population[24,25] since dilated cardiomyopathy patients who are successfully transplanted eventually achieve high functional status; additionally, using productivity estimates specific to a population with a disease or disability may inadvertently undervalue a life-extending treatment, which raises ethical concerns.[26] We also valued and included time costs or foregone productivity of caregivers (see Appendix S1). All costs are in 2017 US dollars (US$); historical costs were inflated using general consumer price indices.

2.3.3 | Health outcomes and utilities

Our main outcome is QALYs which were estimated by assigning health utilities to each health state in the model (Table 1). Health utilities for the various states in the model were taken from the literature. The model operates on monthly cycles calculating quality-adjusted life-months which are aggregated into annual QALYs. We did not use age-specific health utilities, though in reality these values could be changing over a person's lifetime. A major limitation is that published health utilities for end-stage heart failure in children have been elicited from adults or estimated through provider expert opinion, yet these have been used in other various CEAs that focus on pediatric heart failure populations (see Appendix S1). Because these utilities are imperfect, we varied them in sensitivity analysis.

TABLE 1 Values for model inputs[a]

Variable	Base	Range	Distribution	Reference
Monthly transition probabilities				
Watchful waiting				
Death from heart failure among patients at home	0.0116	0.0058-0.0232	Beta	Pietra, 2012, Davies, 2017[14,17]
Permanent hospitalization among patients at home	0.0149	0.0075-0.0298	Beta	Birnbaum, 2015[15]
Temporary hospitalization among patients at home	0.0491	0.0245-0.1472	Beta	Birnbaum, 2015[15]
Permanent hospitalization among patients at temporarily in the hospital	0.0149	0.0112-0.0149	Beta	Birnbaum, 2015[15]
Death from heart failure among patients in the hospital (temporary and permanent)	0.0361	0.0271-0.0451	Beta	Almond, 2009[16]
VAD implantation among patients at home	0.0629	0.0315-0.0944	Beta	Rossano, 2019, ISHLT, 2019[1,18]
VAD implantation among patients in the hospital (temporary and permanent)	0.0629	0.0472-0.0786	Beta	Rossano, 2019, ISHLT, 2019[1,18]
Transplantation among patients at home or in the hospital (temporary and permanent)	0.0829	0.0621-0.1036	Beta	Davies, 2017[17]
VAD				
Temporary hospitalization among VAD patients at home	0.0924	0-0.1155	Beta	VanderPluym, 2019[12]
Permanent hospitalization among VAD patients at home and temporarily in the hospital	0	0-0.0083	Beta	Morales, 2019[6]
Transition to home (ie, recovery) among patients temporarily in the hospital	0.0672	0.0504-0.0839	Beta	Morales, 2019[6]
Transplantation among VAD patients at home or in the hospital (temporary or permanent)	0.1032	0.0722-0.1341	Beta	ISHLT, 2019, Rossano, 2018[18,42]
Death from heart failure among VAD patients at home or in the hospital (temporary or permanent)	0.0070	0.0035-0.0141	Beta	Morales, 2019[6]
Transplantation				
Death before the first 12 mo of transplantation	0.0055	0.0041-0.0068	Beta	ISHLT, 2019, Rossano, 2018[18,42]
Death on or after the first 12 mo of transplantation	0.0028	0.0014-0.0057	Beta	ISHLT, 2019, Rossano, 2018[18,42]
Monthly costs (in 2017 US$)[b]				
Watchful waiting of patients at home	426	61-3648	Gamma	Feingold, 2010[21]
Watchful waiting of patients permanently in the hospital	104,065	53,077-198,033	Gamma	Godown, 2019[20]
Watchful waiting of patients temporarily in the hospital	56,109	28,617-106,773	Gamma	Godown, 2019[20]

(Continues)

TABLE 1 (Continued)

Variable	Base	Range	Distribution	Reference
One-time cost of heart transplantation	551,971	402,165-806,154	Gamma	Godown, 2019[20]
Post-transplant care before the first 12 mo	2,539	534-5,338	Gamma	Feingold, 2015[22]
Post-transplant care on and after the first 12 mo	1,940	534-5,338	Gamma	Feingold, 2015[22]
One-time cost of VAD implantation	252,470	181,030-455,259	Gamma	Rossano, 2018[4]
Care for VAD patients at home	3,300	2,475-4,125	Gamma	Magnetta, 2018[23]
Care for VAD patients permanently in the hospital	98,995	74,246-123,743	Gamma	Magnetta, 2018[23]
Care for VAD patients temporarily in the hospital	49,497	37,123-61,872	Gamma	Magnetta, 2018[23]
Health state utilities				
Watchful waiting and VAD at home	0.7104	0.888-0.5328	Beta	Feingold, 2010[21]
Watchful waiting and VAD temporarily in the hospital	0.6	0.75-0.45	Beta	Göhler, 2008[43]
Watchful waiting and VAD permanently in the hospital	0.7404	0.9252-0.5556	Beta	Göhler, 2008[43]
Transplant before the first 12 mo	0.8004	1.0-0.6	Beta	Feingold, 2010[21]
Transplant on and after the first 12 mo	0.87	1.0-0.6528	Beta	Brown, 2009[44]

[a]Base estimate based on literature, and range set by the authors.

[b]These costs are for treatment only. See Appendix S1 for other cost inputs.

2.4 | Analysis

2.4.1 | Cost-effectiveness

The summary metric of CEAs is the ICER, defined as the cost per unit of health outcome gained. The ICER is calculated by dividing the incremental costs by the incremental benefits of one alternative versus the other, and we present ICERs from the healthcare and societal perspectives. We discounted future benefits and costs to present value using a 3% rate in the base case analysis.

An intervention is typically considered cost-effective if its ICER meets or is below a cost-effectiveness threshold. The cost-effectiveness threshold represents a decision-maker's willingness to pay for an additional unit of health benefit, which in this study is measured in QALYs. Thus, thresholds are used by healthcare agencies worldwide as a convenient decision rule or benchmark to determine whether interventions are of good value. The threshold can also be seen as a measure of opportunity cost, or the amount of health that is displaced by additional spending in the health sector.[10,27,28] In this study, we consider an intervention to be cost-effective if its ICER is <$100 000 per QALY gained, a commonly used threshold in the US,[10,29] which is within the threshold range (ie, $50 000-150 000 per QALY gained) identified by the ACC and the AHA in their joint value assessment framework.[30]

2.4.2 | Sensitivity analyses

Because of limitations in the data, several parameters we included in the model are associated with uncertainty; similarly, rapid changes and improvements in mechanical support technologies and procedures suggest that treatment outcomes may improve over time and improve the performance and cost-effectiveness of VADs. To explore the impact of uncertainty on our findings, we conducted three types of sensitivity analyses, namely one-way, two-way, and PA. Complete descriptions of each type of sensitivity analysis are found in the Appendix S1.

3 | RESULTS

3.1 | Base case results

The base case results, which are the average results of the PA, are presented in Table 2. Across 10 000 simulations, the average incremental costs and QALYs of immediate VAD implantation from a healthcare perspective are $156 639 (± 51 339) and 0.97 (± 0.32), respectively, translating to an average ICER of $162 123 per QALY gained. From a societal perspective, the average ICER is $189 428 per QALY gained.

TABLE 2 Base case results from societal and healthcare perspectives[a]

	Societal perspective		Healthcare perspective	
Outcome	**Watchful waiting**	**VAD**	**Watchful waiting**	**VAD**
Mean QALYs (SD)[b]	9.89 (1.65)	10.87 (1.81)	9.89(1.62)	10.85(1.78)
Mean cost (SD)	836,015 (103,460)	1,019,947 (111,840)	528,814(62,285)	685,453(64,125)
Cost-effectiveness	**Societal perspective**		**Healthcare perspective**	
Mean incremental cost (SD)	183,932 (50,902)		156,639 (51,339)	
Mean incremental QALYs (SD)	0.97 (0.32)		0.97 (0.32)	
Mean cost per QALY gained ($)[b]	189,428		162,123	

SD, standard deviation.

[a]All costs are in 2017 US$ and have been discounted to present time.

[b]Refers to lifetime QALYs and are discounted to the present value.

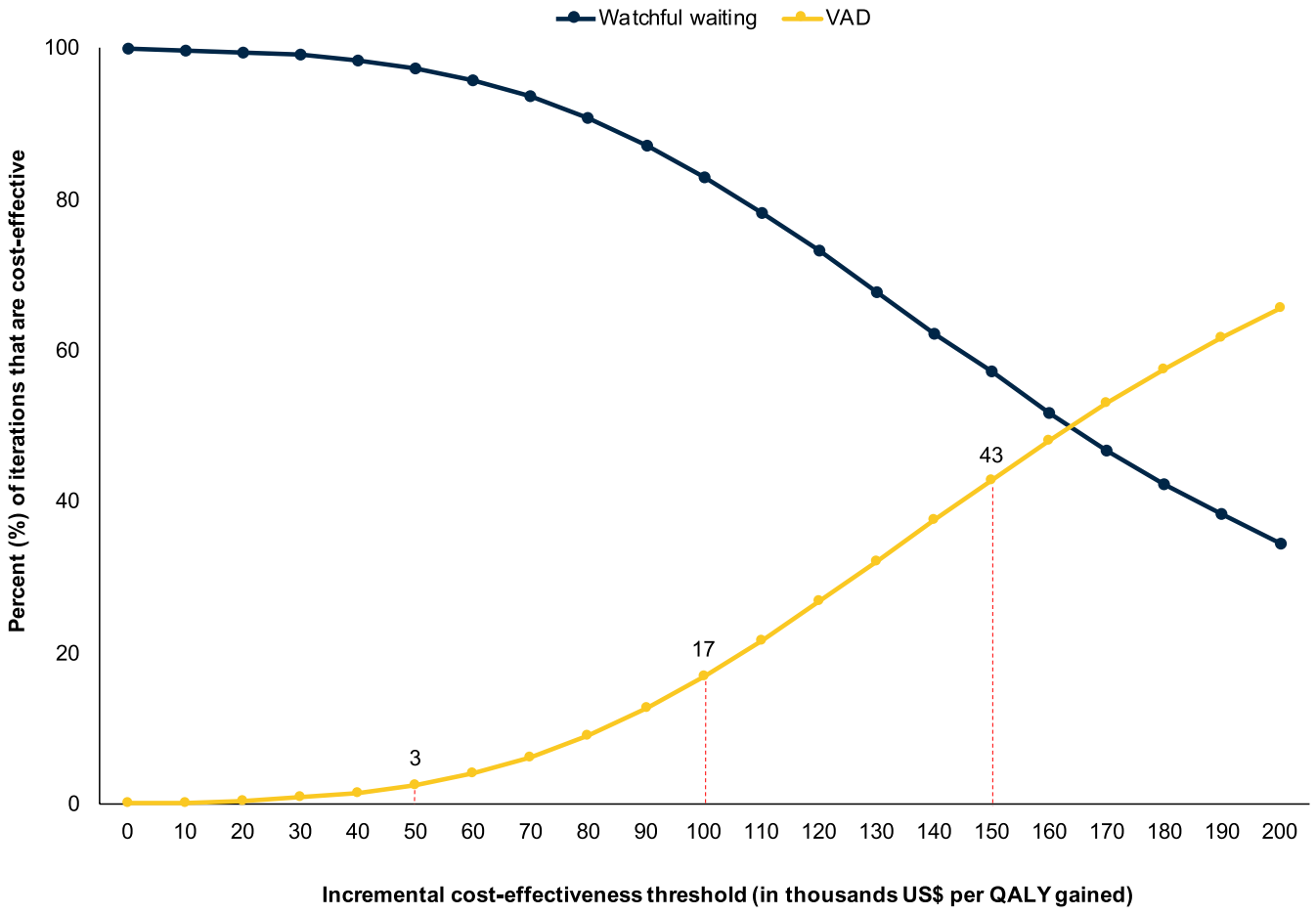

FIGURE 2 Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves plot the probability that each alternative is cost-effective (ie, has a higher net monetary value) over a range of ICER thresholds. The red vertical dashed line from left to right represent the $50 000, $100 000 and $150 000 per QALY gained thresholds. WW, watchful waiting

Figure 2 shows the cost-effectiveness acceptability curves from a healthcare perspective. Watchful waiting is more likely to be cost-effective (ie, higher net monetary benefit) than immediate VAD implantation at cost-effectiveness thresholds below ~$170 000 per QALY gained. VAD implantation has a 3%, 17%, and 43% chance of being cost-effective at cost-effectiveness thresholds of $50 000, $100 000, and $150 000 per QALY gained, respectively.

3.2 | Sensitivity analyses

Figure 3 shows the partial results of the one-way sensitivity analysis from a healthcare perspective (see Figure S2 for a societal perspective). The most influential parameters on the ICER were three transition probabilities (temporary hospitalization among watchful waiting patients at home, death among watchful waiting patients at home, and death 12 months after transplantation) and two cost inputs (VAD implantation and permanent hospitalization among watchful waiting patients). For example, the ICER for VADs ranged from $166 705 to $479 351 per QALY gained when the cost of VAD implantation was changed from $181 030 to $252 470 (Figure 3). At higher values, two parameters associated with watchful waiting (probability of temporary hospitalization among patients at home and cost of permanent hospitalization) make VADs cost-effective.

We used the top five most influential parameters from the one-way sensitivity analysis (Figure 3) in a series of threshold analyses to determine the parameter values that will bring VAD's ICER at or below the commonly used $100 000 per QALY threshold. The results, shown in Table 3, suggest that the costs of VADs need to improve, or the costs and risks of inotropic therapy need to be worse, before VADs can be deemed cost-effective when compared to a watchful waiting approach. For example, the cost of VAD implantation, a significant source of cost in the VAD scenario, needs to decrease by about 51% (holding all other parameter base estimates constant) in order for VADs to be cost-effective compared to watchful waiting. Similarly, if the cost of watchful waiting patients permanently in the hospital increased by 80%, VADs would be cost-effective. If the probability of temporary hospitalization among watchful waiting patients increased by 169%, VADs would be cost-effective. If the probability of death among watchful waiting patients was 5.3 times higher, then VADs would also be cost-effective.

Our analysis also found that no increases in survival among VAD patients would make the ICER of VAD implantation reach the $100 000 per QALY threshold without a concurrent increase in the probability of death among watchful waiting patients; in other words, VADs need not only to improve, but watchful waiting needs to be worse for early VAD implantation to be cost-effective.

For the two-way sensitivity analysis, we simultaneously varied the value of two parameters, and the results are shown in Figure 4 and Figures S3-S7 in the Supplementary Material. The red-shaded areas in the six figures mark the values that both parameters being evaluated would need to be in order for VADs to be cost-effective when compared to watchful waiting based on an ICER threshold of $100 000 per QALY gained. In Figure 4 and Figure S3, we found that not only does the cost of VAD implantation need to significantly decrease for VADs to be cost-effective, but the cost and probability of hospitalization among watchful waiting patients also need to increase significantly. Figures S4-S7 further reveal different conditions that VADs may be cost-effective.

4 | DISCUSSION

Though VADs as a bridge to transplantation improve the health of children with inotrope-dependent heart failure, VAD implantation is not currently a cost-effective strategy compared to watchful waiting based on commonly used ICER thresholds and available costs and probabilities. Sensitivity analyses suggest that VADs can be cost-effective if the costs of implantation are significantly lower or if hospitalization costs or mortality rates among watchful waiting patients are higher than average.

Though the cost-effectiveness of VADs in adult populations has been extensively explored as both bridges to transplantation and destination therapies, pediatric populations have been the focus of only a few other published cost-effectiveness studies to our knowledge. Recently, Evers et al (2019) demonstrated that continuous-flow VADs are a cost-effective strategy compared with pulsatile-flow VADs in INTERMACS 1 or 2 patients that may be eligible for either device type.[13] Our study builds on their findings by studying

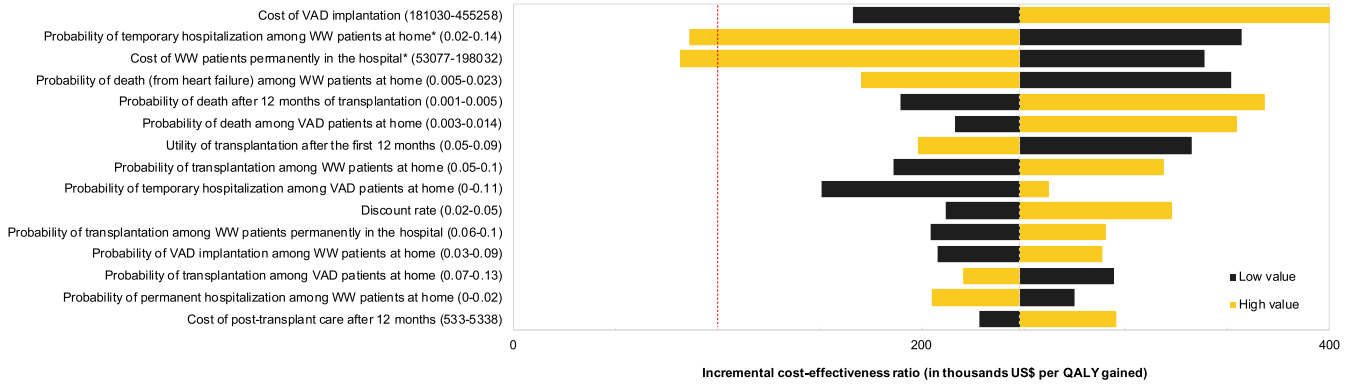

FIGURE 3 Tornado diagram for healthcare perspective. A tornado diagram shows the full ICER range when a parameter value in the model is varied from its lowest to highest bounds while keeping the other parameter values constant. Parameters are ordered by how strongly they influence the ICER (ie, wider range), and only the top 15 most influential parameters are included. Parameters with an asterisk (*) denote those whose extreme values make VADs a cost-effective intervention. The white vertical dashed line in the middle of the bars represents the ICER in the base case for the healthcare perspective, and the red vertical dashed line represents the $100 000 per QALY threshold. WW, watchful waiting

TABLE 3 Results of threshold analysis

Parameter (ranking from one-way sensitivity analysis)[a]	Base value (range)	Value needed to achieve cost-effectiveness[b]	Difference needed to achieve cost-effectiveness (percent change from base value)
Cost[c] of VAD implantation (1)	252,470 (181,030-455,259)	122,521	-129,949 (−51%)
Probability of temporary hospitalization among WW patients at home (2)	0.0491 (0.0245-0.1472)	0.1318	0.0827 (169%)
Cost[c] of WW patients permanently in the hospital (3)	104,065 (53,077-198,033)	187,660	83,595 (80%)
Probability of death among WW patients at home (4)	0.0116 (0.0058-0.0232)	0.0730	0.0614 (529%)
Probability of death after 12 mo of transplantation (5)	0.0028 (0.0014-0.0057)	NA	NA

Abbreviations: NA, not applicable; US$, United States dollar; WW, watchful waiting.

[a]Parameters are based on monthly cycles.

[b]Cost-effectiveness was determined using a $100 000 per QALY gained threshold. "NA" means that no change in the value of the parameter can make VAD cost-effective.

[c]In 2017 US$

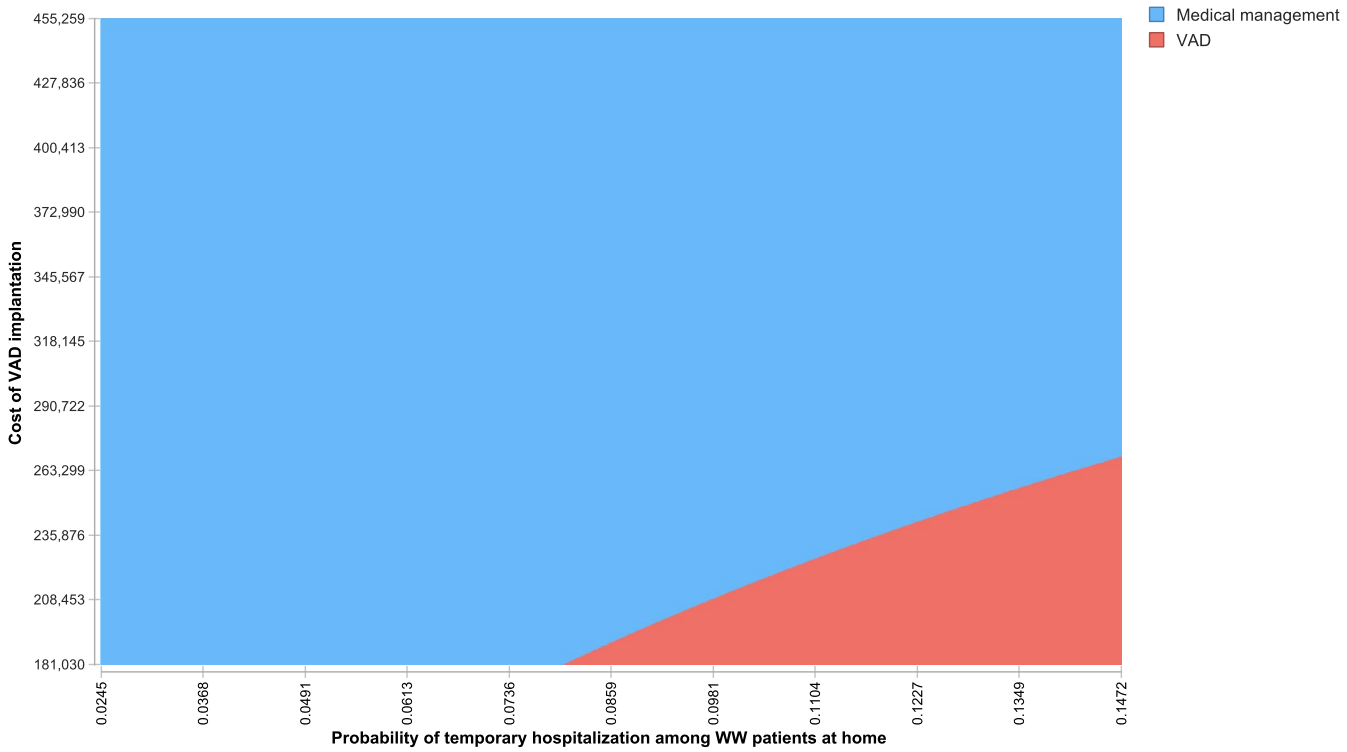

FIGURE 4 Two-way sensitivity analyses comparing cost of VAD implantation and the probability of temporary hospitalization among watchful waiting patients. The two-way sensitivity analysis shows the range of values that two parameters in the simulation model need to be (denoted by the red area) in order for VADs to be cost-effective based on a $100 000 per QALY gained threshold. The ranges for the x- and y-axes are the same as in Table 1. WW, watchful waiting

the cost-effectiveness of continuous-flow VADs specifically in the INTERMACS 3 pediatric population in comparison to ongoing medical management which represents a clinical scenario that remains controvertible.

Using data from PHIS, Mahle et al (2008) estimated that VADs as a bridge to transplantation have an ICER of $119 937 (2007 US$) when compared to extracorporeal membrane oxygenation support.[31] Over the last decade, VAD support has evolved significantly and has quickly become standard of care in patients with end-stage heart failure; our analysis provides a necessary update and focuses on the efficiency of the timing of VAD implantation in children. Another CEA by Magnetta et al (2018) on children with Duchenne muscular dystrophy

found that VADs as a destination therapy had an ICER of $179 086 (2016 US$) per QALY gained when compared to optimal medical management.[23] They reported that the ICER of VAD only fell below the $100 000 per QALY threshold when VAD implantation costs were less than $113 142, and we found similar results in our current study. We estimate that the cost of VAD implantation—which is largely comprised of the costs of the device/hardware and surgery[13]—would have to be less than $122 521 for VADs to be cost-effective. Our analysis also showed that for patients on chronic inotropic therapy at particularly high risk for readmission, prolonged or complicated hospitalization, or mortality, early VAD implantation can be cost-effective. In practice, this could be sicker or medically complex children at high risk of infection or nonadherence who may require recurrent or permanent hospitalization on continuous intravenous therapy.

Based on recent data, we anticipate that costs will decrease as centers gain experience implanting VADs in children. Prolonged length of stay and low discharge rate after pediatric VAD implantation increase costs significantly.[4] Among numerous efforts to standardize practice and improve quality, the ACTION collaborative recently launched a multi-center project to specifically increase the rate of discharges across the network. There is hope that the focus on collaboration and quality improvement will steadily improve overall outcomes and cost-effectiveness of this therapy in the near future.[32]

Among adult heart failure patients, CEAs have universally reported that VADs provide a survival benefit, but their cost-effectiveness as either a bridge to transplantation or destination therapy is mixed. For example, work by Alba et al (2013) found that VADs are cost-effective for high- and medium-risk patients.[33] Several studies however found that VADs are not cost-effective due to increased lifetime costs associated with readmission and maintenance in the US and elsewhere.[34,35] Compared to CEAs of adult populations, our estimate of the incremental health benefit of VADs compared with ongoing inotrope support in children is lower. One reason may be that the costs of VAD implantation are significantly higher, and children are less likely to be discharged following implant.[6,34] Additionally, mortality for children on chronic inotropic therapy appears to be lower than what has been reported in adults.[14,36]

There are no universally accepted criteria to guide selection of patients and timing of VAD implant. In adults, outcomes data support that all patients that meet INTERMACS profile 3 ("stable but inotrope dependent") and severely symptomatic and motivated non-inotrope-dependent patients should be considered for VAD implantation.[37] Adults with more severe INTERMACS profiles 2 and 3 are associated with increased mortality.[38] However, in children optimal timing of VAD implantation may be different. Unlike adults, pediatric patients implanted with INTERMACS profile 2 ("progressive decline") experience similar survival after VAD implant when compared with less severe profiles (≥3).[6] Our findings in this analysis provide additional evidence that for stable inotrope-dependent children (INTERMACS profile 3), a watchful waiting approach instead of early VAD implantation may provide more value. However, if inotrope-dependent patients are assessed to be at significantly higher risk for decompensation, earlier VAD implantation becomes a better option both clinically and from a cost perspective. Studies to better understand and stratify risks in children on chronic inotrope therapy are warranted.

In this analysis, the ICER of early VAD implantation approaches but does not reach the "intermediate value" threshold of the ACC/AHA.[30] However, pediatric VADs may be considered cost-effective if the threshold used to judge their value are higher, and this may be possible under different value frameworks which are used in other countries. For example, Norway and the Netherlands weight their ICER thresholds based on the health loss associated with a disease as a way to incorporate societal preferences for prioritizing people with severe conditions, as well as younger individuals who have a lot of life years to lose from untreated disease (a principle called "fair innings"), in resource allocation.[39] Similarly, the UK, which bases National Health Service coverage decisions and drug prices on CEAs, uses different thresholds for rare diseases and end-of-life care.[40] Though cost-effectiveness is considered in decision-making in the US, no comparable value framework currently exists to account for distributional considerations. With the high mortality associated with pediatric heart failure, VADs and other interventions to treat severe conditions may be seen as valuable under different criteria.

4.1 | Limitations

There are several limitations to this CEA (all assumptions and limitations are further detailed in the Appendix S1). First, we used various sources of cost data and transition probabilities, and some sources were not specific to the age cohort we modeled. Additionally, our reliance on retrospective analyses of patients on watchful waiting and VADs may introduce bias in our estimates of treatment effectiveness; for example, VAD implantation in children is a much newer area than inotropy, which may lead to an underestimation of the effectiveness of VADs. We, however, address parameter uncertainty in the sensitivity analyses, and we found that main conclusions of the study are not impacted by small or large changes in input values. Second, the published health utilities we and others have used were elicited from adults or through expert opinion. While previous studies have explored the health-related quality of life of children with heart disease, including patients on transplant waitlists, the methods used are not preference-based and cannot be used as utilities. The lack of health utility data is due, in part, to the unique challenges of eliciting utilities from children. Future research should focus on eliciting health utilities from pediatric heart failure patients. Third, the Markov model necessarily simplifies the clinical experience of patients with end-stage heart failure and may exclude certain events that affect the estimation of VAD's costs and health benefits; for example, we exclude cases of VAD reimplantation, which, though rare events, can lead to significant economic and quality of life costs on patients and their families. We also excluded certain opportunity costs associated with extended hospitalizations due to a lack of data, such as the foregone benefit of longer bed-days, which limits the number of hospital resources available to other patients—a driver

of long waitlists.[41] The generalizability of this study is limited; the cohort modeled the most common presentation, but there are other causes of heart failure in children and the analysis may not be applicable to other disease states.

It is also worth noting the strengths and limitations of CEA. CEA is an economic evaluation method that compares the relative costs and health benefits of alternative or competing interventions. CEA is used widely around the world to guide adoption of health technologies as well as resource allocation in healthcare and public health at the population level. While CEAs can and should inform decision-making, they should not be the only decision rule clinicians rely on, especially those who are treating patients with complex conditions such as end-stage heart failure in pediatrics.

4.2 | Conclusion

Our analysis shows that immediate or early VAD implantation as a BTT in children who develop stable, inotrope-dependent heart failure is not yet a cost-effective strategy based on historical data and commonly employed thresholds. However, early VAD implantation can be cost-effective in patients at higher risk for decompensation. Pediatric VADs will likely become more cost-effective as implantation costs and overall outcomes are expected to improve through increased experience, innovation, and collaboration.

5 | AUTHORS' CONTRIBUTORS

ALVA designed the study, collected and analyzed data, prepared the manuscript, and is the guarantor of the study. DWH designed the study, analyzed the data, prepared the manuscript, and provided oversight throughout the study. JL, KRS, and MSS collected data and prepared the manuscript. DMP conceived and designed the study, collected data, prepared the manuscript, and provided oversight throughout the study. All authors have approved the final submitted version.

CONFLICT OF INTEREST

None.

ETHICS STATEMENT

This study did not involve patients and qualifies as an evaluation, which is exempt from ethical review.

PATIENT CONSENT

No patients were involved in this study.

DATA AVAILABILITY STATEMENT

All input parameters used in the model to generate the results presented in this study are reported in the main text and Supplementary Material.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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