The Efficacy of Thoratec Implantable Ventricular Assist Devices Compared to Syncardia Total Artificial Hearts as Bridge-to-Transplantation Therapy in Adults with Biventricular Heart Failure

Alexandria Davenport

Physician Assistant Program

Arcadia University

Evidence Based Practice

October 14, 2019

Abstract

Introduction: Systolic heart failure is a chronic condition in which there is a decrease in the heart's ability to pump blood to the body. While there are several treatments for the symptoms of heart failure, the only curative treatment for most causes of chronic heart failure is a heart transplant. Due to the limited number of heart donors, 72.2% of patients in need of a heart transplant in 2017 spent up to 2 years waiting for a transplant. Mechanical circulatory support has been used to increase patient survival to transplantation. In the past, these machines were external devices that limited patients to hospitals while they waited for a transplant. Recently, devices have been created that are implantable, with the purpose of increasing patient's quality of life by allowing for hospital discharge. Therefore, this review compares the use of Syncardia's total artificial heart to Thoratec's implantable ventricular assist device (I) in waitlist survival (O) in adult patients in biventricular systolic heart failure (P).

Methods: A literature search was conducted through Google Scholar in November 2018. A total of seven articles consisting of two prospective cohort and five retrospective cohort studies were selected based on publication date, type and brand of ventricular support device used, and sample population.

Results: The evidence collected by the three studies directly comparing biventricular assists devices as a whole to Syncardia's total artificial heart showed no significant difference in survival to transplantation. One of the four supplementary studies independently showed significant survival to transplantation in Thoratec implantable ventricular assist device patients and two studies independently showed significant survival to transplantation in Syncardia total artificial heart patients. Six of the seven total studies showed survival to successful transplantation in the total artificial heart or the implantable ventricular assist device after a year on mechanical circulatory support.

Discussion: Of the three studies comparing survival to transplantation between biventricular assist device patients and total artificial heart patients, no significant differences were found. Of the other four articles examining overall survival to transplantation on the total artificial heart and the implantable assist devices, all the studies showed significant positive results. Due to the limited sample sizes and inability to randomize samples, further research on the topic is necessary.

Conclusion: In 2017, 3,529 adults in America were on the United Network for Organ Sharing (UNOS) list waiting for a donor heart. Ventricular assist devices are often used to bridge patients with severe heart failure to transplantation. The seven studies selected for review found that there is not a significant difference in waitlist survival between patients with a Syncardia total artificial heart and a Thoratec implantable ventricular assist device. While more research is recommended to create a set of guidelines for biventricular assist device selection, currently the decision is between a patient and their clinical care team.

Introduction

Systolic heart failure is defined as a decrease in the heart's ability to pump to due at least one of four determinants: decreased heart rate, decreased contractility of the myocardium, decreased ventricular preload, or increased ventricular afterload.[1] According to the 2013 to 2016 National Health and Nutrition Examination Survey (NHANES), it is estimated that 6.2 million Americans have been diagnosed with heart failure.[2] The most common cause of systolic heart failure in developed countries (including the United States) is ischemic cardiomyopathy from a previous myocardial infarction (heart attack). Heart failure is classified as left-sided, right-sided, or biventricular, however biventricular failure is more prevalent than single-sided failure. In 2012, the cost of heart failure on the health care system was $30.7 billion. It is estimated that heart failure is the underlying cause of death for 1 in 8 deaths in America.

Treatments for heart failure depends on the patient's ejection fraction (the ratio of the amount of blood pumped out of the heart to the amount of blood in the heart) and severity of symptoms. Symptom severity is categorized in four classes created by the New York Heart Association (NYHA), which are summarized below.[3,4]

NYHA Class	**Symptom Severity**
Class I	No symptoms with normal activity
Class II	Mild symptoms with normal activity
Class III	Severe symptoms with normal activity, asymptomatic at rest
Class IV	Symptoms at rest

NYHA Class I can be prolonged and NYHA Classes II to IV are often treated pharmacologically. An implantable cardioverter-defibrillator (ICD) may be indicated in patients with a decreased ejection fraction and heart rate. Patients in NYHA Classes III or IV with

symptoms refractory to medication and the ICD are candidates for ventricular assist devices (VADs) and/or transplantation.[3] For patients who underwent heart transplantation between 2010 and 2012, the 1-year survival was 90.5% and the 5-year survival was 79.1%.[5] However, in 2017, 3,529 adults in America were on the United Network for Organ Sharing (UNOS) list waiting for a donor heart, but only 2,811 (79%) transplantations were performed, and 580 people (16%) died while waiting or became too sick to transplant.[5]

Due to the limited number of heart donors 72.2% of patients in need of a heart transplant in 2017 spent up to 2 years waiting for a transplant.[6] Historically, patients with biventricular heart failure would have a left VAD and a right VAD implanted. In 2004, the FDA approved the Thoratec Implantable VAD and the Syncardia Total Artificial Heart (TAH), both for patients with biventricular heart failure.[7,8] Both mechanical cardiovascular support options can be used to help patients survive until a donor heart is available. This paper poses the following question: In adults diagnosed with end stage biventricular heart failure (P), is there a difference in the waitlist survival rates (O) between Thoratec IVADs and Syncardia TAHs (I) as a bridge-to-transplant therapy?

Methods

A literature search was performed in November 2018 in Google Scholar using the terms "'biventricular' thoratec 'IVAD.'" This search was limited to articles published in scholarly journals with publication dates of 2007 or later. This search yielded 263 articles. The articles were then excluded based on the following: 1. Studies that focused on pediatric populations. 2. Case studies 3. Studies focusing only on left or right heart failure. These exclusion criteria narrowed the number of articles to 5. The "cited by" feature was then used, with the basis being

the article entitled “Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device” and a search of the cited articles using the search term “biventricular” resulted in 79 articles. The exclusion criteria were applied, which narrowed the number of articles to 4. The “cited by” feature was used again, based on the previously mentioned article, with the search term “syncardia” that resulted in 27 articles. The previously mentioned exclusion criteria were applied, narrowing the number of articles to 2.

Results

Fitzpatrick JR, MD, Frederick JR, MD, Hiesinger W, MD, et al. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. *The Journal of Thoracic and Cardiovascular Surgery*. 2009;137:971-977.

The purpose of this article was to investigate differences in outcome between patients who received a planned BiVAD and patients who receive a BiVAD after right-sided failure on an LVAD. The use of left-sided mechanical circulatory support is a major risk factor for right-sided heart failure, leading to the need for concurrent right-sided support or biventricular support. Not all patients with left ventricular assist devices (LVADs) will develop the need for a right ventricular assist device (RVAD) or a biventricular assist device (BiVAD). Estimating the risk of a patient developing right-sided heart failure will help clinicians choose between implanting a BiVAD or an LVAD.

The study was designed in an observational cohort fashion. The inclusion criterion was all patients who received an LVAD implantation at the Hospital of the University of Pennsylvania between April 1995 and June 2007 for a sample size of 99 patients needing biventricular support; 71 planned BiVADs and 28 delayed BiVADs**.** Data was collected retrospectively, however the groups were defined as P-BiVAD (patients who received a BiVAD as part of their operative plan), D-BiVAD (patients that received a BiVAD after first receiving an

LVAD), and patients that only had a LVAD, which acted as a control group. The only statistically significant ($p < 0.05$) differences between the P-BiVAD and D-BiVAD groups were preoperative heart rate (100.1 ± 21.6 beats/min in the P-BiVAD group and 113.9 ± 22.4 beats/min in the D-BiVAD group; $p = 0.0299$) and diastolic blood pressure (57.5 ± 12.5 mmHg in the P-BiVAD group and 51.2 ± 10.2 mmHg in the D-BiVAD group; $p = 0.0389$). Other preoperative characteristics were similar between the groups. Treatment outcomes were measured by successful bridging to transplantation, survival to hospital discharge, and 1-year survival.

Though LVAD only patients did significantly better than the P-BiVAD and D-BiVAD patients in terms of survival to hospital discharge, 1-year survival, and successful bridging to transplantation, the authors attribute this to BiVAD patients being more critically ill and having worse outcomes than univentricular support patients nationwide. However, between the two BiVAD groups, P-BiVAD patients had increased survival to hospital discharge (51% vs 29%; $p < 0.05$) and increased 1-year survival (48% vs 25%; $p = 0.025$). P-BiVAD patients also trended toward more successful bridging to transplantation (65% vs 45%; $p < 0.10$).

This study was limited by the selection of the model and timing of implantation due to the clinical judgement of heart failure cardiologists and the surgical team at one facility. While the judgements and timing of implantation in disease progression may be similar because it is one facility, there was no defined protocol. Therefore, patients were not randomly selected for devices, however most preoperative qualities between groups remained similar.

Slaughter MS, Tsui SS, El-Banayosy A, et al. Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device. *The Journal of Thoracic and Cardiovascular Surgery.* 2007;133:1573-1580.e2.

The primary objective of this study was to evaluate the safety and effectiveness of the pulsatile-flow Thoratec Implantable Ventricular Assist Device (IVAD) in terms of ventricular assist device flow index, survival, and adverse events as compared to Thoratec Paracorporeal Ventricular Assist Device (PVAD). This article was chosen not for this comparison, but because it reported on the outcomes of implantation of the Thoratec IVAD, specifically, as an option for patients with biventricular heart failure instead of another pulsatile-flow or a continuous-flow biventricular assist device (BiVAD). This article also reported the outcomes of patients who required only left ventricular support as well as patients who required biventricular support.

This study was a clinical trial with a prospective cohort design that took place in 12 medical centers, 9 in the United States and 3 in Europe with a sample size of 39 patients. 15 patients needed biventricular support and 25 patients needed only left ventricular support. 30 patients were initially indicated for bridge-to-transplantation and 9 were indicated for post-cardiotomy ventricular failure. 35 of the patients were in the New York Heart Association functional class IV prior to implantation. The mean age of 48 years (18 – 71 years). The IVAD and PVAD groups differed significantly in the following baseline characteristics: cardiac index (1.8 L/min*m^2 vs 1.4 L/min*m^2; $p = 0.002$), mean arterial pressure (69 mmHg vs 61 mmHg; $p = 0.006$), and systolic blood pressure (92 mmHg vs 76 mmHg; $p < 0.001$) were all higher in the IVAD group. White blood cell count was higher in the PVAD group (9,400 cells/μL vs 13,600 cells/μL; $p = 0.001$).

The IVAD was implanted in patients with acute or chronic heart failure that met indications for mechanical ventricular support for bridge-to-transplantation or postcardiotomy

failure. Adverse events definitions used were based on the Food and Drug Administration (FDA) requirements at the start of the trial. Comparisons to the PVAD were based on a previous trial with 100 patients. The measurements of major variables included ventricular assist device flow index, survival, and rates of adverse events as defined by the FDA, all of which are unbiased outcome criteria and therefore reliable. Internal validity was limited by the lack of randomization, which could not be achieved between the two groups as they took place at different periods of time. External validity was achieved by the similarity between the two groups.

Statistical comparisons between the PVAD and IVAD groups were conducted using the Fisher exact test for 2 x 2 categorical variables and an unpaired *t*-test was used for continuous variables. Risk ratios were calculated for the rates of adverse events. A p value of < 0.05 was considered significant. The IVAD patients were at significantly decreased risk for all adverse events except respiratory failure, pleural effusion, cardiac tamponade, and hemolysis. 44% of the 3,938 patient-days were spent out of the hospital. The average duration of support was 108 days until patients could receive a transplant or their heart had recovered enough to be weaned from mechanical support (9 – 597 days). 18 IVAD patients were able to be discharged home while on the device. Of the IVAD patients, 70% of the total patients and 57% of the BiVAD patients survived to recovery or transplantation, compared to the PVAD patients, in which 63% total patients and 48% BiVAD patients survived.

The limitations of this study as well as other studies in this review is that the article gives no indication on if this length of time is enough to show the efficacy and a small sample size with a lack a randomization. Though the authors did not note a specific length of the trial, the longest duration of support in this trial was 597 days and none of the devices in the trial failed.

However, the objective is to prolong function until transplantation or recovery, which was achieved in 70% of patients. This study is important because it is one of the first to use the Thoratec IVAD, especially comparing its use as an LVAD and as a BiVAD. The results of this study are significant not only because of the survival and adverse reactions, but because of the amount of time it allowed for patients to spend outside of the hospital while they allow their heart to recover or wait for a transplant.

Torregrossa G, Michiel M, Varghese R, et al. Results With Syncardia Total Artificial Heart Beyond 1 Year. *ASAIO Journal*. 2014;60:626-634.

The purpose of this article was to assess the long-term safety of SynCardia TAHs. This is important because the standard of care for heart failure is transplantation and there is a lack of donor hearts, leading to long wait times and high waitlist mortality. The sample size was very small at just 47 participants with a median age of 49 years. The inclusion criteria were patients who received a SynCardia TAH between 1989 and December 2011 and had the device implanted for more than 1 year. The study was a retrospective cohort study from 10 health centers, three centers in the United States and seven in Europe. The range of support time was 365 to 1,374 days. The methods of surgical implantations were not recorded. The outcomes recorded were survival to transplant, adverse reactions, antithrombotic therapy, cause of death, and device problems and were assessed using the records available from the enrolled centers. Differences between proportions were analyzed using the Fisher exact test. P values of < 0.05 were considered significant.

This study investigated the survival and adverse effects of use of the SynCardia TAH for longer than a year. The results of this study showed that 72% of patients were successfully transplanted after a year or more with the SynCardia TAH. 10% of patients experienced a device

failure. The most common adverse effects were systemic infections (53%), local infections (27%), thromboembolic events (19%), and hemorrhagic events (14%). 1 patient was still being supported by the TAH at the conclusion of the study (> 1,373 days). While previous studies have demonstrated the short-term efficacy of the TAH, this is one of the longest studies. With the addition of European centers, the researchers had the ability to also show the efficacy of the Excor drive support for further portability and freedom for patients to be discharged. The device was not FDA approved at the time of publication but has since been approved.

The study was valid because the main inclusion criteria were that the patients were already receiving support for at least a year at the start of the study and that the center from which they were receiving care had complete medical records. However, due to the small sample size, the accuracy of the information being the responsibility of the centers sending the information, and possible international differences in procedures, healthcare models, and available technology (ex: the Excor driver) there is still room for bias and confounders, challenging the internal validity of the article.

The authors provided explanations for many of the adverse events due to the TAH and the antithrombic therapy as well as the causes of death in the 24% of patients that died while on the device. It was not clear why the authors ended the trial when they did but one patient was still on device support when the study ended. However, the objective was to prolong life until transplantation, which was achieved in 72% of patients.

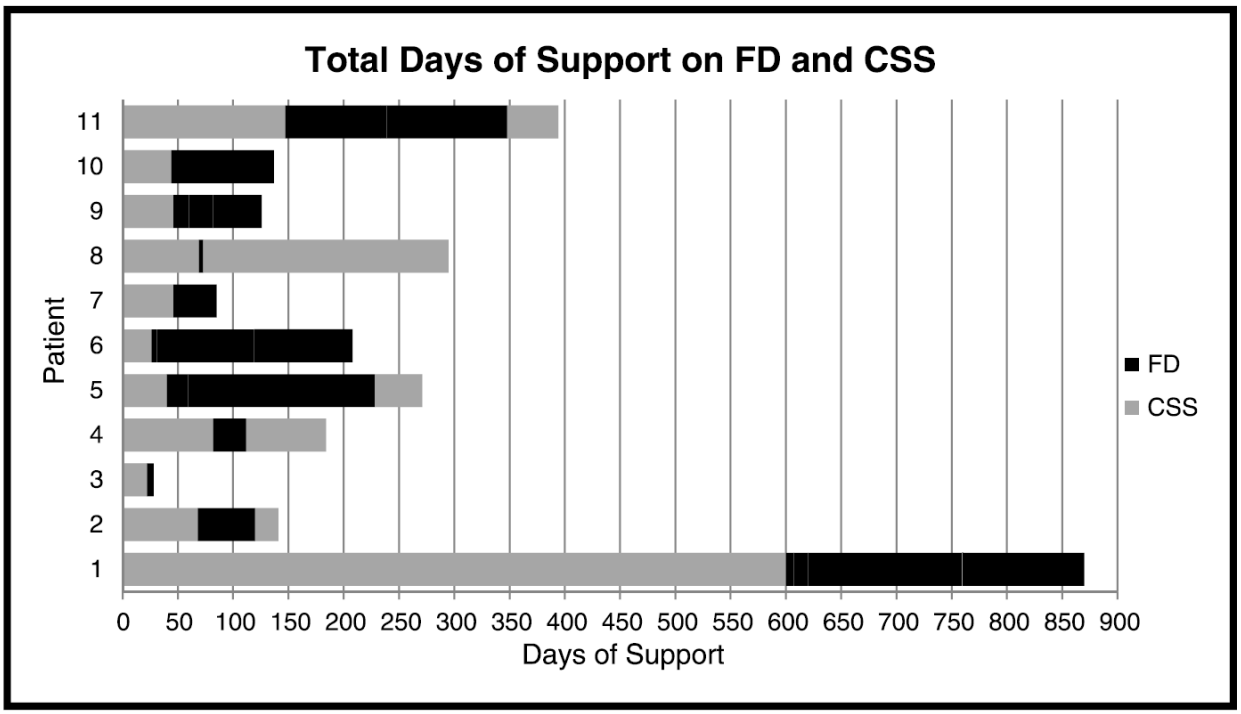
Shah NR, Jaroszewski DE, Ashfaq A, et al. SynCardia Portable Freedom Driver: A Single-Center Experience With 11 Patients. *Innovations (Philadelphia, PA)*. 2015;10:188-194.

The study was done to assess the efficacy of the Freedom Driver, a portable driver for the SynCardia TAH. This is significant because it would improve quality of life for patients while on

lengthy waitlists. The inclusion criterion was that the TAH had to be implanted before the start of the study. This was a single-center study and this limitation led to a very small sample size of 11. The study was a prospective, cohort study that took place in one hospital in the United States. Patients had follow-ups for 18 months (at 3, 6, and 18 months) after implantation of the Freedom Driver, where a 6-minute walking distance and the Kansas City Cardiomyopathy Questionnaire (KCCQ) was recorded. The questionnaire measured physical limitations, symptoms, self-efficacy, social interference, and quality of life.

The study was valid because the inclusion criteria were simple and specific with an increased standardization of procedures due to the singular setting. The singular setting combined with the rarity of TAH's nationwide lead to a very small sample size, greatly limiting the validity of the study. Also, due to the unpredictability of transplants, not all of the patients could have proper follow-up, further shrinking an already small sample size. A limitation on the internal validity of this study was the number of discharges, since they were influenced by concurrent medical illnesses and a lack of social support at home.

The average number of total days with the TAH was 194 days with a range of 34 – 863 days. The average number of total days on the Freedom Driver was 84.8 days with a range of 4 to 264 days. A timeline of the patients on the Freedom Driver (FD) and standard circulatory support (CSS) can be seen below, pulled directly from the article:



The results of this study showed that 10 of the patients were successfully transplanted. Six patients had to be returned to the regular driver console due to systemic hypertension, pulmonary edema, or patient preference before their transplants. 2 of those patients were successfully returned to the Freedom Driver before their transplants. 5 patients could be discharged home with the Freedom Driver, however 4 of them required at least one hospital readmission. Of the 8 patients that had at least 2 follow-up KCCQs, 7 patients scores increased over time.

The largest limitations of this study are that it has a sample size that is too small and it lacks post-transplant outcomes. The small sample size negative impacts the power of such a study. Also, while the study does include the outcome of successful transplantation, the lack of post-transplant outcomes as a long-term outcome also limits the impact of the study. However, this small cohort study is an important early step to show the possible role of the Freedom Driver in increasing patients' quality of life while awaiting transplants.

Kirsch M, Mazzucotelli JP, Roussel J et al. Survival after biventricular mechanical circulatory support: Does the type of device matter? *Journal of Heart and Lung Transplantation*. 2012;31:501-508.

This study focused primarily on the survival while on mechanical support and after transplantation based on mechanical support device. Biventricular mechanical circulatory support can be delivered via paracorporeal devices, implantable devices, and total artificial hearts. The categories can be further broken down between pulsatile and continuous flow devices. Research comparing outcomes between these classes of support can assist in establishing protocols and deciding the best treatment for each patient.

The inclusion criterion was patients in end-stage heart failure or cardiogenic shock between 2000 and 2010. The exclusion criteria were patients receiving BiVAD support for post-cardiotomy shock, early cardiac allograft failure; after prior isolated LVAD implantation; patients only needing temporary RVAD support; patients who have mechanical support as destination therapy. Treatment groups were differentiated by the time of biventricular mechanical support they received: paracorporeal support (using Thoratec p-VAD, MEDOS, and Excor n = 255) vs implantable support (using Thoratec IVAD n = 38) vs a total artificial heart (using Syncardia TAH n = 90) for a total of 383 participants. P values were given with the patient demographics. There was a significant ($p > 0.05$) difference between the groups in terms of age (TAH patients were significantly older with an average of 48.0 ± 10.9 years old), number of patients with myocarditis (11% of all patients had myocarditis and had a paracorporeal BiVAD), and preoperative BUN (significantly higher for implantable BiVAD at 15.1 ± 9.8 mmol/liter). No other significant differences between groups were reported.

The outcomes measured were survival until transplantation, recovery, or death, adverse reactions on mechanical support, and post-transplant survival at 1 month, and 1, 3, and 5 years. Survival data was analyzed with Kaplan-Meier techniques for estimation of survival

probabilities. Data was collected retrospectively from the French multicenter registry Groupe de Reflexion sur l'Assistance Mecanique (GRAM; Reflection Group on Mechanical Circulatory Support) so groups were not assigned by the research team. Patients were then followed prospectively, in an observational cohort fashion.

The average duration of support was 82.8 ± 107.4 days and did not differ significantly between the three groups ($p = 0.53$). Mortality while on mechanical support and post-transplant survival at 1 month, and 1, 3, and 5 years also were not significantly different ($p = 0.16$ and $p = 0.84$, respectively). TAH patients had significantly lower rates of stroke ($p < 0.0001$) and a trend toward improved survival if they needed 90 days or more on support ($p = 0.08$). This led the authors to conclude that, while overall survival may not differ between the groups, if patients are expected to need long-term support, the TAH may improve survival. They also concluded that providers may consider the TAH for patients that have a higher risk of stroke or a history of stroke.

The largest limitations recognized by the authors include voluntary registration of the GRAM registry, other issues that arrive with retrospective data from multiple centers such as collecting baseline laboratory values, and large differences in group distribution due to reimbursement issues. Specifically, they mention that this could have contributed to the small sample size of IVAD participants. The comparability of this study to United States based studies is limited due to several factors but most importantly standard of care. The article mentions that, in the United States, it is the standard of care not to implant BiVADs until later in the course of the patient's disease. Conversely, in France, BiVADs are implanted earlier in the course of disease, possibly skewing the French results toward more positive outcomes.

Levin AP, Jaramillo N, Garan AR et al. Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure. The Journal of Thoracic and Cardiovascular Surgery. 2016;151:530-535.e2.

This study was investigated differences in survival between several different biventricular mechanical support configurations in short- and long-term use. Current FDA-approved configuration variations include implanted or paracorporeal, continuous-flow or pulsatile-flow, and a total artificial heart, a biventricular device, or two univentricular devices. Pulsatile flow BiVADs (PF-BiVADs) mimic the natural arterial flow of the cardiovascular system. Continuous flow BiVADs (CF-BiVADs) lack pulsatility and provides a pre-set steady rate of blood flow to the body. The article mentions that previous studies have shown that the sheer and strain forces created by the pulsatile flow VADs reinforce natural endothelial regulation within arteries, however continuous flow VADs tend to be smaller, less prone to clots, and more durable. For reference, the Thoratec IVAD and the Syncardia TAH are both pulsatile flow systems.

The study design was retrospective cohort using deidentified patient information provided by the United Network for Organ Sharing, creating a total sample size of 298 patients. 172 TAH patients, 28 CF-BiVAD patients, and 98 PF-BiVAD patients. The inclusion criterion was adult candidates that were registered for a single-organ heart transplant and received one of the support configurations listed above. The groups were defined by their mechanical support configuration: TAH (total artificial heart; n = 172), CF-BiVAD (continuous-flow biventricular assist device; n = 28), and PF-BiVAD (pulsatile-flow biventricular assist device; n = 98). Baseline characteristics between the groups were similar except for a statistical difference in body surface area ($p = 0.046$), rate of ischemia ($p = 0.035$), region in the US ($p < 0.001$), and race ($p = 0.042$).

The outcome was measured as survival after implantation, transplantation rates, and post-transplantation survival over 4 years and 5 months (January 2010 to June 2014). The results of the study were statistically nonsignificant differences between TAH, CF-BiVAD patients, and PF-BiVAD patients in terms of survival on device, successful transplantation, and post-transplant survival. 6-month post-implantation survival were as follows: 69.4% in TAH patients (95% CI: 60.6, 76.6), 56.8% in CF-BiVAD patients (95% CI: 32.2, 75.4), and 74.9% in PF-BiVAD patients (95% CI: 62.9, 83.5). 6-month survival post-transplantation were as follows: 89.3% in TAH patients (95% CI: 80.9, 94.1), 83.0% in CF-BiVAD patients (95% CI: 45.7, 95.6), and 87.6% in PF-BiVAD patients (95% CI: 76.8, 93.6). The most significant predictor of post implantation mortality and post transplantation mortality was baseline body surface area.

As with previous studies, the internal validity is limited by the small sample size and the lack of device specific complications due to data being collected retrospectively from a registry. The distribution of devices differed by regions in the United States, introducing a bias and negatively impacting internal validity of the study.

Cheng A, Trivedi JR, Van Berkel VH, Massey HT, Slaughter MS. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. *Journal of Cardiac Surgery*. 2016;31:648-653.

The purpose of this article, and this literature review overall, was to compare the survival probability of adult patient with biventricular heart failure with a BiVAD to a TAH. This article also examined complication rates while on support and after transplant between the two support devices. The inclusion criterion was all adult patients in the United Network of Organ Sharing database that underwent heart transplantation between January 2005 and December 2014. Patients were excluded (1) if they were not receiving mechanical circulatory support at the time

of transplantation or (2) if they required only temporary right ventricular support. Data was collected retrospectively in an observational, cohort design and only patients with the following devices were included: Syncardia TAH, biventricular Thoratec paracorporeal PVAD, Thoratec implantable IVAD, Heartmate II, or Heartware HVAD. These criteria created a sample size of 212 TAH patients and 366 BiVAD patients.

The BiVAD and TAH groups were significantly different statistically ($p < 0.05$) in the following preoperative characteristics: age (49.8 ± 12.9 years in TAH patients and 47.2 ± 13.9 years in BiVAD patients; $p = 0.04$), gender (87% of TAH patients were male and 74% of BiVAD patients were male; $p < 0.0001$), BMI (27.3 ± 5.2 kg/m^2 in TAH patients and 25.6 ± 4.7 kg/m^2 in BiVAD patients; $p < 0.0001$), UNOS Status 1A (94% of TAH patients and 86% of BiVAD patients; $p = 0.002$), average pulmonary arterial pressure (33.4 ± 12.3 mmHg in TAH patients and 30.5 ± 10.7 mmHg in BiVAD patients; $p = 0.02$), creatinine (1.7 ± 1.2 mg/dL in TAH patients and 1.3 ± 0.8mg/dL in BiVAD; $p < 0.0001$), and days on the waitlist (169.5 ± 255.2 days for TAH patients and 142.3 ± 245.6 days for BiVAD patients $p = 0.009$). The outcomes measured were complications while on the device, complications after transplantation, and survival probability by total days on the waiting list.

The difference between TAH and BiVAD support in terms of waitlist survival was not significant. Post-transplant survival was higher by 5% at 30 days, 5% at 1 year, and 6% at 3 years in the BiVAD group, but this outcome only approached statistical significance ($p = 0.06$). In terms of waitlist complication rates, the rate of renal failure was higher in the TAH group by 14% ($p < 0.0001$) and the rate of infection was higher in the BiVAD group by 6% ($p = 0.005$). Rates of renal failure were higher in the TAH group post-transplantation by 12% ($p = 0.0001$) as

well. Despite these differences, waitlist survival did not significantly differ between the two groups.

The authors concluded that BiVADs are equal to TAH as a bridge-to-transplantation options for patients, however, they have the added benefit of being explanted once myocardial recovery has occurred, which the TAH is lacking. Neither device is complication-free however the TAH also requires anticoagulation regiments that most BiVADs do not. While this information may be used in the overall decision-making process of clinicians, the internal validity of this study is limited by the large amount of statistically significant differences between the two groups, 7 out of 12 characteristics examined. This is especially important because those differences demonstrate that TAH patients tended to be in more critical condition than BiVAD patients. For example, a significantly greater proportion of TAH patients were UNOS Status 1A, indicating the highest medical priority of translation. TAH patients also had higher pulmonary arterial pressure, indicating right sided heart strain, and elevated creatinine, indicating end-organ damage to kidneys. For the purposes of this article, the validity is also limited by the fact that BiVAD devices other than the Thoratec iVAD were used without any indication of the proportion of Thoratec iVAD patients examined.

Discussion

Mechanical circulatory support devices for patients in systolic heart failure has grown immensely in the last 3 decades. With the growing number of devices available, clinicians need to know how to choose the device that will most successfully bridge patients to transplantation. The purpose of this study was to examine the Thoratec implantable ventricular assist device (IVAD) and the Syncardia total artificial heart (TAH), two devices that have the potential to increase quality of life while most patients spend between 6 months and two years waiting for a

heart transplant. An extensive investigation using Google Scholar provided 7 studies meeting the selection criteria, 5 retrospective cohort designed, 1 prospective cohort designed, and 1 clinical trial. While randomized controlled trials are the scientific gold standard for showing relationships between an intervention and an outcome, randomization, blinding, and placebos could not be employed in any of the above studies due to the nature of the heart failure, variability in treatment, surgeon discretion, and patient variability in terms of comorbidities and insurance acceptance.

Of the three studies (Kirsch et al., Levin et al., and Cheng et al.) that directly compared waitlist survival between BiVADs, none of the authors found a significant difference between BiVAD and TAH patients. However, Kirsch et al. found TAH patients had significantly lower rates of ischemic stroke and a trend toward improved survival for patients that required 90 days or more on support. Cheng et al. found that, while waitlist survival did not significantly differ between TAH and BiVAD patients, in terms of waitlist complications, the rate of renal failure was higher in the TAH group and the rate of infection was higher in the BiVAD group.

Trends of the UNOS registry showed that, in 2017, 72.2% of patients in need of a heart transplant spent up to 2 years on the waitlist. With that in mind, it is important to examine the recorded durations of mechanical circulatory support in the articles. The research done by Torregrossa et al. examined the use of the TAH specifically for longer than one year. The authors found that 72% of patients were successfully transplanted after a year or more with the SynCardia TAH. Similarly, Slaughter et al. was chosen for this review partially because it indicated the long-term support ability of the Thoratec IVAD, in which the mean duration of support with successful transplant of 108 days with a maximum of 597 days. Six of the seven total studies showed survival to successful transplantation in the TAH or the IVAD after a year

on mechanical circulatory support. This is significant because 51.7% of patients on the UNOS registry for heart transplants in 2017 waited up to a year for a transplant.

With most patients spending up to 2 years on the waitlist, the ability for hospital discharge and normal quality of life is important. For this reason, the research done by Shah et al. with the Syncardia portable Freedom Driver pneumatic pump was included in this review. Shah and his colleagues found that 90% of the patients were successfully transplanted. 45% patients could be discharged home with the Freedom Driver. Most importantly, the study showed that 63% of patients showed an increase in quality of life with the Freedom Driver. However, as previously mentioned, the overall effect of the article is limited by such a small sample size.

One of the larger limitations of many studies (except for Shah et al.) was the use of multiple healthcare centers because it limited standardization of the circumstances in which different mechanical circulatory systems were used. All the studies lacked a protocol, allowing for device selection to be decided by clinician discretion. Also, as mentioned by Kirsch et al., in America, biventricular support is usually held until the patients are in more critical states, leading to worse outcomes. This is compared to in France, where clinicians are less likely to wait to employ biventricular support. Research from Fitzpatrick et al. was included in this study for the purposes of arguing that biventricular support should not be held until it is needed after LVAD support has failed. Planned BiVAD patients had increased survival to hospital discharge and increased 1-year survival, as well as they trended toward more successful bridging to transplantation. Similarly, the study with the largest sample size, Cheng et al. with data gathered from the national UNOS registry, showed that TAH patients had significantly more critical baseline values, specifically in terms of UNOS Status, average pulmonary arterial pressure, and creatinine when compared to BiVAD patients.

Conclusion

Systolic heart failure is defined simply as a decrease in the heart's ability to pump. An estimated that 6.2 million Americans have been diagnosed with heart failure in 2016. It is estimated that heart failure is the underlying cause of death for 1 in 8 deaths in America. In 2012, the cost of heart failure on the health care system was $30.7 billion. Patients in severe heart failure (NYHA Classes III or IV) with symptoms refractory to medication and the ICD are candidates for transplantation. However, in 2017, 3,529 adults in America were on the United Network for Organ Sharing list waiting for a donor heart, but only 2,811 (79%) transplantations were performed, and 580 people (16%) died while waiting or became too sick to transplant. Ventricular assist devices and other mechanical circulatory support devices may be employed to keep patients alive long enough to receive a heart transplant, for which over 70% of patients wait up to 2 years. Clinicians should choose the type of mechanical circulatory support devices for their patients based on what will give the patients the best chance of survival while on a lengthy waitlist. The purpose of this review was to compare the Thoratec IVAD to the Syncardia TAH in terms of waitlist survival.

Though each of the studies lacked randomization and blinding due to medical necessity, the results show that there is not a significant difference in waitlist survival between the IVAD and the TAH or as biventricular assist devices as a whole and the TAH. While randomization and blinding would not be possible, future prospective studies could attempt to employ a treatment protocol for standardization of device selection. A step further would be a case-control design if possible. However, randomized control trials are impossible for research of this nature because clinicians should do what is best for the patient's survival and thus there will always be selection bias. All of the studies also lacked long-term post-transplant outcomes and

complications that may have been influenced by the configuration of the patient's mechanical circulatory support device. Inclusion of survival beyond one-year post-transplant would be helpful in clinical decision making as well.

This review has highlighted the fact that there is not enough evidence at this time to show that one device is better than another. The IVAD and the TAH each have their advantages and disadvantages in terms of size, portability, complication rates, and patient tolerance. Although the results of these studies do not justify a standardization of mechanical circulatory support treatment, healthcare providers should continue to research and inform patients of all the configurations available to them.

References

1. Klabunde RE. *Cardiovascular Physiology Concepts.* Second ed. Baltimore, MD: Lippincott Williams & Wilkins/Wolters Kluwer; 2012.

2. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139:e56-e66.

3. Bashore TM, Granger CB, Jackson KP, Patel MR. Heart Disease. In: Papadakis MA, McPhee SJ, Rabow MW. eds. *Current Medical Diagnosis & Treatment 2019* New York, NY: McGraw-Hill. http://accessmedicine.mhmedical.com/content.aspx?bookid=2449&sectionid=194435482

4. Dolgin M, New York Heart Association. Criteria Committee. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* Ninth ed. Boston: Little, Brown; 1994.

5. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2017 Annual Data Report: Heart. *American Journal of Transplantation*. 2019;19:323-403.

6. Organ Procurement and Transplantation Network. Waitlist: Waiting Time by Waiting List Status. https://optn.transplant.hrsa.gov/data/view-data-reports/build-advanced/

7. Slaughter MS, Tsui SSL, El-Banayosy A, Kormos RL, Icenogle TB, Hill JD. The thoratec IVAD: a new implantable ventricular assist device. *Journal of Heart and Lung Transplantation*. 2004;23:S149-S149.

8. Slepian MJ, Alemu Y, Soares JS, Smith R, Einav S, Bluestein D. The Syncardia™ total artificial heart: in vivo , in vitro , and computational modeling studies. *Journal of Biomechanics*. 2013;46:266-275.

9. Fitzpatrick JR, MD, Frederick JR, MD, Hiesinger W, MD, et al. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. *The Journal of Thoracic and Cardiovascular Surgery*. 2009;137:971-977.

10. Slaughter MS, Tsui SS, El-Banayosy A, et al. Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device. *The Journal of Thoracic and Cardiovascular Surgery*. 2007;133:1573-1580.e2.

11. Torregrossa G, Michiel M, Varghese R, et al. Results With Syncardia Total Artificial Heart Beyond 1 Year. *ASAIO Journal*. 2014;60:626-634.

12. Shah NR, Jaroszewski DE, Ashfaq A, et al. SynCardia Portable Freedom Driver: A Single-Center Experience With 11 Patients. *Innovations (Philadelphia, PA)*. 2015;10:188-194.

13. Kirsch M, Mazzucotelli JP, Roussel J et al. Survival after biventricular mechanical circulatory support: Does the type of device matter? *Journal of Heart and Lung Transplantation*. 2012;31:501-508.

14. Levin AP, Jaramillo N, Garan AR et al. Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure. The Journal of Thoracic and Cardiovascular Surgery. 2016;151:530-535.e2.

15. Cheng A, Trivedi JR, Van Berkel VH, Massey HT, Slaughter MS. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. *Journal of Cardiac Surgery*. 2016;31:648-653.

Appendices

Appendix A: Comparison of Study Designs

Study	Design	Total N	Population	Configurations	Outcome measure
Slaughter et al	Prospective, nonrandomized clinical trial	39	38% BiVAD 77% BTT	100% Implantable BiVAD	Ventricular assist device flow index Survival to recovery Survival to transplantation Adverse events
Torregrosssa et al	Retrospective Cohort Study	47	100% BiVAD 100% BTT	100% TAH	Survival to transplantation Adverse reactions Cause of death Antithrombotic therapy Device malfunctions
Kirsch et al	Retrospective Cohort Study	383	100% BiVAD	67% Paracorporeal BiVAD 25% TAH 12% Implantable BiVAD	Survival to recovery Survival to transplantation Adverse reactions
Cheng et al	Retrospective Cohort Study	578	100% BiVAD	37% TAH 63% BiVAD	Adverse reactions Survival to transplantation Post-transplant survival Cause of death

Levin et al	Retrospective Cohort Study	298	100% BiVAD	57.7% TAH 9.4% Continuous Flow BiVAD 32.9% Pulsatile Flow BiVAD	Post-implantation survival Survival to transplantation Post-transplant survival
Shah et al	Prospective Cohort Study	11	100% BiVAD 100% BTT	TAH (100%)	KCCQ Survival to transplantation 6-minute walk distance Cause of death Adverse reactions
Fitzpatrick et al	Retrospective Cohort Study	99	100% BiVAD	71.7% Planned BiVADs 28.3% Delayed BiVADs	Successful bridging to transplantation Survival to hospital discharge 1-year post-transplant survival

Key: BiVAD = biventricular assist device; BTT = bridge-to-transplant; IVAD = Thoratec implantable assist device; TAH = Syncardia total artificial heart; LVAD = left ventricular assist device; RVAD = right ventricular assist device; KCCQ = Kansas City Cardiomyopathy Questionnaire

Appendix B: Validity Assessment

Study	Blinding	Adequate Timeline	Follow up	Intention to treat analysis	Power
Slaughter et al	I	A	A	A	M
Torregrosssa et al	I	A	A	A	I
Kirsch et al	I	A	A	A	M
Cheng et al	I	A	A	A	A
Levin et al	I	A	A	A	M
Shah et al	I	A	A	A	I
Fitzpatrick et al	I	A	A	A	M

Key: A=Adequate, M=Marginal, I=Inadequate evidence

Appendix C: Summary of Results

Study	Configuration	Survival to Transplantation	Adverse Reactions
Slaughter et al	100% Implantable BiVAD	S	S
Torregrosssa et al	100% TAH	S	S
Kirsch et al	67% Paracorporeal BiVAD 25% TAH 12% Implantable BiVAD	NS	NS
Cheng et al	37% TAH 63% BiVAD	NS	S
Levin et al	57.7% TAH 9.4% Continuous Flow BiVAD 32.9% Pulsatile Flow BiVAD	NS	NS
Shah et al	100% TAH	S	S
Fitzpatrick et al	71.7% Planned BiVADs 28.3% Delayed BiVADs	S	N/A

Key: S=Significant; NS=Not significant; N/A=Not applicable