

LEFT VENTRICULAR ASSIST DEVICE THERAPY IN HEART FAILURE: A META-ANALYSIS

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ABSTRACT

Background: The current treatment options available for end-stage heart failure include heart transplantation (HTx) and left ventricular assist devices (LVADs). Despite comparable efficacy and safety profiles, the reliability of LVAD therapy as an alternative to the standard HTx still controversial. Moreover, the choice among different LVADs types in candidate patients is unclear.

Aim of the Work: To compare HTx vs LVADs in adult end stage heart failure population, evaluate destination therapy (DT) vs bridge to therapy (BTT) as indications for LVADs, and characterizes individual safety profiles for commercially available LVADs including Heart Ware, Heart Mate II, and Heart Mate III.

Patients and Methods: A systematic search of Egyptian knowledge bank (EKB), PubMed, and Cochrane databases was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Four types of comparisons were set in the current analysis: HTx vs LVADs, DT vs BTT, Heart Ware vs Heart Mate II, and Heart Mate II vs Heart Mate III. The primary endpoint assessed was the all-cause mortality. Secondary endpoints were the complication rates relevant to either modality including organ failure, infection rates and device related complications (for LVADs only).

Results: The present study systemically analyzed 6734 patients derived from 12 studies including 10 observational and 2 randomized controlled trials (RCTs). Comparing HTx to LVAD, there were no significant differences between both modalities regarding mortality, stroke, infection, bleeding, hospital readmission, and renal failure. However, HTx demonstrated significantly higher right ventricular failure (RVF) rates ($P = 0.005$). When comparing DT vs BTT indications, non-significant differences were found regarding the rates of mortality, infection, bleeding, RVF, and device malfunction. Nevertheless, significantly lower rates of stroke were demonstrated with BTT ($P = 0.02$). Comparison between different LVADs demonstrated significantly higher rates VAD infections ($P = 0.03$), neurological complications ($P < 0.001$), and RVF in Heart Ware compared to Heart Mate II. Conversely, Heart Mate III demonstrated significantly lower rates of stroke ($P = 0.02$) and device malfunction ($P < 0.001$) compared to Heart Mate II.

Conclusion: The findings of this meta-analysis indicate that LVAD may serve as a potential alternative to heart transplantation in patients with end-stage heart failure.

Keywords: Heart transplantation, Destination therapy, Bridge to therapy, Egyptian knowledge bank

INTRODUCTION:

Due to its increasing prevalence, complication, mortality, and growing health care costs, heart failure (HF) gained a particular interest among different cardiovascular diseases. In Egypt, heart failure has gradually become one of the most prevalent cardiovascular disorders, especially in the elderly. Heart failure is now possibly the leading cause of hospitalization in Egyptian cardiac departments ⁽¹⁾. There have been substantial advances in the definition, diagnostic modalities, and treatment of HF over the past four decades. In clinical practice, newly developed HF medications and circulatory support devices have been widely adopted ⁽²⁾.

Patients with end-stage heart failure represent about 0.5-5% of total cases ⁽³⁾. These patients suffer from significantly high hospitalization rates, poor quality of life, and increasing mortality rates (ranging between 25-50%). The current treatment options available for the end-stage heart failure patient population are heart transplantation (HTx) or left ventricular assist devices (LVADs) with either bridge to transplantation (BTT) or as destination therapy (DT). HTx remains the standard treatment for this patient category; however, it is limited by donor availability, waitlist mortality, primary graft failure, cardiac allograft vasculopathy, hypertension/hyperlipidemia, and malignancy ⁽⁴⁾. LVADs were then introduced either as a potential alternative for HTx (DT) or to improve the survival rates in candidates waiting for transplant therapy. Estimates of survival rates with LVADs are continuously evolving during 1-month (96%), 1- (83%), and 2-year (73%) follow up ⁽⁵⁾. Nevertheless, LVAD therapy is limited by device-related infections, gastrointestinal (GI) bleeding, ventricular arrhythmias, LVAD malfunction, pump thrombosis, neurological emergencies,

and right ventricular failure⁽⁶⁾. Therefore, to maximize both safety and efficacy of LVAD therapy, candidate patients should be assessed for LVADs selection criteria including Left Ventricular Ejection Fraction (LVEF) < 25%, NYHA IIIb–IV symptoms for at least 45 of the last 60 days, refractory heart failure symptoms despite optimal medical and device therapy, Peak Maximal oxygen consumption (VO₂) < 14 mL/kg/min, continued need for IV inotropic therapy due to symptomatic hypotension, worsening end organ function, or persistent pulmonary edema, IV inotropic medication use for ≥14 days, or intra-aortic balloon pump support for ≥ seven days⁽⁷⁾.

The technology of mechanical circulatory support implemented in LVADs as well as the surgical techniques, have been greatly evolved during the past years. According to the MOMENTUM 3 trial, the advance in mechanical circulatory support technique from conventional centrifugal pumps implemented in Heart Ware and Heart Mate II to the fully magnetically levitated centrifugal flow pump implemented in Heart Mate III resulted in a significant improvement in survival rates⁽⁸⁾. Nevertheless, the comparative rates of complications, including bleeding, infection, stroke, and device malfunction still questionable.

AIM OF THE WORK:

The current work aimed at: (1) Evaluating the safety and efficacy of left ventricular assist device (LVAD) therapy as an alternative treatment strategy for heart transplantation (HTx) in patients with end-stage heart failure. (2) Comparing outcomes of destination therapy (DT) vs. bridge therapy (BT) as indications for LVAD therapy. (3) Comparing the complication rates between different LVADs, including Heart Ware, Heart Mate II, and Heart Mate III.

PATIENTS AND METHODS:

Search strategy and study selection:

A systematic search of the PubMed, google scholar, Embase, Egyptian knowledge bank (EKB), MEDLINE and Cochrane Central Register databases for randomized controlled trials (RCTs) was conducted. Abstracts from recent major cardiovascular conferences e.g., American Heart Association, American College of Cardiology, and Transcatheter Cardiovascular Therapeutics, were also screened for any additional trials addressing the same topic of interest. The study is planned to be conducted in concurrence with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁽⁹⁾. The search applied the following keywords: Left ventricular assist device, ventricular-assist device heart transplantation, decompensated heart failure. The results of the literature search were downloaded into Mendeley citation manager, and duplicate citations were identified and removed. Subsequently, the studies were double-checked for inclusion in our analysis. References of the relevant studies, review articles, and commentaries were also assessed for other potential studies missed by the literature search.

Selection criteria:

Studies which compared outcomes of patients with end-stage heart failure treated with either left ventricular assist devices (LVADs) or heart transplantation, was assessed using the following PICOS criteria:

1. **Population:** adult patients with end-stage heart failure (pediatric studies were excluded).
2. **Intervention:** Left ventricular assist devices (LVADs).
3. **Comparison intervention:** Heart transplantation (HTx).

4. **Outcome:** any primary or secondary outcome of the present meta-analysis.

5. **Study design:** Observational or randomized clinical trials (RCTs).

Inclusion criteria include:

1. Studies including adult population (age between 18-99).
2. Studies presenting head to head comparisons between heart transplantation and LVAD and/or LVAD vs other LVAD type.
3. Studies that reported outcomes for one-year mortality.

Exclusion criteria include:

1. Studies including pediatric age range.
2. Studies published in non-English language.
3. Studies published before 2010.
4. Studies including patients with hepatic or renal impairment or patients with neurologic deficits.

Data extraction:

The data on study characteristics (i.e., year of publication; country and center; setting; study design and methodology; patient demographic characteristics (gender, age, race); HF etiology; LVAD strategy (BTT or DT); complication rate; readmission rate per year of support, stroke, infections, cost and mortality, quality assessment data (i.e., assessment of blindness, selection bias, etc.) were extracted from each individual study. The numbers of clinical events in each arm were tabulated.

Study quality assessment:

The quality of evidence was assessed at the individual study level and each outcome level. The Cochrane Collaboration's tool for assessing the risk of bias was implied to evaluate individual study risk of bias. Trials with >2 high-risk components considered as having a moderate risk of bias, and trials

with >4 high-risk components considered as having a high risk of bias.

The overall quality of evidence for each outcome was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) tool, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.

Assessment of publication bias:

Publication bias was assessed by the construction of a funnel plot and confirmed by Egger’s test.

Endpoint assessment:

The primary outcome of interest was either a composite end-point of death, early mortality (≤ 1 year), or late mortality (> 1 year). Secondary endpoints assessed were the rates of complications related to either HTx or LVAD therapy, including bleeding, infection, and organ damage rates.

Statistical analysis:

Review Manager 5.2 (Cochrane Collaboration) was employed to analyze the results. Dichotomous data were calculated with risk ratios, and continuous data were assessed with weighted mean difference, each with 95% confidence intervals. Weighted

frequencies were used to describe categorical variables, and weighted means with standard deviations were used to describe continuous variables, using the sample size of each trial as the weight.

A two-sided P-value of <0.05 with a confidence interval (CI) of 95% was considered statistically significant for all statistical analyses.

Heterogeneity was analyzed using the χ^2 test; $I^2 < 50\%$ and $P \leq .05$ indicated significant heterogeneity, and the random-effects model was used. If these criteria were not satisfied, the fixed-effects model was applied instead. Random effects inverse variance weighted incidences were calculated for the outcomes with 95% confidence intervals (CI) using R statistical package (version 4.0.0). Random effects risk ratios (RR) or odds ratio (OR) by DerSimonian and Laird method were calculated for all outcomes in the different arms of comparisons⁽¹⁰⁾. I^2 test was also used for assessment of the degree of heterogeneity among the included trials with values <25%, 25%–50%, and >50% corresponding to low, intermediate, and high evidence of heterogeneity⁽¹¹⁾.

RESULTS:

Table (1): Characteristics of the included studies

Study	Study design	LV Device (s)	No. of patients	Location
Ammirati et al. 2015 ⁽¹²⁾	Retrospective-prospective	HeartMate II/ Heart Ware HVAD	213	Italy
Attisani et al. 2012 ⁽¹³⁾	Retrospective	BiVAD	49	Italy
Droogne et al. 2014 ⁽¹⁴⁾	Prospective	Heart Mate II	38	United States
Majure et al. 2015 ⁽¹⁵⁾	Retrospective	HVAD/Heart Mate II	104	United States
Mehra et al. 2018 (MOMENTUM 3) ⁽¹⁶⁾	Multi-center RCT	HeartMate III/ Heart Mate II	366	United States
Mishra et al. 2016 ⁽¹⁷⁾	Retrospective	Heart Ware/ LVADV	278	Norway
Morgan et al. 2016 ⁽¹⁸⁾	Retrospective	HVAD/ Heart Mate II	240	United States
Rogers et al. 2017 (ENDURANCE) ⁽¹⁹⁾	Multi-center RCT	Heart Ware/ Heart Mate II	446	United States
Schumer et al. 2015 ⁽²⁰⁾	Retrospective	HVAD/Heart Mate II	4,737	United States
Sorabella et al. 2015 ⁽²⁰⁾	Retrospective	CF-LVAD	113	United States
Williams et al. 2011 ⁽²¹⁾	Prospective	CF-LVAD	42	United States
Zhigalov et al. 2018 ⁽²²⁾	Retrospective	HVAD/Heart Mate II /Heart Mate III	108	United States

Left Ventricular Assist Device Therapy In Heart Failure: A Meta-Analysis

Table (2): Risk of bias assessment.

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Ammirati et al. 2012	High	High	High	Unclear	Low	Unclear
Attisani et al. 2012	High	High	High	Low	High	High
Droogne et al. 2014	High	High	High	Unclear	High	Unclear
Majure et al. 2015	High	High	High	Low	Low	High
Mehra et al. 2018	Low	High	High	Low	Low	Low
Mishra et al. 2016	High	High	High	Low	Unclear	High
Morgan et al. 2016	High	High	High	Low	Low	Unclear
Rogers et al. 2017	Low	High	High	Low	Low	Low
Schumer et al. 2015	High	High	High	Low	High	Low
Sorabella et al. 2015	High	High	High	Low	Low	Unclear
Williams et al. 2011	High	High	High	low	High	High
Zhigalov et al. 2018	High	High	High	low	low	High

Table (3): Synthesis on the comparative safety profiles of different left ventricular assist devices.

Device	Mortality	VAD Infections	Neurologic events	Bleeding	RV Failure	Device Malfunction	Pump thrombosis
HeartWare	Neutral risk	High risk	High risk	Neutral risk	High risk	Neutral risk	Low risk
HeartMate II	Neutral risk	Neutral risk	Neutral risk	Neutral risk	Neutral risk	Neutral risk	Neutral risk
HeartMate III	Neutral risk	Neutral risk	Low risk	Neutral risk	Neutral risk	Low risk	Low risk

Low risk
 Neutral risk
 High risk

DISCUSSION:

The management of heart failure patients in their end-stage disease is a growing challenge. Despite increasing survival obtained from improving medical treatment and prevention of sudden cardiac death, a percentage of patients with end-stage heart failure continue to require heart transplantation (HTx) or durable mechanical support [e.g., left ventricular assist devices (LVAD)] to prolong life⁽⁷⁾. HTx remains the gold standard for end-stage heart disease in adults. However, because of the limited donor heart availability and the multiple common contraindications, this option is available only for a limited number of patients⁽²³⁾. LVADs have progressively evolved in their indication, becoming a treatment to support end-stage HF patients in several different clinical scenarios: as a bridge to heart transplantation, as destination therapy, as a bridge to decision or even as recovery⁽²⁴⁾. Nevertheless, LVAD therapy suffers many adverse effects,

including risks of VAD or non-VAD related infections, renal failure, right ventricular failure, stroke, pump thrombosis associated with device malfunction⁽²⁵⁾.

The current analysis was performed for the purpose of quantitative analysis of the relevant studies to answer 3 study questions regarding LVADs application in the management of end-stage heart failure patients. First, whether there are any clinically meaningful differences between LVAD and HTx in this patient population. Second, if there are differences in outcomes obtained from patients undergoing LVAD implantation for the purpose of destination therapy (DT) or bridge to therapy (BTT). Finally, if there are differences in LVAD outcomes obtained from the different commercially available devices (Heart Ware, Heart Mate II, and Heart Mate III).

The present study systemically analyzed 6734 patients derived from 12 studies

including 10 observational and 2 randomized controlled trials (RCTs). Of note, performing an RCT with LVADs is complex and expensive⁽²⁶⁾. This explains the limited number of the included RCTs in the current analysis.

The main findings of the current analysis are that LVADs and heart transplantation have comparable outcomes in patients with advanced heart failure, suggesting that LVADs may be considered as a potential alternative for HTx for this patient population. Importantly, we found a significantly higher rate of right ventricular failure with HTx, limiting their application in patients with coinciding right-sided heart disease(s). When comparing BTT to DT as competing modalities for LVADs, we found similar outcomes except for stroke, which was statistically lower in BTT. Moreover, the results of the comparison of different LVADs demonstrated an explicit distinction between Heart Ware, Heart Mate II & Heart Mate III. Heart Ware devices were associated with significantly higher rates of VAD infections, neurologic events, and RV failure compared to other devices. In contrast, Heart Mate III demonstrated the least rates of neurological events and device malfunction among the studies LVAD types. Importantly, the current findings and the results from similar analyses should be interpreted with caution, as there are no consensus criteria on endpoints definitions, which threatens consistency of the findings among the studies.

Regarding comparison of LVAD to HTx, we found slight differences between the two interventions, indicating growing evidence of the applicability of LVADs as an alternative management strategy in patients with end stage heart failure. The overall mortality rates were similar (OR= 1.51, 95% CI = 0.81-2.81). Similarly, in their meta-analysis, Oikonomou et al. demonstrated non-significant differences in all-cause 1-year mortality regardless the underlying indication of LVAD therapy [LVAD BTT and HTx (pooled OR: 0.91; 95% CI: 0.62–1.32; I² =21.2%), or between LVAD

DT and HTx (pooled OR: 1.49; 95% OR: 0.48–4.66; I² =82.8%)]⁽²⁷⁾. More recently, Suarez-Pierre et al. agreed with our results and indicated that there is not a statistically significant difference in 1-year mortality between HTx and BTT LVAD patients not only for 1-year mortality but also for early (30-day) or 2- and 5-year mortality⁽²⁸⁾. Exceptionally, Attisani *et al.* in their observational study, suggested a HTx superiority for in-hospital mortality⁽²⁹⁾. In this study, patients on the waiting list for HTx were compared with urgent conditions and patients managed with LVAD as a BTT. In-hospital mortality was found to be significantly higher for HTx waiting list patients compared to BTT LVAD patients (42.3% vs. 4.3%, P=0.002). Another discrepancy encountered in the included studies was reported by Mishra *et al.* found that DT LVAD patients had inferior short term survival comparing to HTx⁽¹⁷⁾. However, the primary objective of their study was comparing the financial costs between LVADs and HTx, and they included a small number of LVAD candidates (n=19).

Secondary endpoint analysis in the present analysis demonstrated also non-significant differences regarding stroke (OR= 1.49, 95% CI= 0.42-5.3), infection (OR= 2.88, 95% CI= 0.6-13.73), bleeding (OR= 1.55, 95% CI= 0.44-5.44), hospital readmission (OR= 0.1, 95% CI= 0.02-26.5), renal failure (OR= 0.8, 95% CI= 0.32-2.02). We found higher rates of right ventricular failure in HTx compared to LVAD (OR= 5.82, 95% CI= 1.71-19.77). It should be noted that LVAD related right ventricular failure is attributed to the systemic inflammation during LVAD implant, which is different from one device to another^(30, 31).

Despite comparable safety outcomes, the choice of either strategy should be individualized on patient-specific basis.

When comparing BTT Vs DT, non-significant differences was found between both indications including rates of overall

mortality (OR= 0.56, 95% CI= 0.08-3.8), infection (OR= 1.16, 95% CI= 0.59-2.28), bleeding (OR= 0.95, 95% CI= 0.57-1.59), renal failure (OR= 0.98, 95% CI= 0.46-2.06), right ventricular failure (OR= 0.92, 95% CI= 0.52-1.60), and device malfunction (OR= 0.94, 95% CI= 0.36-2.43). However, lower stroke rates were concluded in BTT compared to DT (OR= 0.45, 95% CI= 0.23-0.87). Of note, none of the included trials demonstrated significantly higher stroke in DT group compared to BTT; however, when pooling the results together, a weak statistical significance was obtained. Generally, candidates of DT are usually of advanced age with associate comorbidities, making the predicted LVAD outcomes are possibly poor when compared to BTT⁽³²⁾. Similar to these findings, recently, Oikonomou *et al.* indicated that outcomes from LVAD therapy as DT or BTT is nearly similar when compared to standard intervention (HTx). In their meta-analysis, the odds ratio of one-year survival was 0.91 (95% CI: 0.62–1.32) for BTT, and 1.49 (95% CI: 0.48–4.66) for DT, indicating that both strategies are non-significantly different from HTx, and hence equivalence can be inferred⁽²⁷⁾. More recently, Miller *et al.*, performed a retrospective analysis of LVAD patients who underwent cardiac transplantation. Their results indicated that the combined overall 1 and 3-year survival was similar⁽³³⁾. Neither the rate of adverse events nor the time to adverse event differed between the two cohorts: (BTT 36% rejection, 23% infection, and 64% readmission vs DT 29% rejection, 32% infection, and 76% readmission). They suggested that transplant outcomes are acceptable for patients initially labeled DT and that a longer duration of LVAD support may not adversely affect posttransplant outcomes⁽³³⁾. Whether a marginal distinction between BTT and DT patients is clinically meaningful remains a questionable issue⁽³⁴⁾. It should be noted that there is a possibility that patients awaiting transplantation on LVAD support may develop contraindications to transplant or

never receive a suitable organ given the paucity of donors, necessitating a long-term need for LVAD, which may serve an acceptable alternative⁽³⁵⁾.

The choice between the available LVADs is another challenge. Since we only included the studies published between 2010-2019, comparisons were made between the newer generations of continuous flow LVADs only (Heart Ware, Heart Mate II, and Heart Mate III), and none of the first-generation devices were included in this analysis.

Comparing Heart Ware to Heart tMate II, overall mortality was not significantly different (OR = 1.31, 95% CI = 0.88-1.94). The risk of VAD infection was significantly higher with Heart Ware (OR= 1.67, 95% CI= 1.06-2.64); however, non-VAD infection rate was similar (OR= 0.95, 95% CI = 0.28-3.15). Rates of bleeding (OR= 1.06, 95% CI = 0.75-1.49), hospital readmission (OR= 1.36, 95% CI =0.89-2.06), and device malfunction (OR= 1.27, 95% CI = 0.83-1.93) were also comparable between both devices. Nevertheless, significantly higher rates of composite end point of neurologic events including both ischemic and hemorrhagic stroke (OR= 2.6, 95% CI= 1.61-4.18), and right ventricular failure (OR= 1.71, 95% CI = 1.18-2.48) were associated with Heart Ware device. Heart Ware demonstrated significantly lower rates of pump thrombosis (OR= 0.38, 95% CI = 0.22-0.68).

In accordance with these findings, in their systematic review, Salih *et al.* included a total of 3 studies with 1,234 patients comparing Heart Mate II to Heart Ware. Their findings indicated that Heart Ware group had similar all-cause mortality (OR 1.29; 95% CI, 0.88-2.02, P = 0.14). Secondary endpoint analysis indicated that driveline infection (OR 0.61; 95% CI, 0.24 - 1.53, P = 0.3), and the rate of gastrointestinal bleeding (OR 0.60; 95% CI, 0.12- 3.05, P = 0.54) were also similar in both devices⁽³⁶⁾. Moreover, rates of stroke were significantly higher in Heart Ware (OR 2.63; 95% CI, 1.87- 3.69, P = 0.00001) compared to

Heart Mate. However, unlike our results, they reported similar rates of driveline infections (OR 0.61; 95% CI, 0.24 - 1.53, P = 0.3). A recent meta-analysis analyzing 76 studies comparing the differences in infection rates between Heart Mate II and Heart Ware demonstrated heterogeneous results, including higher, lower, or insignificant VAD infection rates comparing Heart Mate II to Heart Ware⁽²⁴⁾. They attributed this discrepancy to limited sample sizes of the underlying studies, different protocols of prophylaxis, and wound dressings, suggesting that the difference in infection rates is primarily related to non-VAD factors. Despite improvements in technical issues such as a hydrodynamic suspension in Heart Ware VADs, and new physiological control algorithms incorporated for safe operation, observational studies concluded that the introduction of new generation LVADs has not markedly reduced the drive-line exit-site infection rates⁽³⁷⁾.

Significant high rates of stroke were found through the present study with Heart Ware. Nevertheless, these results should be interpreted with great caution, as this conclusion was drawn from only two studies, with a larger weight given to (ENDURANCE trial) due to the higher sample size (n=446) and the randomized design⁽³⁸⁾. The results of the ENDURANCE trial revealed that the risk for stroke was two to three times higher with the Heart Ware device than with the Heart Mate II. However, the trial had several significant limitations, including a lack of adherence to anticoagulation and antiplatelet protocols, and changes in the Heart Ware device design during the trial. Additionally, the pathogenesis of stroke is complex and related to the characteristics of blood flow in the pump, activation of the coagulation cascade via contact of blood components with the metal housing of the device, ingestion of the thrombus from the native ventricle, and the requisite use of anticoagulation therapy to prevent device thrombosis^(39,40). A systematic review by Cho et al. investigating Heart Ware and HMII stroke rates found much

heterogeneity in the data, and no strong conclusions were drawn regarding a difference in outcomes between the 2 devices⁽⁴¹⁾.

Surprisingly, a lower incidence of pump thrombosis was reported in the current work with Heart Ware compared to Heart Mate II. It is noteworthy that the higher pump thrombosis rate associated with Heart Mate II was not associated with significantly different device malfunctions compared to Heart Ware in the present analysis (p = 0.27). Among the included studies comparing rates of pump thrombosis between the two devices, only Majure et al. reported statistically significant higher rates of pump thrombosis associated with Heart Mate II in our analysis⁽¹⁵⁾. In contrast to our findings, Salih et al. concluded that in a patient with end-stage heart failure, the use of Heart Mate II is associated with significantly reduced risk of pump thrombosis compared to Heart Ware⁽³⁶⁾. An increase in device thrombosis with the Heart Mate II was reported in 2014⁽⁴²⁾, but appears to have been mitigated in a 2017 study that focused on meticulous surgical implantation technique and post-implantation medical therapy⁽³⁶⁾. Our conclusion regarding the rates of pump thrombosis with Heart Mate II was solely extended from the results of Majure et al., who demonstrated an explicitly higher pump thrombosis rate with Heart Mate II (P<0.01)⁽¹⁵⁾. The small difference in thrombosis rate shouldn't be overemphasized; since we found a corresponding non-significant difference in the associated device malfunction (p = 0.27). Nevertheless, it should be noted that device malfunctions other than pump thrombosis is a very common complication within 1 year postoperatively⁽⁴³⁾, and influenced by numerous factors including implantation technique; anatomical constraints; and complications such as infection and bleeding, anticoagulation, pump settings and device design⁽³¹⁾.

Comparing Heart Mate III to Heart Mate II was also associated with significant trends. The overall mortality rates (OR= 0.79, 95%

CI= 0.46-1.35), VAD infections (OR= 1.24, 95%CI = 0.76-2.03), bleeding (OR= 0.68, 95% CI = 0.45, 1.02), right ventricular failure (OR = 1.18, 95% CI = 0.76-1.84), pump thrombosis (OR= 0.09, 95% CI = 0-2.71) were similar comparing both devices. However, Heart Mate III was associated with lower rates of device malfunction (OR=0.1, 95% CI = 0.03-0.29), and stroke (OR = 0.47, 95% CI = 0.26-0.86).

The current results contributed primarily by the findings of the MOMENTUM 3 trial, a randomized controlled trial of the Heart Mate 3 (HM3) continuous-flow centrifugal pump versus the Heart Mate II (HMII) axial-flow pump in patients with advanced heart failure, regardless of the intended goal of support (bridge to transplantation or destination therapy). The pivotal 2-year primary endpoint analysis of this trial was analyzed (n= 366). In this study, the HM3 was superior to the HMII for the primary endpoint of survival free of disabling stroke (modified Rankin Scale [mRS] score >3 assessed at the 60-day follow-up) or reoperation for the pump replacement. In a notable finding, the HM3 was associated with a significant reduction in any stroke event compared with the HMII pump⁽¹⁶⁾.

In a more recent study, post-hoc analysis of long-term stroke in the MOMENTUM 3 study reported an increase in the prevalence of neurologic events in Heart Mate II compared to Heart Mate III patients at long-term follow-up (3% vs 12.1%, $P=0.01$)⁽⁴⁴⁾. A fully magnetically levitated rotor, wider blood flow paths, and intrinsic pulse is designed to mitigate stasis within the device itself with the goal of preventing thromboembolic complications such as pump thrombosis and stroke.

In similar context, the reduced blood stasis observed with the magnetic properties of Heart Mate III was associated with a significant reduction of device malfunction rates in the current analysis. In spite of the non-significant difference in rates of pump thrombosis, significance was reported clearly

in the results of Momentum 3 trial⁽¹⁶⁾. According to Momentum trial results, at two years, 98.6% of patients avoided thrombosis (clotting) in their pump (vs. 86.1 % with Heart Mate II). An insignificant difference in pump thrombosis was reported in the study of Zhigalov et al. however, this discrepancy is primarily attributed to the relatively smaller sample size (n=108)⁽²²⁾. In 2020, a secondary analysis of MOMENTUM 3 trial confirmed statistically lower rates of pump thrombosis associated with Heart Mate III, irrespective to the indication of LVAD therapy (BTT or DT) (RRs: BTT group, 0.03 [95% CI, 0.00-0.21]; DT group, 0.10 [95% CI, 0.04-0.24])⁽⁴⁵⁾.

To the best of our knowledge, the current analysis included all studies obtained from careful bibliographic search, including observational and randomized controlled trials published in the last 10 years assessing LVADs in end-stage heart failure. So, it can be valid to quantitatively synthesize an evidence regarding treatment decisions in patients with end-stage heart failure. The present meta-analysis provides evidence-based guidance to the individualized selection of a specific device for patients who are candidates for LVADs. Publication bias was adequately addressed through the study using the funnel plots which demonstrate symmetry without significant trends, confirming the validity of the results. However, like all of the similar meta-analyses, many limitations do exist.

The included retrospective studies (n= 8) are associated with potential information bias. Endpoints for LVAD and HTx may not be directly comparable. The included studies demonstrated heterogeneous patient populations at baseline with different rates of comorbidities. In some studies, patients who were initially managed as BTT were converted to DT LVAD, principally due to the lack of available heart transplant donors. This overlap limited our ability to clearly differentiate these two groups of patients. Therefore, the results of comparing HTx to LVADs should be interpreted with caution. Moreover, future

head to head comparison of both modalities should be addressed in larger clinical trials.

Conclusion:

The findings of this meta-analysis indicate that LVAD may serve as a potential alternative to heart transplantation in patients with end-stage heart failure. In particular, patients with right ventricular heart failure comorbidity are preferentially recommended for LVADs regardless of the indication for LVAD (BTT or DT). The choice between the candidate device for each patient should be personalized according to the baseline comorbidities to achieve the maximum benefit. Whenever possible, Heart Mate III should be indicated as the LVAD of choice due to its favorable safety profile.

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Left Ventricular Assist Device Therapy In Heart Failure: A Meta-Analysis

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دراسة بعدية لاستخدام الأجهزة المساعدة للبطين الأيسر في علاج فشل عضلة القلب
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المقدمة: تشمل خيارات العلاج الحالية المتاحة لفشل القلب في المرحلة النهائية زرع القلب (HTx) وأجهزة مساعدة البطين الأيسر (LVADs). على الرغم من جوانب الفعالية والأمان المماثلة، فإن موثوقية علاج LVAD كبديل لـ HTx القياسي لا تزال مثيرة للجدل. علاوة على ذلك، فإن الاختيار بين أنواع أجهزة مساعدة البطين الأيسر في المرضى المرشحين غير واضح.

الهدف من البحث: مقارنة زراعة القلب مقابل الأجهزة المساعدة للبطين الأيسر في فئة فشل عضلة القلب في المرحلة النهائية للبالغين. تقييم طرق العلاج المباشر (DT) مقابل الجسر إلى العلاج (BTT) كمحددات مختلفة للأجهزة المساعدة للبطين الأيسر. مقارنة درجات الأمان و الفاعلية لأنواع المختلفة من الأجهزة المساعدة للبطين الأيسر المتاحة تجاريًا بما في ذلك Heart Ware و Heart Mate II و Heart Mate III.

المرضى وطرق البحث: إتمدت الدراسة علي بحث منهجي من خلال قواعد بيانات بنك المعرفة المصري (EKB) و PubMed و Cochrane وفقًا لإرشادات عناصر التقارير المفضلة للمراجعات المنهجية والتحليلات الوصفية (PRISMA). تم تعيين الدراسات التي احتوت علي أي من أربعة أنواع من المقارنات في التحليل الحالي: مقارنة زرع القلب مقابل الأجهزة المساعدة للبطين الأيسر ومقارنة العلاج المباشر (DT) مقابل العلاج المؤقت (BTT) بالأجهزة المساعدة للبطين الأيسر ومقارنة جهاز ال Heart Ware بجهاز ال Heart Mate II ومقارنة جهاز ال Heart Mate II بجهاز ال Heart Mate III.

النتائج: حللت الدراسة الحالية بشكل منهجي ٦٧٣٤ مريضًا من خلال ١٢ دراسة بما في ذلك ١٠ تجارب قائمة على الملاحظة و ٢ معشاة ذات شواهد (RCTs). بمقارنة زراعة القلب بالأجهزة المساعدة للبطين الأيسر (LVAD)، لم تكن هناك فروق ذات دلالة إحصائية بين كلا الطريقتين فيما يتعلق بمعدلات الوفيات والسكتة الدماغية والعدوى والنزيف وإعادة الدخول إلى المستشفى والفشل الكلوي. ومع ذلك، أظهرت أجهزة البطين الأيسر المساعدة معدلات فشل البطين الأيمن أقل بشكل ملحوظ ($P=0.005$). عند مقارنة مؤشرات العلاج المباشر بالأجهزة (DT) مقابل العلاج المؤقت (BTT)، تم العثور على اختلافات ليست ذات دلالة فيما يتعلق بمعدلات الوفيات والعدوى والنزيف وفشل البطين الأيمن وعطل الجهاز. ومع ذلك، تم إظهار معدلات أقل من السكتة الدماغية باستخدام العلاج المؤقت بالأجهزة ($P=0.02$).

الاستنتاج: تشكل أجهزة المساعدة البطينية (LVAD) بديلاً محتملاً لزراعة القلب في مرضي الفشل القلبي في المرحلة الأخيرة. و يجب أن يكون الاختيار بين أنواع الأجهزة بشكل فردي لكل مريض وفقًا للأمراض المصاحبة لتحقيق أقصى فائدة. كلما كان ذلك ممكنًا، يجب الإشارة إلى Heart Mate III على أنه الاختيار المفضل بين الأجهزة المختلفة نظرًا لمعدلات الأمان العالية له مقارنة بأنواع الأجهزة الأخرى.