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**A network meta-analysis comparing left ventricular assist devices in adult patients with end-stage heart failure**

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## **ABSTRACT**

**Background:** Left ventricular assist devices (LVAD) are an approved treatment for end-stage heart failure (HF). Several devices have been developed over the years, including two new-generation ones (HeartMate 3 and HeartWare), but uncertainty persists on their comparative effectiveness. We conducted a network meta-analysis on randomized trials on LVAD for adults with HF.

**Methods and Results:** Pertinent studies were searched in several databases. Selected outcomes were extracted, including death, stroke, and bleeding. Incident relative risks (RR) were computed with network meta-analysis, with 95% confidence intervals and P-scores (with highest values indicating the best therapy). Four trials were identified, one comparing HeartMate VE vs medical management, one HeartMate II vs HeartMate XVE, one HeartMate 3 vs HeartMate II, and one HeartWare vs HeartMate II, totaling 1069 patients followed for an average of 20 months. Using HeartMate XVE/VE as benchmark, continuous-flow LVADs provided significant better outcome for death, the RR for death was 0.71 (95% confidence interval=0.44-1.14; P-score=0.914) for HeartMate 3, 0.98 (0.61-1.56; 0.404) for HeartWare, 0.80 (0.55-1.17; 0.748) for HeartMate II, and 1.47 (1.19-1.82; 0.016) for medical management. Appraising other outcomes, continuous-flow devices proved better than first-generation pulsatile-flow devices for bleeding, device failure, device thrombosis, drive-line exit-site infection, renal dysfunction, respiratory failure, stroke and sepsis.

**Conclusions:** New-generation LVAD represent a paradigm shift in the management of end-stage HF. Further technological refinements and higher quality and larger trials are crucial to improve decision-making and clinical outcomes in this challenging clinical setting.

## **Key-Words**

Heart failure; Left ventricular assist device; Meta-analysis; Network meta-analysis; Ventricular assist device.

## **ABBREVIATIONS AND ACRONYMS**

HF            Heart failure

INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support

LVAD        Left ventricular assist device

PRISMA     Preferred Reporting Items for Systematic Reviews and Meta-Analyses

P-score     Probability of being the best treatment

RCT         Randomized controlled trial

RR          Relative risk

## **INTRODUCTION**

Technologic improvements in mechanical circulatory support joined to the relative shortage of donor organs have stemmed the adoption of left ventricular assist devices (LVAD) for end-stage heart failure (HF) (1). These pumps have improved the quality of life and overall survival of patients when all other therapeutic options are exhausted. Moreover, LVAD have progressively evolved their indication, now termed “device strategy”, becoming a treatment to support end-stage HF patients in several different clinical scenarios: as a bridge to heart transplantation, as a destination therapy or more recently, as bridge to decision or even as recovery (2-4).

In addition to trends in device strategy, patients profile at the time of implant, defined by INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), have evolved (5). Risk stratification of candidates for LVAD implantation has proved to be critical for appropriate LVAD candidate selection to help foster good patient outcomes and ensure appropriate resource utilization (6-8). Initially the implantable pulsatile pump, HeartMate VE demonstrated its benefits compared to medical management alone in end-stage heart failure patients (9). Then, with the advent of continuous-flow pumps, LVADs gained momentum and the HeartMate II has become widely adopted (10). Yet, a larger use of LVADs was associated with an increased risk of pump thrombosis (11), in comparison with the low rate of thrombosis reported in the pivotal trials. To overcome this risk, the use of magnetic levitation instead of mechanical bearings has been introduced in two different LVAD devices (12, 13).

Despite such advances in technology and evidence, uncertainty persists on the comparative effectiveness and safety of LVAD. We thus aimed to conduct a systematic review and network meta-analysis of randomized trials on LVAD for HF,

in order to steer technologists, decision-makers, physicians and patients in this challenging clinical setting (14).

## **METHODS**

### **Design**

This review was registered on the PROSPERO International Prospective Register of Systematic Reviews ([https://www.crd.york.ac.uk/prospero/display\\_record.asp?ID=CRD42017057734](https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42017057734)), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table 1S) (15). All reviewing activities were conducted by two independent reviewers (EC, GBZ) in keeping with established methods (16, 17), with divergences solved after consensus.

### **Search and selection**

Potentially pertinent randomized controlled trials (RCT) on VAD were searched in PubMed using the dedicated Clinical Queries filter for clinical trials (set with the Therapy/Broad options) and the words “ventricular”, “assist”, and “device\*”. Additional searches involved the Cochrane Library and clinicaltrials.gov. Searches were last updated on February 28, 2017, without language restrictions. We screened potentially relevant citations at the title/abstract level, then retrieved full-texts of apparently pertinent trials, and finally selected randomized controlled trials on LVAD in adult patients with end-stage HF.

### **Abstraction and appraisal**

Baseline, procedural, and outcome data were abstracted, the latter according to the intention-to-treat principle whenever possible. The primary end-point was all cause death. Secondary end-points were bleeding, infection, and stroke. Additional endpoints were acute myocardial infarction, device failure, device thrombosis, drive-line exit-site infection, hemolysis, hepatic dysfunction, neurological dysfunction, psychiatric event, renal dysfunction, respiratory dysfunction, right ventricular failure, and sepsis. Definitions recommended by INTERMACS were used whenever possible (4).

The internal validity and risk of bias of included trials were appraised according to the Risk of Bias Assessment Tool recommended by the Cochrane Collaboration (18).

### **Data synthesis and analysis**

For descriptive purposes, dichotomous variables were reported as counts (%) and compared with the Fisher exact test, and continuous variables were reported as mean $\pm$ standard deviation and compared with analysis of variance. For inferential purposes, network meta-analysis with a frequentist approach and a fixed-effect method was used to compare the incidence of adverse events between different LVAD using the netmeta R package (R Foundation for Statistical Computing, Vienna, Austria), and reported as incident relative risks (RR), with point estimates and 95% confidence intervals. Notably, a fixed effect model will yield exactly the same results as a random effects model if there is no closed loop in the network. Probability-scores (P-score) were generated to identify the best to worst treatment, taking into account precision and accuracy of effect (19). These are estimates of the ranking of each treatment versus the others, and summarize as stated above the degree of uncertainty in effect based on point estimates, confidence intervals and p-values. Notably,

statistical inconsistency and small study effects were not appraised formally given the star-shaped evidence network (Figure 1) (20, 21).

## RESULTS

From 2987 citations, 4 RCTs were included in the study, one comparing the HeartMate VE vs medical management (REMATCH), one the HeartMate II vs the HeartMate XVE (HeartMate II), one the HeartMate 3 vs HeartMate II (MOMENTUM 3), and one HeartWare vs HeartMate II (ENDURANCE), totaling 1069 patients followed for an average of 20 (6 to 24) months (Table 1; Table 2S) (9, 10, 12, 13). Trials were of high quality, notwithstanding the inherent limitation of the open design (Table 2S).

Comparison of study and patient characteristics for descriptive purposes is provided in Table 2. Specifically, patient age, serum creatinine, prevalence of ischemic heart disease as cause of HF, and prevalence of prior stroke decreased over the years, whereas body surface area, systolic blood pressure, the use of beta-blockers and cardiac resynchronization therapy increased (all  $p < 0.05$ ). Trends for cardiac index, diabetes, INTERMACS profile, use of IV inotropic drugs, diuretics, and angiotensinogen-converting enzyme inhibitors were not self-evident, despite significant differences between trials. In particular, the INTERMACS profile 1-3 describes advanced HF patients dependent on inotropic support, while INTERMACS profile 4-7 describe ambulatory advanced heart failure patients. The difference observed among the trials are in favor of more critically advanced HF patients, with progressive organ dysfunction despite inotropic support, enrolled in the studies, which should be taken into account when comparing the adverse events rate.



Incident rate reported as event/100 patients followed for 1 year and incident rate ratios are provided in detail in [Table 3](#).

Inferential analysis for death, using HeartMate XVE/VE as benchmark, showed that the RR for death was 0.71 (95% confidence interval=0.44-1.14; P-score=0.914) for HeartMate 3, 0.80 (0.55-1.17; 0.748) for HeartMate II, 0.98 (0.61-1.56; 0.404) for HeartWare, and 1.47 (1.19-2.03; 0.016) for medical management (Figure 2; Tables 3S-4S).

Appraising other outcomes (Tables 5S-33S; Figures 2S-16S), new-generation devices (HeartMate 3 and/or HeartWare) proved better than earlier devices (HeartMate II and HeartMate XVE/VE) for bleeding requiring surgical management (P-score=0.62 for HeartMate 3 and 0.43 for HeartWare), device thrombosis (P-score=0.84 for HeartMate 3 and 0.37 for HeartWare), hemolysis (P-score=0.66 for HeartMate 3), hepatic dysfunction ((P-score=0.67 for HeartWare), and stroke (P-score=0.70 for HeartMate 3).

Instead, new-generation devices proved worse adverse events than the earlier continuous-flow device, the HeartMate II, for acute myocardial infarction (P-score=0.92 for HeartMate II in comparison of 0.44 for HeartWare), device failure (P-score=0.76 for HeartMate II in comparison to 0.41 for HeartWare), drive-line exit-site infection (P-score=0.72 for HeartMate II in comparison to 0.39 for HeartWare and 0.13 for HeartMate 3), neurologic dysfunction (P-score=0.62 for HeartMate II in comparison to 0.54 for HeartMate 3 and 0.15 for HeartWare), psychiatric event (P-score=0.81 for HeartMate II in comparison to 0.41 for HeartWare), renal dysfunction (P-score=0.91 for HeartMate II in comparison to 0.64 for HeartWare and for HeartMate 3), respiratory failure (P-score=0.92 for HeartMate II in comparison to 0.59 for HeartWare and 0.49 for HeartMate 3), right ventricular failure (P-score=0.73

for HeartMate II in comparison to 0.46 for HeartMate 3 and 0.31 for HeartWare), and sepsis (P-score=0.72 for HeartMate II in comparison to 0.42 for HeartMate 3 and 0.38 for HeartWare). Overall the continuous-flow devices showed a significant reduction in the adverse event in comparison with the axial-flow devices HeartMate VE/XVE. (Figure 3, Summarizing Figure).

## **DISCUSSION**

LVAD are technological tools originally intended to provide circulatory support for patients at risk of death from refractory, end-stage HF. However, LVAD have progressively evolved their indication, becoming a treatment to support end-stage HF patients in several different clinical scenarios: as a bridge to heart transplantation, as a destination therapy, as bridge to decision or even as recovery (1). Following the creation of the INTERMACS registry, patient profile at the time of implant continues to evolve (5). With first-generation devices the majority of LVAD implantations were accordingly performed in patients hospitalized and dependent on intravenous inotropic support, whereas today the trend is becoming the anticipated implantation in ambulatory advanced HF patient with the aim of an improvement in survival and maximization of life quality (22, 23). Despite that, the most recent randomized trials have been performed with more critically HF patients, as demonstrated by the increased number of patients in INTERMACS profile 1-3. Since the natural commitment of LVAD is eventual heart transplantation, lifetime support or a bridge to recovery, research efforts of the last years have been focused mainly on improving overall device safety, durability and performance (24, 25). However, since these treatment strategies are complex, multifaceted and not devoid of several adverse effects that impose a significant burden on patients and public health, and there are no

conclusive trials comparing different devices, we aimed at summarizing the evidence base on LVAD for adult patients with end-stage HF.

The main findings of the present meta-analysis including 4 RCTs and 1069 patients are: [1] overall, mortality is significantly reduced with all LVAD as compared with medical management, in particular with the new-generation LVAD; [2] despite advances in technology, continuous-flow pumps maintain a high risk of adverse events, but significantly less than first-generation pulsatile-flow devices; [3] the risk of many clinically relevant adverse events, such as drive-line exit-site infection, hepatic dysfunction, neurological dysfunction, renal dysfunction, right ventricular dysfunction, stroke and sepsis, is markedly reduced with centrifugal continuous-flow pumps as compared with first-generation pulsatile-flow pumps.

It is established that survival after LVAD implant has improved significantly (9, 10, 12, 13, 26-29), and with newer generation devices outcomes might continue to improve. One of the key benefits of LVAD implantation, over the hemodynamic support, is the ability to unload the left ventricle and reverse pathologic remodeling. This may allow for recovery of myocardial function and for a reduction of pulmonary vascular resistance in preparation for transplantation (30-33). Of note, advantages of continuous-flow pumps over pulsatile first-generation LVAD, include miniaturized size, increased mechanical durability and hemodynamic efficiency, and improved bridge to transplant rates (1). Optimization of the medical management and a better understanding of the risk factors for early mortality after LVAD implantation as advanced age, female gender, obesity, INTERMACS profile 1-2, previous stroke, renal dysfunction, previous or concomitant need for cardiac surgery and receiving LVAD support in a less experienced center (4, 34) will help in patient selection process and further increase survival after LVAD implant.

Performing a RCT of LVAD is complex and expensive, and no RCT have been conducted on LVAD approved solely in Europe, despite the availability of observational studies and registries on these devices (35). Indeed, a higher degree of freedom to implant devices exists in Europe, as resulted by the first report of the EUROMACS registry (29), despite the weaker evidence based. Indeed, this meta-analysis is the first work that could help in the complex decision to implant a specific LVAD, but further larger studies are needed to compare different LVADs. Although most RCTs have measured nominally identical safety and effectiveness endpoints, no consensus criteria on endpoint definitions exist that could provide consistency across studies and further facilitate the comparative evaluation of these devices, as it happens for coronary stents (36) and transcatheter aortic valve implantation (37).

Moreover, the present meta-analysis raise a crucial question: how come that, despite the technological advances, newer LVAD have not yet resolved the high rate of adverse events, which remains one of the most important issues with LVAD support as destination therapy (38)? The first important issue with continuous flow pumps is the method used to suspend the rotor. Early versions (HeartMate II) used solid bearings, meanwhile newer pumps, some of which are approved for use in the EU, use either magnetic levitation ("maglev") or hydrodynamic suspension (HeartMate III, HeartWare). In theory this operating mode implies that magnetically levitated pump rotor does not make any contact with any other part of the system and accordingly should prevents damage to passing blood cells also reducing the chance of a clot formation due to the pumping mechanism. Moreover, in newer pumps, physiologic control algorithms are incorporated for safe operation. The HeartMate III, for example, actually matches its pumping action to the natural heartbeat of the patient. This makes the blood flow more natural and should also help avoid clot

formation by pump washing. Once again, since there is no friction in magnetically levitated pump and therefore less wear and tear on the rotor, consequently technical failure of these pumps should be reduced in comparison to first generation device. Up-to-date only short-term (6 months) results from the Momentum 3 trial have been published (12), but long-term data from a larger cohort of all-comer HF patients will be pivotal to demonstrate the superiority of HeartMate 3 over HeartMate II (39). Despite the above-mentioned technical issues, it is noteworthy that the introduction of new-generation LVADs have not markedly reduced the adverse events rate, in particular sepsis, right ventricular dysfunction and drive-line exit-site infection. We might speculate that the study populations are markedly different, as demonstrated by the significant changes in the INTERMACS profile, therefore we must critically read the results. In terms of resource use, on top of differences in device cost, adverse events are one of the other major drivers of implantation and follow-up costs (40), therefore the high rate of adverse events even with the newer generation LVADs still represents a missed opportunity. Last but not least, in the absence of larger trials comparing different devices, being aware of which adverse event is the most probable one with the use of a specific LVAD may help surgeons and HF team specialists in choosing the most appropriate LVAD for a specific patient.

This work has all the limitations typical of network meta-analyses based on a star-shaped evidence network. Moreover, small study effect and inconsistency appraisal were beyond our scope. An important underlying assumption was also lumping together HeartMate VE and HeartMate XVE in the same treatment group. Though, this is amply justified by the minor modifications made to the HeartMate VE leading to the HeartMate XVE, such as redesigned percutaneous lead (41). Finally, P-scores provide a probability ranking but cannot be equated to statistical significance

tests, and simply provide a summary of the uncertainty/certainty in treatment ranking based on point estimates and confidence intervals of effect, even if the single point estimate and confidence interval appear not significant.

In conclusion, new-generation LVAD represent a paradigm shift in the management of end-stage HF with a significant reduction in mortality in comparison with medical therapy for newer generation LVAD. Further technological refinements, higher quality and larger trials are crucial to improve decision-making and clinical outcomes in this challenging clinical setting.

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### **Figure Legend**

**Figure 1.** Evidence network geometry.

**Figure 2.** Forest plot for death. CI=confidence interval. RR=relative risk.

**Figure 3. Summarizing Figure.** Synthesis on the comparative effectiveness of left ventricular assist devices in patients with end-stage heart failure, focusing on death and several other key clinical outcomes, identifying the best to worst treatments.