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ORIGINAL ARTICLE

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A network meta-analysis of randomized trials and observational studies on left ventricular assist devices in adult patients with end-stage heart failure

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Key question

Are there any differences among the available left ventricular assist devices (LVADs) in end-stage heart failure after the Momentum3 2-year follow-up?

Key finding(s)

No significant differences in survival rate exist in newer-generation LVADs.
All performed better than medical management.

Take-home message

Significant differences exist among the newer-generation LVADs in terms of adverse events, in particular stroke and sepsis.

Therapy	Bleeding	Death	Device Thrombosis	Drive-Line Exit-Site Infection	Hepatic Dysfunction	Neurologic Dysfunction	Renal Dysfunction	Respiratory Failure	Right Ventricular Failure	Sepsis	Stroke
HeartMate 3	1	2	1	2	3	2	2	3	2	1	1
HeartWare	2	2	2	3	1	3	2	2	3	3	4
HeartMate II	3	1	4	1	3	1	1	1	1	1	2
HeartMate XVE/VE	4	4	2	4	2	3	4	4	4	4	3

Legend: 1=Best; 2=Second; 3=Third; 4=Fourth

Abstract

OBJECTIVES: The use of left ventricular assist devices (LVADs) is an approved treatment option for end-stage heart failure. Several devices have been developed over the years, including 2 newer ones (HeartMate 3 and HeartWare), but an overall comparative analysis has never been performed. We conducted a network meta-analysis of randomized trials on LVAD for adults with end-stage heart failure.

METHODS: Pertinent studies were searched in several databases. Selected outcomes were extracted, including death, stroke and bleeding. Incident relative risks were computed with network meta-analysis with 95% confidence intervals (CIs) and *P*-scores (with highest values indicating the best therapy).

RESULTS: Four randomized clinical trials and 4 observational studies were identified, totalling 2248 patients. Using HeartMate XVE/VE as the benchmark, all LVADs provided a significant better outcome for survival rate in comparison with medical therapy, without significant differences among newer LVADs. The relative risk for death was 0.79 (95% 0.60–1.04; *P*-score 0.89) for HeartMate II, 0.85 (95% CI 0.62–1.17; *P*-score 0.64) for HeartWare, 0.88 (95% CI 0.59–1.31; *P*-score 0.60) for HeartMate 3 and 1.48 (95% CI 1.21–1.80; *P*-score 0.01) for medical management. While appraising other outcomes, new generation devices (HeartMate 3 and HeartWare) proved better than older generation devices for bleeding, device thrombosis, hepatic dysfunction, renal dysfunction, respiratory dysfunction, right ventricular failure and sepsis with significant differences among them.

CONCLUSIONS: In the management of end-stage heart failure, LVADs provided significant improvement in terms of survival rate compared to medical therapy, but no significant differences exist among LVADs. Despite the reduction of adverse events over time, further technological refinements will be crucial to improve this technology to better address decision-making and to improve clinical outcomes.

Keywords: Heart failure • Left ventricular assist device • Meta-analysis • Network meta-analysis • Ventricular assist device

INTRODUCTION

Technological improvements in mechanical circulatory support, together with the relative shortage of donor organs, have driven the adoption of left ventricular assist devices (LVADs) for end-stage heart failure (HF) [1]. These pumps have improved the quality of life and the overall survival of patients when all other therapeutic options are exhausted. Moreover, LVADs have progressively evolved in their indication, now termed 'device strategy': as a bridge to heart transplantation, as a destination therapy or more recently, as a bridge to decision or to candidacy or as recovery [1, 2].

In addition to trends in device strategy, the profiles of patients at the time of implant, defined by INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), have evolved [3]. 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 [4–6]. First, the implantable pulsatile pump, HeartMate VE, demonstrated its benefits compared to medical management alone in end-stage HF patients [7]. Then, with the advent of continuous-flow pumps, LVADs gained momentum, and the HeartMate II has become widely adopted [8]. Yet, a larger use of LVADs was associated with an increased risk of pump thrombosis [9], 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 2 different LVADs [10, 11].

Despite such advances in technology and evidence, uncertainty persists on the comparative effectiveness and safety of LVADs. We thus aimed to conduct a systematic review and network meta-analysis of randomized trials on the use of LVADs for HF, in order to steer technologists, decision-makers, physicians and patients in this challenging clinical setting to evaluate potential differences in survival and adverse events rate.

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) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Material, Table S1) [12]. All reviewing activities were conducted by 2 independent reviewers (E.C. and G.B.Z.) in keeping with established methods [13] with divergences solved after consensus.

Search and selection

Potentially pertinent randomized controlled trials (RCTs) on the use of ventricular assist devices 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 10 June 2018 without language restrictions. We screened potentially relevant citations at the title or abstract level, then retrieved full texts of apparently pertinent trials and finally selected RCTs on LVAD in adult patients with end-stage HF (Supplementary Material, Fig. S1).

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 end points were acute myocardial infarction, device failure, device thrombosis, drive-line exit-site infection, haemolysis, hepatic dysfunction, neurological dysfunction, psychiatric event, renal dysfunction, respiratory dysfunction, right ventricular failure and sepsis. Definitions recommended by INTERMACS were used whenever possible [3].

The internal validity and risk of bias of the included trials were appraised according to the Risk of Bias Assessment Tool that was recommended by the Cochrane Collaboration (Supplementary Material, Table S2) [14].

Data synthesis and analysis

For descriptive purposes, dichotomous variables were reported as counts (%) and continuous variables as mean ± standard deviation. For inferential purposes, frequentist fixed-effect network meta-analysis was used to compare the incidence of adverse events between different LVADs, reporting incident relative risks, with point estimates and 95% confidence intervals (CIs). A random-effect analysis was conducted for sensitivity purposes, providing results that were similar in direction and magnitude of the effect to the fixed-effect one. Probability scores (*P*-score)

were generated to identify the best-to-worst treatment, taking into account precision and accuracy of effect [15]. Small-study effects were not appraised formally, given the sparse evidence network (Supplementary Material, Fig. S2). The netmeta R package (R Foundation for Statistical Computing, Vienna, Austria) was used for computations.

RESULTS

Systematic review

From 4983 citations, 4 RCTs were included in the study: 1 comparing the HeartMate VE versus medical management (REMATCH), 1 the HeartMate II versus the HeartMate XVE (HeartMate II), 1 the HeartMate 3 versus HeartMate II (MOMENTUM 3) and 1 HeartWare versus HeartMate II (ENDURANCE), totalling 1141 patients followed up for 24 months (Table 1; Supplementary Material, Table S2) [7, 8, 10, 11]. Trials were of high quality, notwithstanding the inherent limitation of the open design (Supplementary Material, Table S3). Additional 4 non-randomized observational studies [16–19] (Supplementary Material, Table S4) were included in the sensitivity analysis of the survival rate, totalling 2248 patients.

Figure 1A and B represent the star-shaped evidence network geometry and the closed-loop-shaped evidence geometry, respectively. Comparison of study and patient characteristics for descriptive purposes is provided in Table 1 and Supplementary Material, Table S5. Specifically, patient age, serum creatinine, prevalence of ischaemic heart disease as the 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. Trends for cardiac index, diabetes, INTERMACS profile, the use of intravenous

Table 1: Study and patient characteristics

Features	REMATCH Rose *et al.* [7] (*N* = 129)	HEARTMATE II Slaughter *et al.* [8] (*N* = 200)	ENDURANCE Rogers *et al.* [11] (*N* = 446)	MOMENTUM 3 Mehra *et al.* [10] (*N* = 366)
Age (years), mean ± SD	67.1 ± 8.7	62.3 ± 12.0	64.7 ± 11.2	60 ± 12
Male gender, *n* (%)	103 (79.8)	169 (84.5)	349 (78.3)	293 (80)
Body surface area (m^2), mean ± SD	NA	2.0 ± 0.3	2.0 ± 0.3	2.1 ± 0.3
Ejection fraction (%), mean ± SD	17 ± 4.8	16.9 ± 5.5	16.8 ± 4.7	17.3 ± 4.9
Cardiac index (l/min/m^2), mean ± SD	1.95 ± 0.8	2.0 ± 0.6	2.13 ± 0.6	2.0 ± 0.6
Systolic blood pressure (mmHg), mean ± SD	102.0 ± 16.1	104 ± 15.4	NA	108.3 ± 14.5
Serum creatinine (mg/dl), mean ± SD	1.75 ± 0.6	1.66 ± 0.6	1.5 ± 0.5	1.4 ± 0.4
Serum sodium (mmol/l), mean ± SD	135.3 ± 4.3	134.4 ± 4.9	135.0 ± 5.6	135.3 ± 3.9
Ischaemic cause of heart failure, *n* (%)	95 (73.6)	133 (66.5)	261 (58.5)	168 (46)
Previous stroke, *n* (%)	NA	32 (16.0)	81 (18.2)	36 (9.8)
INTERMACS profiles 1–3, *n* (%)	88 (68.2)	158 (79.0)	327 (73.3)	304 (83.0)
IV inotropic drugs, *n* (%)	88 (68.2)	158 (79.0)	317 (71.0)	319 (87.1)
Diuretics, *n* (%)	124 (96.1)	180 (90.0)	360 (80.7)	331 (90.4)
ACEi or AIIRA, *n* (%)	91 (70.5)	80 (40.0)	134 (30.0)	124 (33.9)
Beta-blockers, *n* (%)	28 (21.7)	109 (54.5)	245 (54.9)	209 (57.1)
CRT, *n* (%)	NA	124 (62)	120 (26.9)	137 (37.4)
Defibrillator, *n* (%)	NA	163 (81.5)	389 (87.2)	245 (66.9)

ACEi: Angiotensinogen-converting enzyme inhibitor; AIIRA: angiotensin II receptor antagonist; CRT: cardiac resynchronization therapy; IV: intravenous; NA: not available; SD: standard deviation.

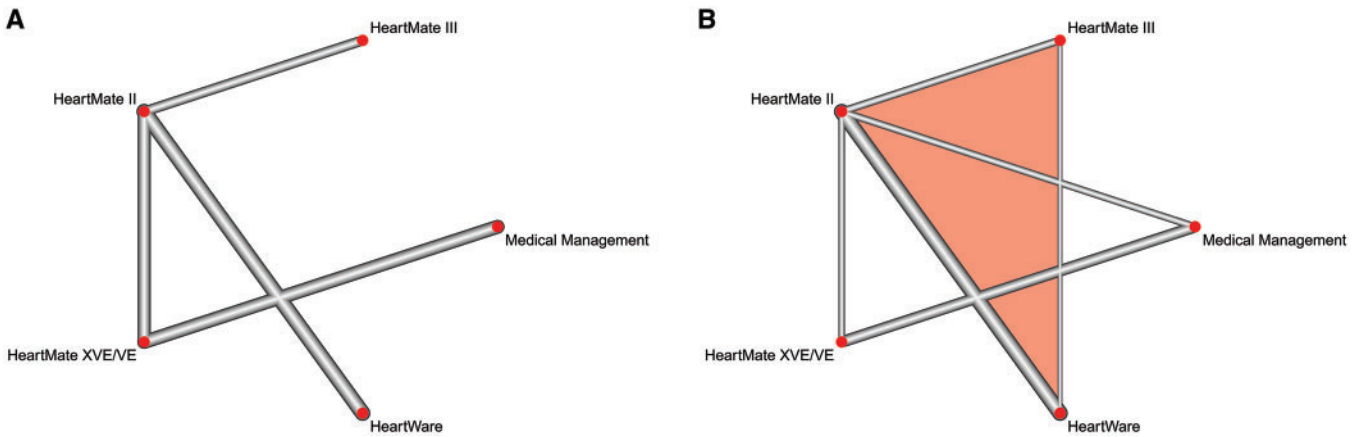

Figure 1: (**A**) Star-shaped evidence network geometry including 4 randomized trials. (**B**) Closed-loop-shaped evidence network geometry including 4 randomized trials and 4 observational studies. In the latter, the analysis method needs to combine estimates of the direct comparisons with estimates of the indirect comparison.

inotropic drugs, diuretics and angiotensinogen-converting enzyme inhibitors were not self-evident, despite differences between trials. In particular, the INTERMACS profiles 1–3 describe advanced HF patients dependent on inotropic support, while INTERMACS profiles 4–7 describe ambulatory advanced HF patients. Incident rate reported as event/100 patients followed up for 1 year and incident rate ratios are provided in detail in Table 2.

Main analysis limited to randomized trials

Inferential analysis for death, using HeartMate XVE/VE as the benchmark, showed that the relative risk for death was 0.62 (95% CI 0.35–1.11; *P*-score 0.94) 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 (Supplementary Material, Fig. S2, Tables S6 and S7).

While appraising other outcomes (Supplementary Material, Tables S8–S28, Figs S3–S10), 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 0.66 for HeartMate 3 and 0.41 for HeartWare), device thrombosis resulting in reoperation or removal of the device (*P*-score 0.88 for HeartMate 3 and 0.37 for HeartWare), hepatic dysfunction (*P*-score 0.63 for HeartWare), sepsis (*P*-score 0.65 for HeartMate 3) and stroke (*P*-score 0.77 for HeartMate 3; Fig. 2).

Instead, new generation devices caused worse adverse events than the earlier continuous-flow device HeartMate II in terms of drive-line exit-site infection (*P*-score 0.69 for HeartMate II in comparison to 0.43 for HeartMate 3 and 0.28 for HeartWare), neurological dysfunction (*P*-score 0.67 for HeartMate II in comparison to 0.43 for HeartMate 3 and 0.16 for HeartWare), renal dysfunction (*P*-score 0.91 for HeartMate II in comparison to 0.66 for HeartMate 3 and 0.62 for HeartWare), respiratory failure (*P*-score 0.83 for HeartMate II in comparison to 0.69 for HeartWare and 0.48 for HeartMate 3) and right ventricular failure (*P*-score 0.70 for HeartMate II in comparison to 0.52 for HeartMate 3 and 0.28 for HeartWare). Overall, the continuous-flow devices showed a significant reduction in the adverse event in comparison with the pulsatile-flow device HeartMate VE/XVE, but the new generation devices (HeartMate 3 and/or HeartWare) did not prove better than the HeartMate II for all the adverse events based on the *P*-score (Fig. 3).

Sensitivity analysis including observational studies

Including effect estimates from observational studies (notably none stemming from multivariable adjustment), inferential analysis for death, using HeartMate XVE/VE as the benchmark, showed that the relative risk for death was 0.88 (95%

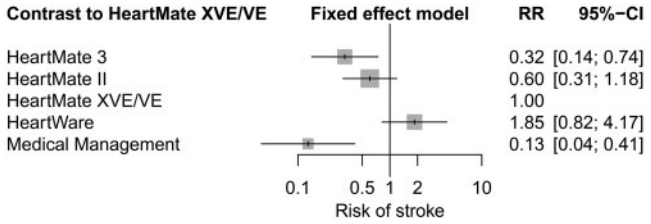

Figure 2: Forest plot for stroke. CI: confidence interval; RR: relative risk.

Table 2: Incident rates reported as event/100 patients followed for 1 year and incident rate ratios[a]

Study	REMATCH (*N* = 129) Rose *et al.* [7]		HEARTMATE II (*N* = 200) Slaughter *et al.* [8]		ENDURANCE (*N* = 446) Rogers *et al.* [11]		MOMENTUM 3 (*N* = 366) Mehra *et al.* [10]	
Events	HeartMate XVE/VE	Medical Management	HeartMate II	HeartMate XVE/VE	HeartWare	HeartMate II	HeartMate 3	HeartMate II
Bleeding requiring surgery	55.8%	5.7%	23.2%	29.3%	13.2%	14.2%	12.4%	17.4%
	IRR 9.74 (5.19–18.27)		IRR 0.79 (0.42–1.49)		IRR 0.93 (0.59–1.45)		IRR 0.66 (0.39–1.14)	
Death	30.1%	44.3%	16.4%	20.4%	19.9%	16.2%	12.8%	20.9%
	IRR 0.68 (0.45–1.02)		IRR 0.80 (0.50–1.29)		IRR 1.22 (0.87–1.70)		IRR 0.61 (0.36–1.02)	
Device thrombosis resulting in reoperation or removal of device	5.9%	NA	2.4%	0.0%	4.6%	7.8%	0.0%	12.2%
					IRR 0.59 (0.31–1.14)			
Drive-line exit-site infection	41.1%	NA	38%	61%	18.2%	13.2%	23.9%	19.8%
			IRR 0.62 (0.40–0.97)		IRR 1.38 (0.89–2.14)		IRR 1.21 (0.78–1.91)	
Hepatic dysfunction	2.2%	0.0%	1.1%	0.0%	3.4%	5.8%	4.3%	4.1%
					IRR 0.58 (0.27–1.24)		IRR 1.05 (0.36–3.25)	
Neurological dysfunction	39%	9%	17%	29%	6.8%	3.4%	11.8%	11.3%
	IRR 4.32 (2.38–7.83)		IRR 0.58 (0.31–1.11)		IRR 1.99 (0.88–4.48)		IRR 1.32 (0.68–2.67)	
Renal dysfunction	25%	18%	10%	34%	12.9%	9.8%	13.2%	10.5%
	IRR 1.39 (0.81–2.36)		IRR 0.29 (0.15–0.55)		IRR 1.32 (0.79–2.20)		IRR 1.26 (0.69–2.40)	
Respiratory dysfunction	NA	NA	31%	80%	28%	24%	23.9%	22.7%
			IRR 0.39 (0.26–0.58)		IRR 1.18 (0.84–1.64)		IRR 1.05 (0.69–1.63)	
Right ventricular failure	16.9%	NA	14.7%	39%	32.4%	23%	31.6%	27.9%
			IRR 0.38 (0.21–0.67)		IRR 1.44 (1.03–2.01)		IRR 1.33 (0.78–1.66)	
Sepsis	60.3%	30%	22.7%	63.4%	20.4%	13.7%	13.7%	13.9%
	IRR 4.09 (2.55–6.54)		IRR 0.36 (0.23–0.57)		IRR 1.49 (0.98–2.28)		IRR 0.98 (0.56–1.74)	
Stroke	19%	5.2%	12.8%	21.9%	29%	9.3%	10.2%	19.2%
	IRR 7.78 (2.83–21.32)		IRR 0.58 (0.28–1.23)		IRR 3.12 (1.97–4.93)		IRR 0.53 (0.30–0.93)	

[a]An event rate of 1.0% equals 1 event in 100 patients followed for 1 year.

IRR: incident rate ratio; NA: not available.

CI 0.59–1.31; *P*-score 0.60) for HeartMate 3, 0.85 (0.62–1.17; 0.64) for HeartWare, 0.79 (0.60–1.04; 0.89) for HeartMate II and 1.48 (1.21–1.80; 0.01) for medical management (Fig. 4; Table 3; Supplementary Material, Table S8). Statistical heterogeneity and inconsistency were not significant, even when the decomposing effects focused on between-design and within-design ones, as was evident at the net-heatplot inspection (Fig. 5). An exploratory analysis using random effects confirmed the main analysis based on fixed effects for effect estimates, inconsistency and hierarchy.

DISCUSSION

LVADs are technological tools originally intended to provide circulatory support for patients at risk of death from refractory end-stage HF. However, 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 a destination therapy, as a 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 [2]. 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 more towards anticipated implantation with the aim of improving in survival and maximizing of the quality of life [20]. Despite that, the most recent randomized trials have been performed with more acute HF patients, as demonstrated by the increased number of patients in INTERMACS profiles 1–3. As the natural outcome of LVAD is eventual heart transplantation, lifetime support or a bridge to recovery, research efforts over the last years have been focused mainly on improving overall device safety, durability and performance [21]. However, as 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 based on the use of LVADs for adult patients with end-stage HF.

The main findings of the present meta-analysis, which involved 4 RCTs and 1141 patients, are as follows: (i) overall, mortality is significantly reduced with all LVADs as compared with medical management, in particular with the new generation LVADs; (ii) despite significant improvements in this field, continuous-flow pumps contribute to a high risk of adverse events even with new generation devices (HeartMate 3 and/or HeartWare) but less than the first-generation pulsatile-flow devices; (iii) the risk of many clinically relevant adverse events, such as drive-line exit-site infection, hepatic dysfunction, neurological dysfunction, renal dysfunction and right ventricular dysfunction, is reduced with centrifugal continuous-flow pumps, but newer generation devices did not provide better outcomes than HeartMate II.

Overall survival after LVAD implantation has improved significantly [7, 8, 10, 11, 22, 23], and with newer generation devices outcomes might continue to improve. One of the key benefits of LVAD implantation over haemodynamic support, is the ability to unload the left ventricle and reverse pathological remodelling [24–26]. This may allow for the recovery of myocardial function and for a reduction of pulmonary vascular resistance in preparation for transplantation [27, 28]. It is noteworthy that advantages of continuous-flow pumps over pulsatile first-generation LVADs include a smaller size, increased mechanical durability and haemodynamic efficiency and improved bridge-to-transplant rates [1].

Performing an RCT with LVADs is complex and expensive, and no RCT has been conducted on LVADs approved solely in Europe, despite the availability of observational studies and a registry on these devices [23]. Indeed, a higher degree of freedom to implant devices exists in Europe, as a result of the EUROMACS registry [23], despite a weaker evidence base. This is the first meta-analysis 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

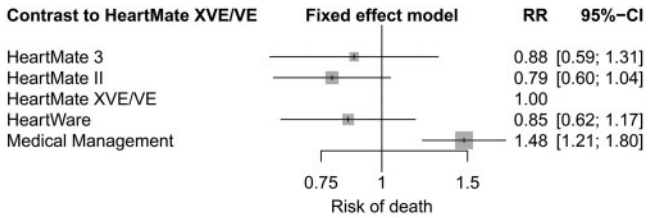

Figure 4: Forest plot for death: sensitivity analysis including randomized trials and observational studies. CI: confidence interval; RR: relative risk.

Therapy	Bleeding	Death	Device Thrombosis	Drive-Line Exit-Site Infection	Hepatic Dysfunction	Neurologic Dysfunction	Renal Dysfunction	Respiratory Failure	Right Ventricular Failure	Sepsis	Stroke
HeartMate 3	1	2	1	2	3	2	2	3	2	1	1
HeartWare	2	2	2	3	1	3	2	2	3	3	4
HeartMate II	3	1	4	1	3	1	1	1	1	1	2
HeartMate XVE/VE	4	4	2	4	2	3	4	4	4	4	3

Legend	1=Best	2=Second	3=Third	4=Fourth

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

Table 3: Relative risk (RR) for death (sensitivity analysis including 4 randomized controlled trials and 4 observational studies)[a]

Therapy	HeartMate 3	HeartMate II	HeartMate XVE/VE	HeartWare	Medical management
HeartMate 3		1.11 (0.83–1.48) $P = 0.489$	0.88 (0.59–1.31) $P = 0.541$	1.03 (0.76–1.40) $P = 0.860$	0.59 (0.40–0.88) $P = 0.008$
HeartMate II	0.90 (0.68–1.20) $P = 0.476$		0.79 (0.60–1.04) $P = 0.092$	0.93 (0.79–1.08) $P = 0.370$	0.53 (0.41–0.70) $P < 0.001$
HeartMate XVE/VE	1.14 (0.77–1.70) $P = 0.528$	1.27 (0.96–1.67) $P = 0.090$		1.17 (0.85–1.61) $P = 0.341$	0.68 (0.56–0.82) $P < 0.001$
HeartWare	0.97 (0.72–1.32) $P = 0.854$	1.08 (0.92–1.26) $P = 0.342$	0.85 (0.62–1.17) $P = 0.320$		0.58 (0.42–0.79) $P < 0.001$
Medical management	1.68 (1.13–2.49) $P = 0.01$	1.87 (1.43–2.45) $P < 0.001$	1.48 (1.21–1.80) $P < 0.001$	1.73 (1.27–2.36) $P < 0.001$	

[a]RR for 1st column item versus row item.

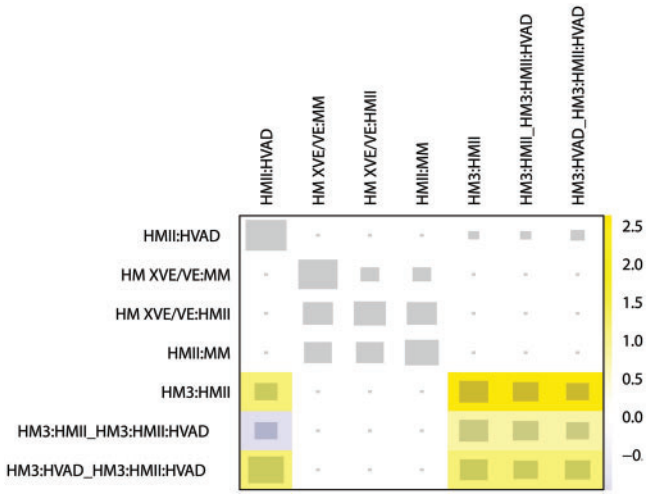

Figure 5: Net heat plot for inconsistency. The net heat plot also showed that there was only slight inconsistency throughout the entire network in terms of death.

identical safety and effectiveness end points, no consensus criteria on end point definitions exist, which could provide consistency across studies and further facilitate the comparative evaluation of these devices as is the case for coronary stents [29] and transcatheter aortic valve implantation. Despite improvements in technical issues such as the introduction of magnetic levitation ('maglev', HeartMate III) or hydrodynamic suspension (HeartWare) and new physiological control algorithms incorporated for safe operation, it is noteworthy that the introduction of new generation LVADs has not markedly reduced the adverse events rate, in particular, sepsis, hepatic dysfunction, 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, and therefore we must critically read the results. Moreover, the operating mode of newer devices does not *per se* imply a better outcome with respect to end points such as sepsis and drive-line exit-site infection. 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 [30], and therefore the high rate of adverse events even with the newer generation LVADs still represents room for improvement. Last but not least, in the absence of larger trials comparing different devices, an awareness of the most probable adverse event linked to a specific LVAD may help surgeons and Heart Team specialists in choosing the most appropriate LVAD for a specific patient.

Limitations

This work has all the limitations typical of any systematic review and network meta-analysis based on sparse studies. Notably, we minimized selection bias for the purpose of this systematic review with a careful bibliographic search, including all available randomized trials. We also conducted a sensitivity analysis including large and moderate-to-high-quality observational studies for increased external validity. Thus, the selection bias in terms of reviewing quality appears minimal. Conversely, we could not address residual selection bias due to the inclusion criteria of shortlisted studies. Moreover, the appraisal of small-study effects and inconsistency was beyond our scope. An important underlying assumption was also lumping together HeartMate VE and HeartMate XVE in the same treatment group. However, this is amply justified by the minor modifications made to the HeartMate VE leading to the HeartMate XVE, such as redesigned percutaneous lead. Finally, *P*-scores provide a probability ranking but cannot be equated to statistical significance tests and simply provide a summary of the uncertainty or certainty in treatment ranking based on point estimates and CIs of effect, even if the single-point estimate and CI appeared to be insignificant. In addition, it should be emphasized that any network meta-analysis builds upon its evidence base and cannot overcome the limitations inherent to the included studies. However, it provides a quantitative estimate of several dimensions of effect, thus guiding future research and potentially, clinical practice. In the present work, we acknowledge that several generation of LVADs were indirectly compared over different phases of management strategies. Accordingly, we can infer that over the years LVADs were applied in the included randomized trials in sicker and more acute patients, obtaining favourable results, which appear relatively similar across the different LVADs, and is always better than medical management only. Complex modelling techniques, such as Markov modelling or similar ones, can also be used in a network meta-analysis setting (e.g. for Bayesian models), but their results are similar, if not less precise, than those stemming from a frequentist framework such as the one herein adopted. Conversely, complex statistical modelling approaches based on individual patient data for covariate adjustment were clearly beyond the scope of this systematic review.

CONCLUSION

In conclusion, in the management of end-stage HF, LVADs provided significant improvement in terms of survival rate compared to medical therapy, but no statistically significant differences were found among different generations of LVADs. Despite the

reduction of adverse events over time, further technological refinements will be crucial to improve this technology, to better address decision-making and to improve clinical outcomes.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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