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ORIGINAL RESEARCH ARTICLE

Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 left ventricular assist device support

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Abstract

Aims Left ventricular assist device therapy has become the cornerstone in the treatment of end-stage heart failure and is increasingly used as destination therapy next to bridge to transplant or recovery. HeartMate 3 (HM3) and HeartWare (HVAD) are centrifugal continuous flow devices implanted intrapericardially and most commonly used worldwide. No randomized controlled trials have been performed yet. Analysis based on large registries may be considered as the best alternative but has the disadvantage of different standard of care between centres and missing data. Bias is introduced, because the decision which device to use was not random, even more so because many centres use only one type of left ventricular assist device. Therefore, we performed a propensity score (PS)-based analysis of long-term clinical outcome of patients that received HM3 or HVAD in a single centre.

Methods and results Between December 2010 and December 2019, 100 patients received HVAD and 81 patients HM3 as primary implantation at the University Medical Centre Utrecht. We performed PS matching with an extensive set of covariates, resulting in 112 matched patients with a median follow-up of 28 months. After PS matching, survival was not significantly different (P = 0.21) but was better for HM3. The cumulative incidences for haemorrhagic stroke (P = 0.01) and pump thrombosis (P = 0.02) were significantly higher for HVAD patients. The cumulative incidences for major bleeding, ischaemic stroke, right heart failure, and driveline infection were not different between the groups. We found no interaction between the surgeon who performed the implantation and survival (P = 0.59, P = 0.78, and P = 0.89). Sensitivity analysis was performed, by PS matching without patients on preoperative temporary support resulting in 74 matched patients. This also resulted in a non-significant difference in survival (P = 0.07). The PS-adjusted Cox regression showed a worse but non-significant (P = 0.10) survival for HVAD patients with hazard ratio 1.71 (95% confidence interval 0.91–3.24).

Conclusions Survival was not significantly different between both groups after PS matching, but was better for HM3, with a significantly lower incidence of haemorrhagic stroke and pump thrombosis for HM3. These results need to be interpreted carefully, because matching may have introduced greater imbalance on unmeasured covariates. A multicentre approach of carefully selected centres is recommended to enlarge the number of matched patients.

Keywords Left ventricular assist device; LVAD; Mechanical circulatory support; MCS; Centrifugal continuous flow pump

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Introduction

The number of patients with heart failure continues to increase. Heart transplantation (HTx) is the gold standard for patients with end-stage heart failure.[1] Because of a shortage of donor hearts, long-term left ventricular assist devices (LVADs) have become an established therapeutic option for these patients, with a 1 year survival of ~80%.[2,3] Even though the use of mechanically circulatory support (MCS) results in improved survival rates, patients often suffer from major complications. Only 20% of the patients are not readmitted to the hospital within the first year after primary implantation.[4] The most common causes of death in patients on LVAD support are neurological dysfunction, multi-organ failure, major infection, and right heart failure. In addition, pump thrombosis is a dreaded complication and may occur early or late after implantation.[5]

Currently, the most frequently implanted LVADs are the HeartWare (HVAD, Medtronic, Minneapolis, MN, USA) and HeartMate 3 (HM3, Abbott, Chicago, IL, USA). Both intrapericardially implanted third-generation pumps are centrifugal continuous flow devices. Three prospective industry-sponsored studies have been performed to evaluate performance of these devices compared with the HeartMate II (HMII), which is an axial flow pump.[6–8] The ENDURANCE trial compared the survival of patients on HVAD and HMII support. They showed a comparable survival but higher post-operative incidence of sepsis, ischaemic and haemorrhagic stroke, and right heart failure for patients implanted with HVAD.[6] Subsequently, a supplementary trial with strict blood pressure management showed a higher 12 month incidence of transient ischaemic attack and stroke with residual deficit for HVAD but a better survival free from disabling stroke and need for device exchange or urgent transplantation or death.[7] HMII and HM3 were compared in the MOMENTUM 3 trial.[8] This randomized controlled trial showed a significantly lower incidence of pump thrombosis (1.1% vs. 15.7%) and ischaemic stroke (6.3% vs. 13.4%) for HM3 compared with HMII. No differences in haemorrhagic stroke, bleeding, driveline infection, or right heart failure were found.[8] In addition, the ELEVATE registry was designed to study 2 year outcome with the HM3, with comparable rates for pump thrombosis (1.5%), stroke (10%), and major infection (57%) when compared with the HM3 population within the MOMENTUM trial.[9]

Ideally, survival of patients implanted with HM3 and HVAD is compared with a randomized controlled trial. However, this has not been performed yet and is also not expected to be initiated. Large registries may be considered as the best alternative due to the amount of included patients. However, these have the disadvantage of different standard of care between centres, missing data, and heterogeneity. Bias is introduced, because the decision which device to use was not random, even more so because many centres use only one type of LVAD. Therefore, we conducted a single-centre retrospective propensity score (PS)-based analysis of patients supported with HM3 and HVAD.

Methods

We conducted an investigator-initiated retrospective single-centre analysis of patients on LVAD support. The study was approved by the local ethics committee of the University Medical Centre Utrecht (UMCU), the Netherlands (METC: 20-195). The need for informed consent was waived, and this study was conducted in accordance with Good Clinical Practice and the 2002 Declaration of Helsinki.

All patients who underwent primary implantation of HVAD or HM3 until December 2019 at the UMCU were eligible. HVAD has been implanted since November 2010, whereas the first HM3 implant was in December 2015. The follow-up period was until November 2020. Baseline characteristics and clinical data were retrieved from the electronic health records and our MCS database, which is based on—but not limited to—the definitions of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). The standard operating technique was a full median sternotomy using cardiopulmonary bypass and was performed by certified surgeons.

Endpoints

The primary endpoint of the study was death or urgent HTx during follow-up. Urgent HTx was defined as HTx for which the patient received a priority status on the waiting list (national 1A, national 1B, or international HU). Patients with non-urgent HTx were censored. Secondary endpoints were first occurrence of pump thrombosis, ischaemic and haemorrhagic stroke, right heart failure, extra-cerebral major bleeding, and driveline infection as defined according to the INTERMACS definitions.[10]

Statistics

Results are presented as mean and standard deviation or median and inter-quartile range (IQR) for continuous variables or as number or percentage for categorical variables. Differences in both groups were tested using Fisher's exact test for categorical variables and the *t*-test or Mann–Whitney *U* test for continuous variables as appropriate. Because the type of LVAD device was not assigned in a randomized controlled manner, we performed PS matching to obtain two comparable groups. The continuous variables that were used to estimate the PS were age, preoperative estimated glomerular filtration rate and bilirubin, body surface area (BSA), body

mass index, and right ventricular (RV) function. Because growing numbers of implantations result in more experience over the years, it is possible that treatment and/or prevention of complications has improved in recent years. Therefore, we also accounted for the moment of implantation, by using the number of months after the start of the study period as a covariate for PS matching. In addition, sex, diabetes mellitus, concomitant surgery, ischaemic cardiomyopathy as underlying disease, preoperative temporary support, INTERMACS = 1, and stroke in medical history were used as binary variables. RV function was classified as 1 (poor), 2 (intermediate), or 3 (good) by two independent cardiologists who were blinded for the type of LVAD. They individually classified the RV of each patient and subsequently discussed the discrepancies to reach agreement on the RV function. The inter-rater reliability was assessed by the intraclass correlation coefficient. Classification was based on the available information of the echocardiography report and right heart catheterization: tricuspid annular plane systolic excursion, degree of tricuspid valve insufficiency, peak systolic velocity of the right ventricle measured with tissue Doppler imaging, right atrial pressure, pulmonary artery pressure, and the RV stroke work index. Concomitant surgery was defined as any other intervention that was conducted during the primary LVAD implantation: heart valve repair or replacement, atrial septal defect closure, coronary artery bypass surgery, or left ventricle aneurysm repair. Preoperative temporary support was defined as being supported with extracorporeal life support, CentriMag, or an intra-aortic balloon pump.

The PS, defined as the probability of being implanted with either HM3 or HVAD, was estimated by multivariable logistic regression with device type as dependent variable. Subsequently, nearest-neighbour PS matching was performed using a calliper width of 0.1. Baseline differences between both groups were tested using the Wilcoxon signed-rank test or McNemar test. The balance of covariates was considered satisfactory for a standardized mean difference (SMD) of $<10\%$. The effect of the surgeon who performed the LVAD implantation on survival was tested. Cox regression was performed within the PS-matched group with survival as dependent variable and device type and the interaction between each of the three main surgeons and device type as independent variables.

For both unmatched and matched patient groups, the primary endpoint was evaluated by Kaplan–Meier analysis censoring for non-urgent transplantation and ongoing support at the end of the follow-up. Difference in survival was assessed by log-rank testing. Competing risk analysis was performed for the PS-matched patients to compare the cumulative incidence of the secondary endpoints, with HTx, death, and ongoing support at follow-up as competing risks. The primary and secondary endpoints were evaluated up to 36 months after implantation. Sensitivity analysis for survival was performed using two methods. First, PS matching was conducted with all patients without preoperative temporary support. Secondly, we used PS-adjusted Cox regression analysis. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using R Version 3.6.3.

Results

Between November 2010 and December 2019, 100 patients received HVAD and 81 patients received HM3 as their first long-term device. All preoperative characteristics of these unmatched patients were complete and are shown in *Table 1*. Patients who received an HVAD were slightly older and had a lower BSA. In addition, more patients with HVAD had a stroke in their medical history, and the number of patients with preoperative temporary support was higher, whereas the number of patients with INTERMACS 2–7 was relatively smaller. Additionally, more HVAD patients had ischaemic cardiomyopathy. The intraclass correlation coefficient of the initial assessment of the RV function assessed by two independent cardiologists was 0.78.

Propensity score matching resulted in 112 matched patients, with SMD of $<10\%$ for all covariates (*Table 1*), indicating a substantial reduction of bias (*Figure 1*). The median follow-up period was 28 (IQR: 26) months. None of the PS-matched patients were weaned during follow-up. Three surgeons implanted 97% of the devices, who individually performed at least 25% of the implantations. Interaction testing was performed for surgeon and device type and was not found to be significant for any of the surgeons (P = 0.59, P = 0.78, and P = 0.89) for the primary outcome.

Survival of unmatched patients (*Figure 2A*) was significantly better for patients on HM3 support (P = 0.0049). After PS matching, a difference in survival was still present (*Figure 2B*), although non-significant (P = 0.21). *Figure 3* illustrates the cumulative incidence for different complication types of the PS-matched patients. Haemorrhagic stroke occurred more frequently in patients on HVAD support (P = 0.01), as well as pump thrombosis (P = 0.02). The incidences for extra-cerebral major bleeding (P = 0.96), ischaemic stroke (P = 0.38), right heart failure (P = 0.63), and driveline infection (P = 0.90) were comparable in both groups.

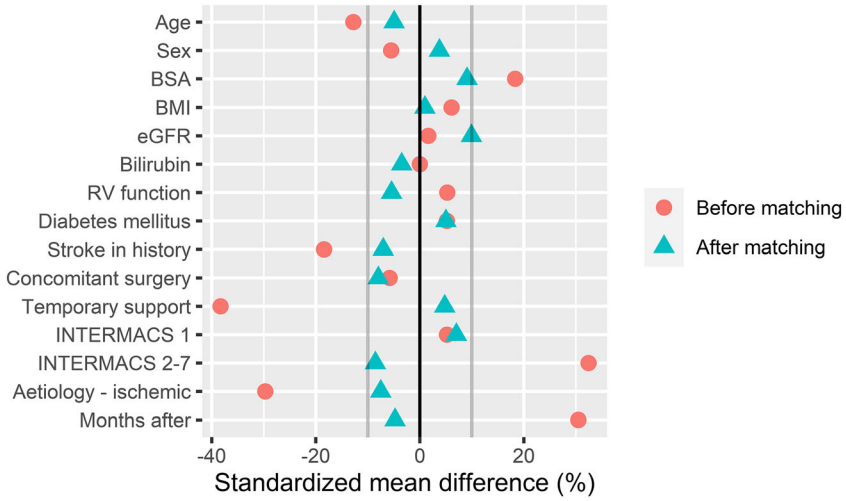
Table 2 provides an overview of the number of PS-matched patients that underwent HTx and the number and causes of deaths. One patient on HVAD support needed urgent transplantation because of severe RV failure. In addition, three HVAD patients received non-urgent HTx, whereas five HM3 patients received non-urgent HTx. One patient on HM3 support died because of ischaemic stroke, and six HVAD patients died because of a haemorrhagic stroke. The patient on HM3 support had an ischaemic stroke 1 day after the surgery and died 3 days afterwards. Six HVAD patients had

Table 1 Baseline characteristics of all patients and PS-matched patients

Covariate	All patients (n = 181)			PS-matched patients (n = 112)		
	HM3 (n = 81)	HVAD (n = 100)	P-value	HM3 (n = 56)	HVAD (n = 56)	P-value
Age (years)	56.0 (14.0)	58.5 (13.0)	0.21	56.0 (13.3)	57.0 (19.5)	0.74
Sex (% male)	65.4	68.0	0.75	66.1	64.3	1.00
BSA (m^2)	1.98 (0.23)	1.94 (0.21)	0.22	1.95 (0.21)	1.93 (0.20)	0.63
BMI (kg/m^2)	24.7 (6.1)	24.1 (5.6)	0.53	23.9 (6.6)	23.8 (6.2)	0.89
eGFR ($mL/min/1.73\ m^2$)	61.0 (41.0)	60.0 (42.3)	0.56	64.5 (38.3)	59.0 (36.8)	0.78
Bilirubin (μmol/L)	19.0 (26.0)	19.0 (18.0)	0.63	20.0 (24.5)	21.0 (19.3)	0.75
RV function (1 = bad, 2 = moderate, 3 = good)	2.19 (0.69)	2.15 (0.64)	0.73	2.18 (0.66)	2.21 (0.65)	0.77
Diabetes mellitus (%)	14.8	13.0	0.83	16.1	14.3	1.00
Stroke in medical history (%)	3.7	8.0	0.35	5.4	7.1	1.00
Concomitant surgery (%)	23.5	26.0	0.73	26.8	30.4	0.86
Temporary support (%)	13.6	29.0	0.02	17.9	16.1	1.00
INTERMACS 1 (%)	6.2	5.0	0.75	7.1	5.4	1.00
INTERMACS 2–7 (%)	80.2	66.0	0.04	75.0	78.6	0.91
Aetiology—dilated CMP (%)	70.4	55.0	0.05	62.5	58.9	0.90
Aetiology—ischaemic CMP (%)	23.5	37.0	0.05	30.4	33.9	0.87
Months after start of study period (no.)	89.0 (24.0)	71.0 (48.3)	0.00	83.0 (24.3)	85.0 (27.8)	0.79

BMI, body mass index; BSA, body surface area; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PS, propensity score; RV, right ventricular.
Continuous data are shown as mean ± standard deviation or median and inter-quartile range. Categorical data are shown as the percentage (%).

Figure 1 Love plot for standardized mean difference before and after propensity score matching comparing covariate values for patients on HeartMate 3 and HeartWare support. BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricular.



a haemorrhagic stroke at a median of 3 (IQR: 5) months after surgery and died after a median of 1 day afterwards.

A PS-matched sensitivity analysis was performed in patients without temporary support resulting in 74 matched patients (Supporting Information, *Table S1*). All covariates were balanced, except for bilirubin, which was higher for HVAD patients, and one HM3 patient had a stroke in medical history, whereas none of the HVAD patients had a prior stroke. Survival of these PS-matched patients was not significantly different (P = 0.07) but was better for patients on HM3 support (Supporting Information, *Figure S1*). Secondly, the PS-adjusted Cox regression showed a worse but non-significant (P = 0.10) survival for HVAD when compared with HM3, with hazard ratio 1.71 (95% confidence interval 0.91–3.24).

Discussion

In this single-centre retrospective study, we compared long-term survival and cumulative incidence of major

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Figure 2 Kaplan–Meier survival of (A) all patients and (B) propensity score-matched patients with 95% confidence interval, with censoring for non-urgent heart transplantation and ongoing support at follow-up.

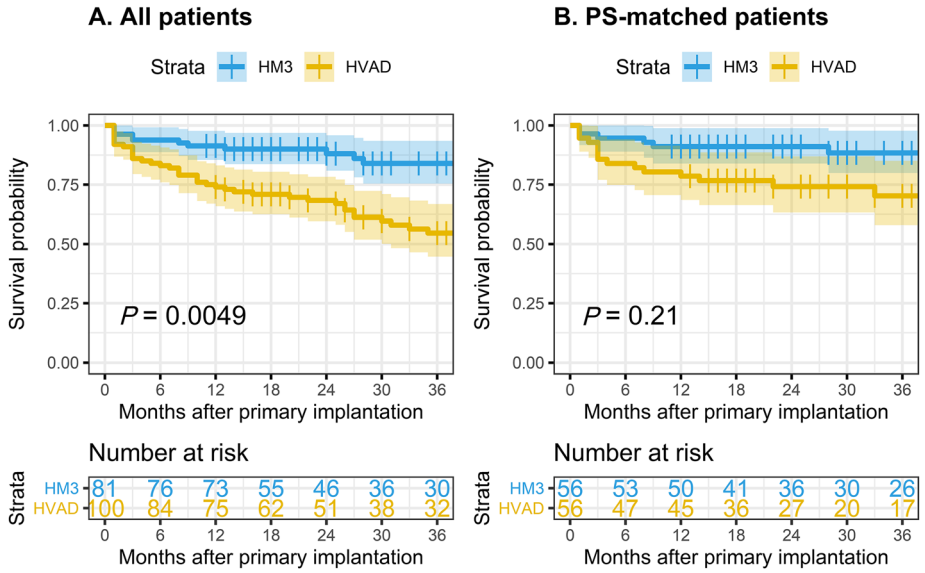
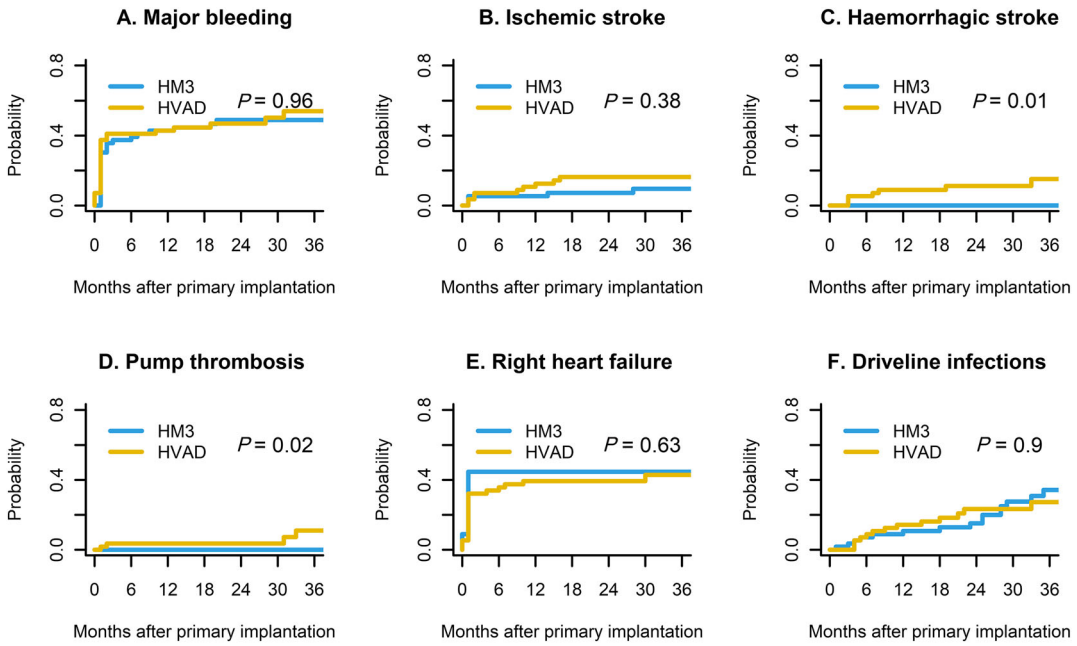


Figure 3 Cumulative risk of propensity score-matched patients with death, heart transplantation, and ongoing support as competing risk. (A) Major bleeding. (B) Ischaemic stroke. (C) Haemorrhagic stroke. (D) Pump thrombosis. (E) Right heart failure. (F) Driveline infections.



complications in patients on HM3 and HVAD support. All patients implanted with HM3 or HVAD between December 2010 and December 2019 within the UMCU were included for a PS-matched analysis. This resulted in a complete and non-heterogeneous dataset of patients with the same standard of care with reduced bias for the measured covariates. Although non-significant, survival was better for patients on HM3 support for the PS-matched patients. This was confirmed by sensitivity analysis with PS matching without patients on temporary support and PS-adjusted Cox regression. The cumulative incidence of haemorrhagic stroke and pump thrombosis was significantly higher for HVAD patients,

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Table 2 Number and causes of death and number of heart transplantations

Endpoint	PS-matched patients (n = 112)	
	HeartMate 3 (n = 56) n (%)	HeartWare (n = 56) n (%)
Cause of death		
Device malfunction	0 (0%)	0 (0%)
Infection	3 (5%)	2 (4%)
Multi-organ failure	5 (9%)	2 (4%)
Ischaemic stroke	1 (2%)	0 (0%)
Haemorrhagic stroke	0 (0%)	6 (11%)
RV failure	0 (0%)	3 (5%)
Other	3 (5%)	3 (5%)
HTx (urgent)	0 (0%)	1 (2%)
HTx (non-urgent)	5 (9%)	3 (5%)

HTx, heart transplantation; PS, propensity score; RV, right ventricular.

whereas incidence of major bleeding, ischaemic stroke, right heart failure, and driveline infection was comparable in both groups.

The baseline characteristics were unbalanced for HM3 and HVAD within the unmatched patient groups, which may partly account for the significant difference in survival. HVAD patients were slightly older than patients on HM3 support. LVAD patients above 70 years old have a higher incidence of gastrointestinal bleeding, and the absolute risk of death is 11% higher when compared with younger patients.[11] More HVAD patients had preoperative temporary support when compared with HM3 patients, which is associated with a worse prognosis.[2] In addition, patients on HVAD support had a lower preoperative INTERMACS, which is also associated with a worse survival. Further, more HVAD patients had ischaemic cardiomyopathy when compared with HM3 patients. Akin *et al*. found that ischaemic cardiomyopathy was more common in patients who died within 90 days after LVAD implantation when compared with other cardiomyopathies.[12] This suggested a possible worse prognosis for patients with ischaemic cardiomyopathy. However, 1 year survival of patients with ischaemic and dilated cardiomyopathy was not significantly different in a retrospective study.[13] HVAD patients had a lower BSA. Smaller patients more often receive an HVAD, because of its smaller size. A retrospective study showed that a small BSA is an independent predictor for mortality after LVAD implantation.[14] Within the UMCU, HM3 is implanted since December 2015, whereas the first HVAD was implanted in November 2010. Because of the growing experience over the years, it is likely that treatment of complications continuously improves over the years. The number of months after the start of the study period was higher in HM3 patients and was used as covariate for PS matching, to have a fair comparison between both groups.

No randomized controlled trials have been performed to compare long-term outcome of HM3 and HVAD. Instead, several retrospective studies were conducted comparing survival and complications of both LVAD types.[15–17] Mueller *et al*. compared short-term outcome of HM3 and HVAD and showed similar 1 year survival (66% vs. 62% for HM3 vs. HVAD, P = 0.372) but found differences in complication rate. Although non-significant, more pump thrombotic events were observed after HVAD implantation.[15] The fully magnetically levitated internal rotor and relatively wide rotor housing of the HM3 or the artificial pulse might explain the lower number of patients with pump thrombosis. In addition, the incidence of cerebral bleedings was significantly higher for HVAD patients. No differences were found for gastrointestinal bleeding, driveline infection, and ischaemic stroke.[15] These results were confirmed by the findings of our study, which had a longer follow-up. Moreover, Schramm *et al*. compared short-term outcome after HVAD and HM3 implantation and reported no difference in survival (median follow-up of 15 months) and freedom from strokes between both groups. During a median follow-up of 15 months, 24% HM3 and 29% HVAD patients died (P = 0.568). Even though not significant, an increased number of strokes for patients on HVAD support were found.[16] In contrast to our results, patients implanted with HM3 developed driveline infections less frequently when compared with HVAD patients. These differences in driveline infections remain unexplained and need further investigation. Finally, Ben Zadok *et al*. compared clinical outcome of HMII, HM3, and HVAD and showed better survival for HM3, accompanied with lower rates of haemorrhagic and ischaemic stroke, pump thrombosis, and non-gastrointestinal bleeding events.[17] In contrast to their approach of uncorrected comparison of all comers (51 patients on either HVAD or HM3 support), our cohort was larger with a longer follow-up. In addition, we used a PS-based analysis to reduce bias.

Even though the majority of the findings of the previously mentioned studies are in line with the current study, some differences were found.[15–17] These differences could be explained by centre-specific performance, but also the used methods and covariates may account for these differences. Schramm *et al*. performed PS matching based on age, sex, serum creatinine levels, INTERMACS, perioperative RV failure, and the implantation strategy (bridge to transplant or destination therapy).[16] Instead, we used preoperative RV function as a covariate instead of perioperative right failure, because we consider the latter an intermediate effect modifier. Mueller *et al*. corrected for age, gender, INTERMACS, and preoperative use of extracorporeal life support.[15] Within our MCS database, patients on temporary support were not assigned to any of the INTERMACS classes. Therefore, in contrast to Schramm *et al*., who used a continuous INTERMACS score, we used a categorical variable for INTERMACS and temporary support, because patients on temporary support clinically differ from patients assigned with INTERMACS 1.[16] Interestingly, within the patient groups of Mueller *et al*. and

Schramm *et al.*, patients on HVAD support had a worse INTERMACS score at implantation than HM3 patients.[15,16] This is in line with the current study. Apparently, patients assigned with INTERMACS 1 or patients on temporary support more often receive an HVAD. More years of experience with implanting HVAD and technical considerations could possibly explain the preference to implant HVAD in patients that urgently need MCS. In addition, there was a preference to implant HVAD in patients that were on CentriMag temporary support. Lastly, our follow-up time was longer than the studies mentioned earlier giving a more reliable indication of long-term results between the two LVAD types.

The current study has some limitations. The most important limitations are the number of patients and the retrospective study design. Our current study and previously conducted retrospective studies all showed no significant difference in survival, but all were in favour of HM3.[15–17] To confirm or disprove a significant difference in survival or specific complications between both devices, it is necessary to increase the number of PS-matched patients. A multicentre approach including all centres that implant both HM3 and HVAD is recommended. Secondly, because the decision which device to use is not always completely random, we performed PS matching, which entails some disadvantages. For a balanced comparison of survival and complication rates, these unmatched patients were excluded from analysis, resulting in a smaller group of patients with a loss of precision and generalizability.[18] Additionally, after PS matching, we assumed having two comparable groups. Nevertheless, not all covariates were unequivocally balanced. Even though the SMD was $<$10% for all measured covariates, these small imbalances may sum up and may together cause a worse survival for patients on HVAD support. Therefore, we performed two sensitivity analyses, which both showed similar results to our primary analysis. Lastly, it is possible to create a greater imbalance for unknown or unmeasured covariates after PS matching.[18] Even though we matched on an extensive set of possible confounders, we cannot rule out any imbalance on unknown or unmeasured covariates. A randomized controlled trial could solve this.

In conclusion, we demonstrated that in a propensity-matched cohort of patients with end-stage heart failure, although non-significant, survival was better for HM3 when compared with HVAD. A significantly higher incidence for haemorrhagic stroke and pump thrombosis was found for HVAD patients after PS matching. To confirm or disprove a difference in survival, a multicentre analysis including all centres that implant both HM3 and HVAD is recommended. Finally, a randomized controlled trial is needed to rule out any effect of unknown or unmeasured covariates.

Conflict of interest

F.W.A., E.A., N.d.J., M.G., J.J.V.D.H., N.P.V.D.K., C.L.M., M.M. M., D.L.O., A-M.O., M.I.F.J.O., and F.Z.R. have no conflicts of interest. The UMCU, which employs L.W.v.L., received consultancy fees from Medtronic, Abbott, Vifor, and Novartis, outside the submitted work. E.E.C.d.W. reports personal fees from Thoratec, SJM, and Abbott, outside the submitted work. L.N. reports a grant from Health~Holland (LSHM19035), outside the submitted work.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of PS-matched patients of the sensitivity analysis, using all patients without pre-operative temporary support.

Figure S1. Kaplan Meier survival of all PS-matched patients without pre-operative support for sensitivity analysis. Censored for non-urgent heart transplantation and ongoing support at follow-up, with 95% Confidence Interval.

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