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CLINICAL RESEARCH
Heart failure

Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry

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Aims The ELEVATE Registry was designed to study long-term outcomes with the Heartmate 3 (HM3), a fully magnetically levitated centrifugal ventricular assist device, in a real-world population following CE-mark approval.

Methods and results A total of 540 patients, implanted in Europe and the Middle East were followed in ELEVATE. The registry included 463 patients receiving the HM3 as primary implant (Primary Implant Cohort), 19 patients underwent a pump upgrade from another device (Pump Exchange Cohort) and 58 patients who had experienced an outcome before having the possibility to sign the Informed Consent, for which only outcome data were collected (Anonymized Cohort). Data collection included demographics, survival, adverse events, EQ-5D Visual Analog Score quality of life (EQ-5D VAS QOL) questionnaire, and 6-min walk distance (6MWD). Mean age was 55.6 ± 11.7 years (89% male, 48% ischaemic cardiomyopathy). Seventy per cent of patients were in INTERMACS Profile 1–3 and 12.7% were on temporary mechanical circulatory support. Primary Implant Cohort survival was 83% after 2 years. In the Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation Primary Implant Cohort, strokes were observed in 10.2%, gastrointestinal bleedings in 9.7%, pump thrombosis in 1.5%, and outflow graft twists in 3.5%. Heartmate 3 implantation resulted in a significant and sustained improvement of functional capacity and QOL.

Conclusion In a real-world population, cohort implanted with the HM3 left ventricular assist device we demonstrate good long-term survival, sustained improvement of functional capacity, and low rates of adverse events (including pump thrombosis).

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Graphical Abstract

ELEVATE Registry - 2 Years Results

Study Design:
Prospective, observational, multinational registry including 540 subjects in 26 centers in Europe, Middle East and Asia

Results:

- At 2 years, the overall Survival rate of patients who received the HM3 as a primary implant (n=463) was 83.4%
- The composite Survival Free from non-surgical bleeding, stroke or pump thrombosis was 65.5% (Figure 1)
- Functional Capacity and Quality of Life (QoL) showed a significant improvement at 6 Months (p<0.001 in both) and the improvement was sustained through the duration of the Study (Figure 2A and 2B)
- Reported Stroke rate (10.2%) as well as suspected Pump Thrombosis rate (1.5%) were low

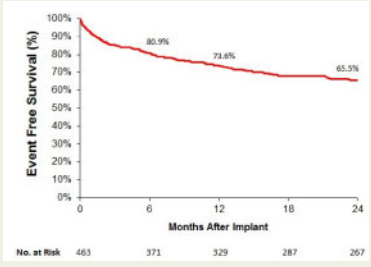

Fig.1: Survival free of non-surgical bleeding, stroke or pump thrombosis

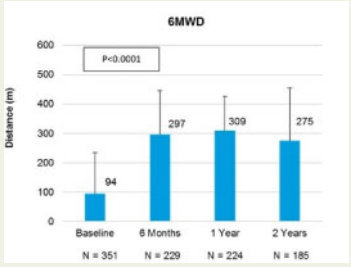

Fig.2A: 6 Minutes Walk Test results

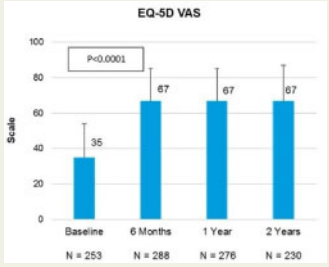

Fig.2B: EQ-5D-5L QoL results

Keywords Heart failure • HeartMate 3 TM • Left ventricular assist device • Outcomes

Introduction

Heart failure (HF) is a growing epidemic, with a prevalence of ~1–2% of adult population in developed countries.[1] It is estimated that 915 000 new cases are diagnosed each year, resulting in over 1 million hospitalizations and costs that account for about 1–3% of total healthcare expenditure in North America, Western Europe, and Latin America.[2,3] The use of left ventricular assist devices (LVADs) as treatment of advanced HF has increased greatly over the last decade[3] as they have demonstrated improved survival over optimal medical management,[4] especially with the newer generation of continuous flow (CF) LVADs which have also been shown to reduce complications such as pump thrombosis and stroke.[5]

The HeartMate 3^{TM} LVAS (HM3) is a new generation, centrifugal CF-LVAD introduced clinically in June 2014[6] and it is intended to provide short- and long-term mechanical circulatory support (e.g. as Bridge to Transplant or Myocardial Recovery, or Destination Therapy) in patients with advanced-stage HF. The pump has introduced technical innovations that are potentially advantageous over prior CF-LVADs such as full magnetic levitation of the rotor, large blood-flow gaps ensuring less trauma to blood components, and generation of an artificial pulse (Supplemental material online). Previously concluded studies using HM3 have demonstrated 1- and 2-year survival of 82% and 83%, respectively, and, importantly, near elimination of reoperations for confirmed pump thrombosis.[7–9] Since the European Conformity Mark (CEM) approval in October of 2015, use of the HM3 has expanded considerably throughout Europe, the Middle East, and Asia. However, real-world data on survival and incidence of adverse events with this device are sparse and it remains unclear if the results observed in the patients selected for the initial clinical trials are reproducible when the device is used commercially.

The ELEVATE Registry, a prospective, predominantly European registry (with additional contributing centres in middle East and Asia) of consecutive, commercial HM3 implants, was implemented to collect clinical data and assess the post-market experience with this device by evaluating clinically relevant endpoints in a real-world scenario. The ELEVATE Registry concluded its 2-year follow-up period in February 2019, and the final results of the post-approval experience with HM3 are reported in this analysis.

Methods

ELEVATE (Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting, ClinicalTrials.gov Identifier:

NCT02497950) is a prospective, observational, multinational registry including patients implanted with HM3 LVAD after commercial approval in Kazakhstan (January 2015) and after CE mark in Europe (October 2015). The registry was conducted in accordance with the Declaration of Helsinki and its protocol and informed consent form were approved by each institution's ethics committee.

Patients were enrolled consecutively in the participating centres—both high- and low-volume sites—from the date of commercial approval in the region, including both patients with a primary LVAD implantation and patients in whom an HM3 replaced another LVAD, while patients declining participation were excluded from the Registry. The initial sample size of the ELEVATE Registry was set at 500 patients in up to 50 centres. During the enrolment period—which lasted between March 2015 and February 2017—it became clear that a proportion of patients had not been included in the Registry because of lack of consent prior to implant (for instance, emergency or comatose patients). In order to best report survival or event rates in real-world conditions, ethics committees were requested a permission to record these patient's outcomes in an anonymized form. Following their approval, this information has been added in the Registry database and established the study size at 540 subjects. Patients were followed for 24 months post-implant or until an outcome (transplanted, explanted, expired, or withdrawn), whichever occurred first. The ELEVATE Registry uses INTERMACS definitions for outcomes and adverse events as previously done in both the CE Mark trial and the MOMENTUM 3 trial. The patient selection and postoperative management did not follow a specified protocol but was performed at the discretion of the investigators, depending on the Standard of Care practice at the enrolling centre.

At baseline, the following data were collected prior to the HM3 LVAD implant: demographics, comorbidities, previous cardiovascular history, haemodynamic profile, laboratory values, and echocardiographic parameters. Functional and clinical status was assessed by New York Heart Association (NYHA) classification, INTERMACS profile, and the 6-min walk test (6MWT). Quality of life was assessed by the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) questionnaire.

At implant, information on surgical approach, total procedure and bypass durations, use of Extracorporeal Life Support (ECLS), outflow graft, and pump placement were collected. Data regarding concurrent procedures and blood product usage were obtained.

Following the implant procedure and hospital discharge, patients were evaluated at 6, 12, and 24 months post-implant for their clinical and functional status. Adverse events per the protocol specified INTERMACS definition were reported as they occurred. Outcomes such as transplant, explant for recovery, death, and withdrawal were also captured.

Standard of care data was collected by the sites and entered in an electronic data capture system hosted by the sponsor. Data were not monitored on site but reviewed remotely and queried for inconsistencies and missing entries, ensuring a high level of reliability.

Statistical analysis

Continuous data are presented as mean with standard deviation or median with interquartile (IQR) values, unless otherwise specified. Categorical data are reported as frequencies and percentages. Survival data are presented using the Kaplan–Meier product method. Patients are censored at the time of transplant or last known follow-up without a reported event (death or adverse event). Hazard ratios are calculated with univariable Cox proportional hazards modelling. Competing risks were analysed using the method of Fine and Grey. There was no imputation of missing data except for the 6MWT distance. For patients not performing the 6MWT due to HF, the distance was imputed as zero metres. The 6MWT and QoL VAS were analysed over time using a repeated measure analysis of variance. Statistical analysis was performed using SAS version 9.3.

Role of the funding source

The ELEVATE Registry was funded by Abbott and its data were collected in an electronic database developed by the sponsor. The sponsor also performed the analysis for this manuscript following the Author's directives and decisions.

Results

Data of a total of 540 patients implanted at 26 centres [median implants per centre = 15.5 pts (IQR 6–30)] were available for this analysis. Out of the 540 patients, full data sets were obtained for 482 patients of which 463 received the HM3 as primary implant and 19 patients received the HM3 as replacement or upgrade from another durable device (Pump Exchange Cohort). In 58 patients, only outcome data were obtained (Anonymized Cohort). The different Cohorts and patients' disposition are illustrated in the consort diagram reported in *Figure 1*. The primary objective of this report is the long-term outcome (2 years) of the Primary Implant Cohort.

The baseline characteristics the ELEVATE Primary implant cohort have previously been reported[10] and are given in *Table 1* (laboratory test results provided in the Supplementary material online, *Table S1*).

The baseline characteristics of the Pump Exchange Cohort and their survival rate are provided for completeness of information in the Supplementary material online, *Table S2* and *Figure S1*, respectively.

All patients received the HM3 for advanced HF with reduced ejection fraction. The majority of patients (70%) were treated with intravenous inotropic therapy prior to HM3 implantation for low cardiac output and were in INTERMACS Profile 1–3. Twelve per cent of patients were on temporary mechanical circulatory support (ECLS, or temporary LVAD/BIVAD) or IABP (6.9%) prior to HM3 implantation (*Table 1*).

Primary implant cohort

Of the 463 patients in the Primary Implant Cohort, 426 (92%) were successfully discharged from the hospital. Median in hospital stay was 29 days (21–47) and median ICU stay 7.5 days (4–21). Twenty-four-month survival in the Primary Implant Cohort was 83.4% (95% CI 79.9–86.8%) and the median duration spent out of hospital was 671.5 days (range 592–698). The majority of patients (73.2%) were alive on their initial device.

Figure 2 reports the competing outcomes curves for both the Primary Implant and the Anonymized cohorts: only 9% of patients were transplanted within the first 2 years after HM3 implantation, 25% of patients expired on their device, the device was explanted in 1% and 1% of patients were lost to follow-up. Infection (25%), multiorgan failure (19%), and stroke (15%) were the leading causes of death (*Table 2*) for the Primary Cohort patients.

After 24 months, the majority of patients were in NYHA classes 1 and 2 (82%, $P < 0.0001$ vs. Baseline) and showed persistent improvement in both 6MWT and QOL (*Figure 3*). The ELEVATE Registry collected 406 echocardiographic data at either 6- or 12-months and 420 at 24-month post-implant: a new onset of moderate to severe aortic

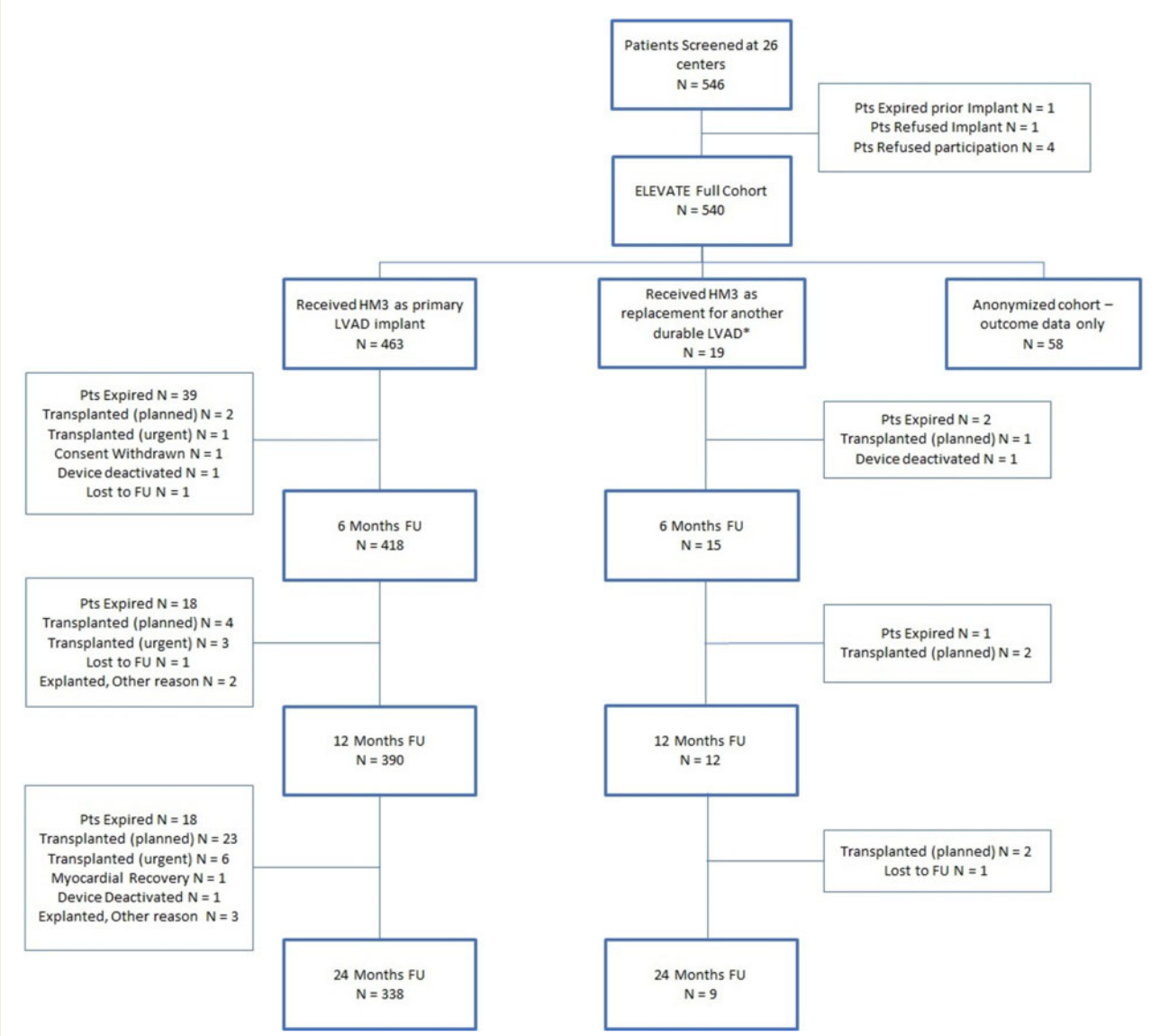

Figure 1 ELEVATE Registry consort diagram.

regurgitation was observed in 19 subjects (4 severe and 15 moderate) at 1 year, while additional 3 new moderate cases were reported for a total of 22 moderate to severe cases by 24 months.

Adverse events are given in *Table 3*. Stroke was observed in 10.2% of patients with similar incidence of ischaemic (5.2%) and haemorrhagic (5.0%) origin. Survival free from Stroke was 78.3% [95% CI 74.5–82.1% (*Figure 4A*)] at 2 years. In order to account for patients who expired, and so would not have experienced a stroke event, a competing risk analysis for stroke using the method of Fine and Grey has been performed for the Primary Implant Cohort and reported in Supplementary material online, *Figure S2*.

Major Bleeding was observed in 33.3% patients (*Figure 4B*), and more specifically gastrointestinal bleeding was reported in 9.7% of patients. Patients in the Primary Implant Cohort who expired or had an outcome—and as such could not contribute at the freedom from Major Bleeding calculation—have been accounted in a competing risk analysis for bleeding using the method of Fine and Grey and reported in the Supplementary material online, *Figure S3*.

Freedom from re-hospitalization at 2 years was 30.9% (95% CI 26.4–35.4%) and the majority of re-hospitalizations were for adverse events (75%). Device malfunctions were observed in 25 (5.4%) patients and included suspected pump thrombosis (1.5%), outflow graft bend relief disconnections (0.4%) and outflow graft twists (3.5%). Freedom from outflow graft twist was 95.5% (95% CI 93.4–97.6%) at 2 years. Six patients (1%) underwent pump or pump component exchange for device malfunctions.

In order to investigate haemocompatibility-related adverse event outcomes, a specific analysis based on survival free of stroke, pump thrombosis or non-surgical bleeding has been performed: at 2 years the survival free from stroke, pump thrombosis, and non-surgical bleeding was 65.5% (Supplementary material online, *Figure S4*).

Table 1 Baseline data: primary implant cohort

	Elevate, *N* = 463	
Age mean (years)	55.6 ± 11.7	
BSA mean (m^2)	2.02 ± 0.23	
BMI mean (kg/m^2)	27.3 ± 5	
eGFR mean (median) [IQR]	65.3 (61.5) [42.8–82.5]	
Male, *n* (%)	412	89%
Female, *n* (%)	51	11%
Indication, *n* (%)		
Bridge to transplant	305	66%
Destination therapy	122	26%
Bridge to candidacy or recovery	36	8%
INTERMACS profile, *n* (%)		
Profile 1	43	9%
Profile 2	102	22%
Profile 3	176	39%
Profile 4	125	27%
Profile 5	8	2%
Profile 6	2	<1%
Not provided	7	
NYHA classification, *n* (%)		
Class IIIA	42	10%
Class IIIB	165	38%
Class IV	231	53%
Not provided	25	
History of respiratory disorders, *n* (%)	159	34.3%
Severe chronic obstructive pulmonary disease	49	10.6%
Diabetes type 1, *n* (%)	18	3.9%
Diabetes type 2, *n* (%)	101	21.8%
History of bleeding disorders, *n* (%)	28	6.0%
History of neurological dysfunction, *n* (%)	76	16.4%
Transient ischaemic attack	16	3.5%
Ischaemic stroke	32	6.9%
Haemorrhagic stroke	6	1.3%
Seizure	6	1.3%
Other	23	5.0%
History of renal insufficiency, *n* (%)	141	30.5%
History of hypertension, *n* (%)	220	47.5%
History of coronary artery disease, *n* (%)	235	50.8%
PCI	179	38.7%
CABG	48	10.4%
History of myocardial infarction, *n* (%)	194	41.9%
History of carotid artery disease, *n* (%)	11	2.4%
History of cardiac arrhythmias, *n* (%)	280	60.5%
AF	179	38.7%
AFL	16	3.5%
VF	43	9.3%
VT	96	20.7%
Valve insufficiency/regurgitation, *n* (%)	331	71.5%
Valve repair/replace, *n* (%)	44	9.5%
Pacemaker/defib ongoing at implant, *n* (%)		
Single/dual chamber pacemaker	8	1.7%
CRT	9	1.9%
CRT-D	114	24.6%
ICD	191	41.2%
Transplant, *n* (%)	0	0.0%
Temporary mechanical circulatory support, *n* (%)	59	12.7%
IABP, *n* (%)	32	6.9%
HF Duration, *n* (%)		
<1 year	119	25.7%
≥1 year	344	74.3%
BP Systolic (mmHg), *n* (mean ± SD)	451	102.3 ± 14.9
BP Diastolic (mmHg), *n* (mean ± SD)	451	65.4 ± 11
Mean BP (mmHg), *n* (mean ± SD)	451	77.7 ± 10.8
PCWP (mmHg), *n* (mean ± SD)	314	24.8 ± 9.4
PAS (mmHg), *n* (mean ± SD)	354	50.8 ± 15.9
PAD (mmHg), *n* (mean ± SD)	341	24.9 ± 9.2
mPAP (mmHg), *n* (mean ± SD)	352	34.6 ± 11.2
CVP (mmHg), *n* (mean ± SD)	247	10.8 ± 6.7
Cardiac Index ($L/min/m^2$), *n* (mean ± SD)	339	1.92 ± 0.56
Cardiac Output (L/min), *n* (mean ± SD)	330	3.81 ± 1.15
PVR (dynes.cm-5), *n* (mean ± SD)	309	393.6 ± 1297.8
LVEF (%), *n* (mean ± SD)	428	18.3 ± 6.3

Full cohort

Two-year survival of the Full Cohort was 74.5% (95% CI 70.8–78.2%). The majority of patients (64.4%) were alive on their initial device. Only 8.2% of patients were transplanted within the first 2 years after HM3 implantation, 25.0% of patients expired on their device, the device was explanted in 1.3% and 0.7% of patients were lost to follow-up. In the Full Cohort, multi-organ failure (31%) was the most frequent cause of death, followed by infection (24%) and stroke (11%). Causes of death for this Cohort are also reported in *Table 2*.

Discussion

The ELEVATE Registry followed a 'real world population' of HM3 patients for the first time. We found that implantation of the HM3 ventricular assist device for advanced HF with reduced ejection fraction is associated with a 2-year survival of 83% for primary VAD implantation and results in a sustained improvement of NYHA functional class and quality of life. Stroke, bleeding, and pump thrombosis rates observed in ELEVATE remained low over the study period.

Two-year survival in ELEVATE for the full cohort, which also included pump upgrades from another device and the anonymized cohort constituted by patients with an outcome prior signing the Informed Consent, was 74.5%. This is comparable with the 2-year survival in the HM3 CE-mark study (74%)[11] and Momentum 3 trial (79%),[9] despite an extremely low transplant rate below 9% as well as liberal inclusion of patients in INTERMACS Profile 1 and on temporary mechanical support, both of which were excluded in the previous

Table 2 Causes of death, primary implant cohort, and full cohort

Cause of death	Primary cohort deaths ($n = 75$)		Full cohort deaths ($n = 135$)	
	Pt	% Pt	Pt	% Pt
Multi-organ failure	14	19	42	31
Infection/sepsis	19	25	32	24
Right heart failure	7	9	12	9
Stroke	11	15	15	11
Bleeding	5	7	6	4
Respiratory failure	2	3	3	2
Inflow cannula obstruction	1	1	1	<1
Outflow graft thrombosis	1	1	1	<1
Other	15[a]	20	23[b]	17

[a]Other includes: unknown (6), suicide (3), brain death (1), cardiac arrest (1), circulatory collapse (1), infaust prognosis (1), and liver failure (1).
[b]Other includes: unknown (6), cardiac failure (4), suicide (3), cardiac arrest (2), brain damage subsequent to cut driveline (1), brain death (1) circulatory collapse (1), infaust prognosis (1), liver failure (1), myocardial infarction (1), cerebral hypoxia (1), and meningoencephalitis (1).

two studies. The low transplant rate observed in ELEVATE results from the severe shortage of donor organs in the participating countries and underlines the need for a stable VAD platform suitable for long-term support. With the recent change of the allocation system, the trend for long-term bridging will also be seen in the USA. Survival for the primary implant and full ELEVATE cohorts is compared favourably to the 70% 12-month and 59% 2-year survival reported for CF-LVADs in the IMACS and Euromacs registries.[12] With 70% of patients in INTERMACS Profile 1-3 and 12% on mechanical circulatory support, the ELEVATE population is comparable to patients in these registries and resembles a 'real world' VAD cohort.[12,13]

HM3 implantation was associated with a sustained improvement in 6MWT and 82% of patients were in NYHA classes I and II 2 years after HM3 implantation. At baseline, the majority of patients were unable to walk due to HF. By 6 months post-HM3 implant the absolute mean distance walked improved by 203 m plateauing thereafter. The plateau after 6 months, however, might reflect a limitation of current assist devices and fixed VAD speeds with limited response to patient activities and warrants further investigation. Quality of life also improved significantly after HM3 implantation. The improvement of quality of life was sustained up to 2 years and was not decreased by the accumulation of adverse events. This is in line with the 2-year results of the CE-mark study and Momentum 3 trial.[9,11]

Thromboembolic and bleeding complications remain frequent after ventricular assist device implantation and limit the merits of therapy.[14] Stroke is the most devastating complication of the latter and is a major driver of mortality and morbidity.[14] Stroke was observed in 10.2% of patients and did account for 15% of deaths in ELEVATE at 2 years. This is comparable to the strokes rate in the Momentum 3 study as well as IMACS and Euromacs and superior to the 24% stroke rate observed in the CE-mark trial.[9,11–13] The massive reduction in strokes compared with the CE-mark trial might reflect growing surgical experience as well as improved medical management and underscores the potential superiority of the HM3 system to previous CF devices.[15–17] Given that almost half of strokes in ELEVATE were haemorrhagic, protocols for reduced anticoagulation might further improve Stroke rates with the HM3 system.[18] The

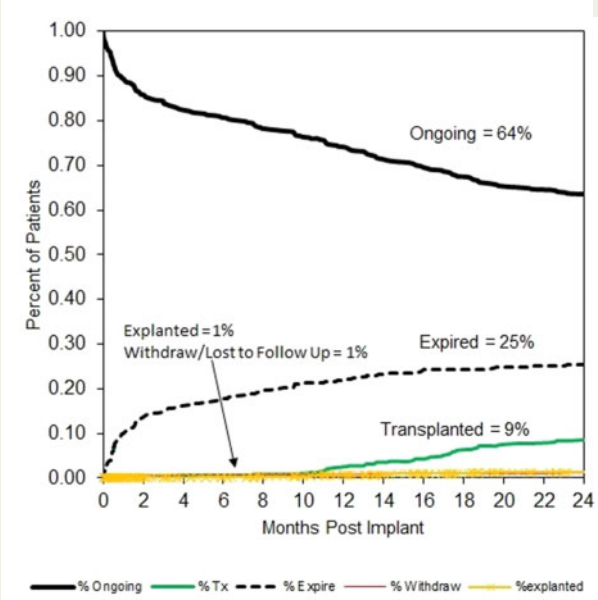

Figure 2 Competing outcomes (primary cohort and anonymized cohort).

HM3 has several design features to improve the pumps haemocompatibility[7] such as artificial pulse and wide blood-flow paths. Gastrointestinal bleeding events have been linked to degradation of high-molecular-weight multimers of Von Willebrand factor and continuous blood flow.[19] Indeed, the amount of high-molecular-weight multimers of Von Willebrand factor degradation with the HM3 is lower compared with other devices[20] and is associated with an overall decrease GI bleeding rate.[9,11,21] Pump thrombosis was only observed in 1.5% of patients which echoes the extremely low pump thrombosis rates observed in the CE-mark study and Momentum 3 trial, clearly superior to previous axial pumps.[16] Outflow graft twist is an HM3-specific complication and affected 3.5% of patients in

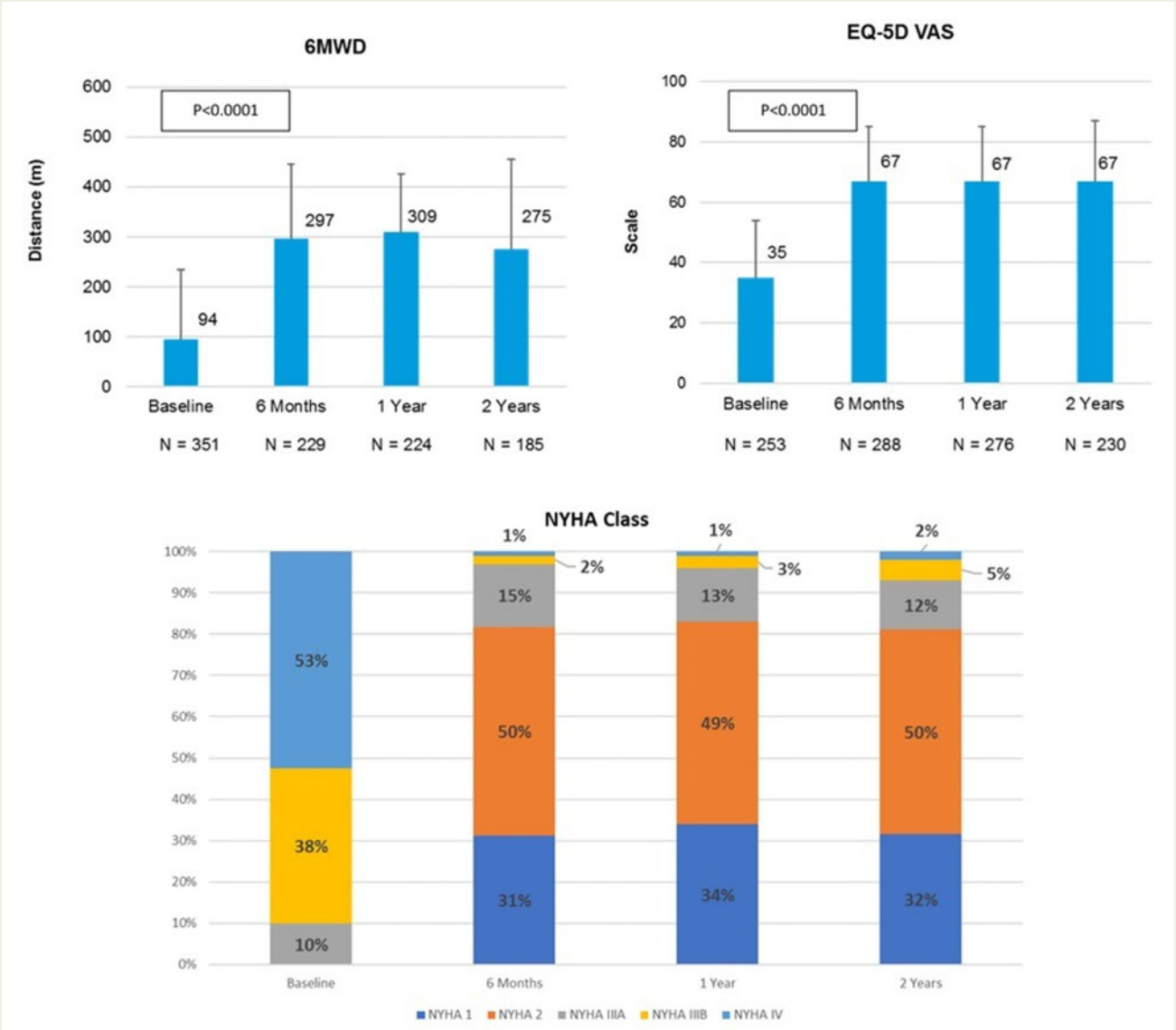

Figure 3 Improvement in 6-min walk distance and EuroQol-5 Dimensions visual analogue scale (VAS)—error bars represent standard deviations, numbers patients that performed the test; Percentage of patients in each NYHA Class per visit.

ELEVATE which compares with the Momentum 3 trial.[20] The problem of outflow graft twists, however, has been meanwhile resolved as a fix has been introduced for new HM3 implants. ELEVATE was designed to study the outcomes with the HM3 system in Europe and Middle East.

Comparing outcomes and adverse event rates of different VAD platforms is subject to significant bias.[22,23] Patient-related risk factors including Intermacs-Level, age, incidence of ischaemic HF, history of stroke or atrial fibrillation, therapy goal (bridge to transplant vs. destination therapy) significantly alter outcomes of VAD therapy. A comparison of different VAD systems and specifically of the HM3 vs. the HVAD system should therefore only be performed in a dedicated trial design balancing patient-related risk factor. In light of this, no attempt to compare different devices was performed.

As the outcomes at 2 years with HM3 pump support begin to get closer to those observed for transplantation and opportunity to perform transplants remains low due to donor scarcity, it is important to determine even longer-term outcomes. Thus, the ELEVATE Investigators prolonged the data collection to 5 years.

Limitations

As with all registries, ELEVATE encompasses some limitations. The main limitation is the presence of the anonymized cohort of 58

Table 3 Adverse events, primary implant cohort

Adverse event	# pts	% pts	# events	EPPY
Arterial non-CNS thromboembolism	6	1.3	6	0.008
Cardiac arrhythmias	100	21.6	134	0.173
Haemolysis	3	0.6	3	0.004
Hepatic dysfunction	16	3.5	17	0.022
Hypertension	22	4.8	25	0.032
Major bleeding	154	33.3	274	0.353
Requiring surgery	57	12.3	71	0.091
Gastrointestinal	45	9.7	61	0.079
Major infection	262	56.6	515	0.663
Sepsis	70	15.1	81	0.104
Driveline	137	29.6	196	0.252
Localized	136	29.4	207	0.266
Inflow or outflow/pump pocket	21	4.5	31	0.040
Ischaemic stroke	24	5.2	24	0.031
Haemorrhagic stroke	23	5.0	24	0.031
Other neurological dysfunction[a]	30	6.5	33	0.042
Pericardial fluid collection	36	7.8	41	0.053
Psychiatric episodes	27	5.8	28	0.036
Renal dysfunction	66	14.3	76	0.098
Respiratory failure	86	18.6	101	0.130
Right heart failure	70	15.1	72	0.093
Requiring RVAD	32	6.9	32	0.041
Venous thromboembolism	3	0.6	3	0.004
Wound dehiscence	14	3.0	15	0.019
Other adverse event[b]	228	49.2	472	0.608

[a]Other neurological dysfunction included TIA, seizures, encelopathy.
[b]Other adverse events includes: Blood and lymphatic system disorders (44), Cardiac disorders (79), Ear and labyrinth disorders (1), Endocrine disorders (11), Eye disorders (2), Gastrointestinal disorders (27), General disorders (42), Hepatobiliary disorders (6), Immune system disorders (1), Infections and infestations (11), Injury-poisoning and procedural complications (6), Investigations (2), Metabolism and nutrition disorders (10), Musculoskeletal and connective tissue disorders (18), Neoplasms benign-malignant and unspecified—including cysts and polyps (5), Nervous system disorders (17), Product Issues (26), Psychiatric disorders (4), Renal and urinary disorders (13), Respiratory-thoracic and mediastinal disorders (78), Skin and subcutaneous tissue disorders (5), Social circumstances (1), Surgical and medical procedures (5), and Vascular disorders (58).

patients. There is a lack of comprehensive data collection in these patients as almost all of them expired prior to being consented. Exclusion of these 58 patients from the adverse event analysis may have impacted the rates presented. However, ethics committee approval was obtained to include information on mortality and time on device in these patients, which enabled us to present accurate survival for 99.3% of all implanted patients. Nonetheless, adverse event rates could be influenced by lack of information on the 58 patients in the anonymized cohort, as they may have experienced higher adverse events rates. The large size of the Registry counteracts but does not eliminate the importance of this source of bias. The Registry included a lower number of female subjects. This is consistent with previous published VAD studies and reflects that the majority of VAD patients are male.[3,5,7] Overall no selection bias exists and ELEVATE patient characteristics are typical for patients receiving a VAD in Europe and Middle East in terms of preoperative Intermacs-Level, presence of temporary mechanical circulatory support, age, gender, risk factors for haemocompatibility-related adverse events and therapy goal (BTT and BTC). Also, the registry was not monitored locally but remotely, meaning that there was no continuous source data verification, however, a very low withdrawal rate was maintained at 2 years 1% (*Figure 1*). The ELEVATE Registry has several strengths compared with other registries. First, it provides consecutive, structured prospective information on a 'real-world' cohort of patients treated with the same implanted device. Second, both small and large centres as well as centres new to the technology and very experienced centres have provided data. Third, although there was no source data verification, entries in the registry were queried to clarify inconsistencies and missing entries ensuring a high level of reliability.

Conclusions

ELEVATE demonstrates good 2-year survival and improvement functional capacity and quality of life with the HM3 system is a real-world population. Low stroke and pump thrombosis rates are sustained up to 2 years.

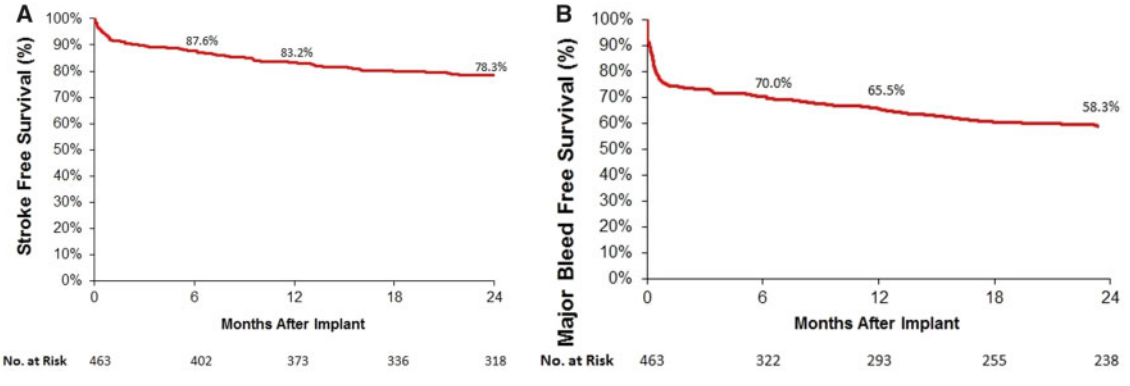

Figure 4 (*A*) Survival free from stroke. (*B*) Survival free from major bleeding.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P2, Authors/Task Force Members. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Failure* 2016; **18**:891–975.
2. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. *ESC Heart Failure* 2014;**1**:4–25.
3. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;**34**:1495–1504.
4. Kirklin JK, Cantor R, Mohacsi P, Gummert J, De By T, Hannan MM, Kormos RL, Schueler S, Lund LH, Nakatani T, Taylor R, Lannon J. First annual IMACS report: a global International Society for Heart and Lung Transplantation Registry for mechanical circulatory support. *J Heart Lung Transplant* 2016;**35**:407–412.
5. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW, Salerno C; MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 2017;**376**:440–450.
6. Schmitto JD, Hanke JS, Rojas SV, Avsar M, Haverich A. First implantation in man of a new magnetically levitated left ventricular assist device (HeartMate III). *J Heart Lung Transplant* 2015;**34**:858–860.
7. Netuka I, Sood P, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Marasco S, Beyersdorf F, Damme L, Schmitto JD. Fully magnetically levitated left ventricular assist system for treating advanced HF: a multicenter study. *J Am Coll Cardiol* 2015;**66**:2579–2589.
8. Krabatsch T, Netuka I, Schmitto JD, Zimpfer D, Garbade J, Rao V, Morshuis M, Beyersdorf F, Marasco S, Damme L, Pya Y. Heartmate 3 fully magnetically levitated left ventricular assist device for the treatment of advanced heart failure -1 year results from the Ce mark trial. *J Cardiothorac Surg* 2017;**12**:23.
9. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC, Yuzefpolskaya M, Salerno C, Walsh MN, Milano CA, Patel CB, Ewald GA, Itoh A, Dean D, Krishnamoorthy A, Cotts WG, Tatooles AJ, Jorde UP, Bruckner BA, Estep JD, Jeevanandam V, Sayer G, Horstmanshof D, Long JW, Gulati S, Skipper ER, O'Connell JB, Heatley G, Sood P, Naka Y; MOMENTUM 3 Investigators. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018;**378**:1386–1395.
10. Gustafsson F, Shaw S, Lavee J, Saeed D, Pya Y, Krabatsch T, Schmitto J, Morshuis M, Chuang J, Damme L, Zimpfer D, Garbade J. Six-month outcomes after treatment of advanced heart failure with a full magnetically levitated continuous flow left ventricular assist device: report from the ELEVATE registry. *Eur Heart J* 2018; **39**:3454–3460.
11. Schmitto JD, Pya Y, Zimpfer D, Krabatsch T, Garbade J, Rao V, Morshuis M, Beyersdorf F, Marasco S, Sood P, Damme L, Netuka I. Long-term evaluation of a fully magnetically levitated circulatory support device for advanced heart failure-two-year results from the HeartMate 3 CE Mark Study. *Eur J Heart Failure* 2019; **21**:90–97.
12. de By T, Mohacsi P, Gahl B, Zittermann A, Krabatsch T, Gustafsson F, Leprince P, Meyns B, Netuka I, Caliskan K, Castedo E, Musumeci F, Vincentelli A, Hetzer R, Gummert J; EUROMACS Members. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. *Eur J Cardiothorac Surg* 2018; **53**:309–316.
13. Kirklin JK, Xie R, Cowger J, de By T, Nakatani T, Schueler S, Taylor R, Lannon J, Mohacsi P, Gummert J, Goldstein D, Caliskan K, Hannan MM. Second annual report from the ISHLT Mechanically Assisted Circulatory Support Registry. *J Heart Lung Transplant* 2018;**37**:685–691.
14. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Failure* 2017;**19**:595–602.
15. Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, Ransom J, Ewald GA, Itoh A, Raval NY, Silvestry SC, Cogswell R, John R, Bhimaraj A, Bruckner BA, Lowes BD, Um JY, Jeevanandam V, Sayer G, Mangi AA, Molina EJ, Sheikh F, Aaronson K, Pagani FD, Cotts WG, Tatooles AJ, Babu A, Chomsky D, Katz JN, Tessmann PB, Dean D, Krishnamoorthy A, Chuang J, Topuria I, Sood P, Goldstein DJ; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device—final report. *N Engl J Med* 2019;**380**:1618–1627.
16. Uriel N, Colombo PC, Cleveland JC, Long JW, Salerno C, Goldstein DJ, Patel CB, Ewald GA, Tatooles AJ, Silvestry SC, John R, Caldeira C, Jeevanandam V, Boyle AJ, Sundareswaran KS, Sood P, Mehra MR. Hemocompatibility-related outcomes in the MOMENTUM 3 trial at 6 months: a randomized controlled study of a fully magnetically levitated pump in advanced heart failure. *Circulation* 2017; **135**:2003–2012.
17. Netuka I, Ivak P, Tucanova Z, Gregor S, Szarszoi O, Sood P, Crandall D, Rimsans J, Connors JM, Mehra MR. Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump-the MAGENTUM 1 study. *J Heart Lung Transplant* 2018;**37**:579–586.
18. Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, Bogaev RC, Frazier OH. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2011;**30**:849–853.
19. Netuka I, Kvasnicka T, Kvasnicka J, Hrachovinova I, Ivak P, Marecek F, Bílková J, Malíková I, Jančová M, Malý J, Sood P, Sundareswaran KS, Connors JM, Mehra MR. Evaluation of von Willebrand factor with a fully magnetically levitated centrifugal continuous-flow left ventricular assist device in advanced heart failure. *J Heart Lung Transplant* 2016;**35**:860–867.
20. Bansal A, Uriel N, Colombo PC, Narisetty K, Long JW, Bhimaraj A, Cleveland JC Jr, Goldstein DJ, Stulak JM, Najjar SS, Lanfear DE, Adler ED, Dembitsky WP, Somo SI, Crandall DL, Chen D, Connors JM, Mehra MR. Effects of a fully magnetically levitated centrifugal-flow or axial-flow left ventricular assist device on von Willebrand factor: a prospective multicenter clinical trial. *J Heart Lung Transplant* 2019;**38**:806–816.
21. Potapov EV, Netuka I, Kaufmann F, Falk V, Mehra MR. Strategy for surgical correction and mitigation of outflow graft twist with a centrifugal-flow left ventricular assist system. *J Heart Lung Transplant* 2018;**37**:670–673.
22. Mahr C, Thinh Pham D, Mokadam NA, Silvestry SC, Cowger J, Kiernan MS, D'alessandro DA, Coglianese EE, Faraz Masood M, Kormos RL, Jacoski MV, Teuteberg JJ. Interpreting neurologic outcomes in a changing trial design landscape: an analysis of heartware left ventricular assist device using a hybrid intention to treat population. *ASAIO J* 2019;**65**:293–296.
23. Li S, Beckman JA, Cheng R, Ibeh C, Creutzfeldt CJ, Bjelkengren J, Herrington J, Stempien-Otero A, Lin S, Levy WC, Fishbein D, Koomalsingh KJ, Zimpfer D, Slaughter MS, Aliseda A, Tirschwell D, Mahr C. Comparison of neurologic event rates among HeartMate II, HeartMate 3, and HVAD. *ASAIO J* 2019;**66**:620–624.