

Primary results of long-term outcomes in the MOMENTUM 3 pivotal trial and continued access protocol study phase: a study of 2200 HeartMate 3 left ventricular assist device implants

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Aim

The MOMENTUM 3 pivotal trial established superiority of the HeartMate 3 (HM3) left ventricular assist device (LVAD), a fully magnetically levitated centrifugal-flow pump, over the HeartMate II axial-flow pump. We now evaluate HM3 LVAD outcomes in a single-arm prospective continuous access protocol (CAP) post-pivotal trial study.

Methods and results

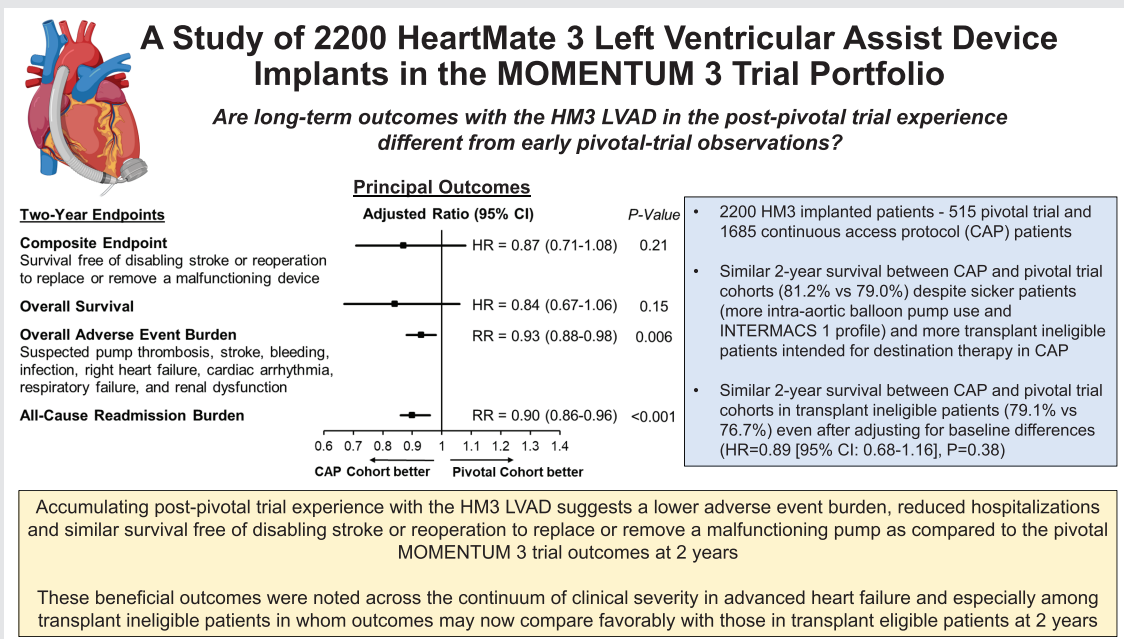
We enrolled 2200 HM3 implanted patients (515 pivotal trial and 1685 CAP patients) and compared outcomes including survival free of disabling stroke or reoperation to replace or remove a malfunctioning device (primary composite endpoint), overall survival and major adverse events at 2 years. The 2-year primary endpoint [76.7% vs. 74.8%; adjusted hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.71–1.08, $P = 0.21$] and overall survival (81.2% vs. 79.0%) were similar among CAP and pivotal cohorts despite sicker patients (more intra-aortic balloon pump use and INTERMACS profile 1) in CAP who were more often intended for destination therapy. Survival was similar between the CAP and pivotal trial in transplant ineligible patients (79.1% vs. 76.7%; adjusted HR 0.89, 95% CI 0.68–1.16, $P = 0.38$). In a pooled analysis, the 2-year primary endpoint was similar between INTERMACS profiles 1–2 ('unstable' advanced heart failure), profile 3 ('stable' on inotropic therapy), and profiles 4–7 ('stable' ambulatory advanced heart failure) (75.7% vs. 77.6% vs. 72.9%, respectively). The net burden of adverse events was lower in CAP (adjusted rate ratio 0.93, 95% CI 0.88–0.98, $P = 0.006$), with consequent decrease in hospitalization.

Conclusions

The primary results of accumulating HM3 LVAD experience suggest a lower adverse event burden and similar survival compared to the pivotal MOMENTUM 3 trial.

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Graphical Abstract



Accumulating post-pivotal trial experience with the HeartMate 3 (HM3) left ventricular assist device (LVAD) suggests a lower adverse event burden, reduced hospitalizations and similar survival free of disabling stroke or reoperation to replace or remove a malfunctioning pump as compared to the pivotal MOMENTUM 3 trial outcomes at 2 years. These beneficial outcomes were noted across the continuum of clinical severity in advanced heart failure and especially among transplant ineligible patients in whom outcomes may now compare favourably with those in transplant eligible patients at 2 years.

Keywords

Left ventricular assist device • Advanced heart failure • Outcome • Learning curve • Clinical trial • MOMENTUM 3

Introduction

Ongoing engineering advances in left ventricular assist devices (LVADs) have led to their application in advanced heart failure patients refractory to medical therapy, with evidence of markedly improved survival and quality of life.¹ The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) randomized clinical trial demonstrated the superiority of the HeartMate 3™ (HM3) LVAD, a fully magnetically levitated centrifugal-flow pump, compared to the HeartMate II™ LVAD, an axial-flow pump, with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years.²⁻⁴ Whether HM3 LVAD clinical outcomes observed within the early phase of application during the pivotal trial can be replicated or improved in a larger cohort as post-trial clinical experience accumulates, remains uncertain.

Early experience with the HM3 LVAD was derived in a single-arm 50 patient study performed by experienced surgical teams and

pointed to reduced pump thrombosis and increased pump durability.^{5,6} The pivotal MOMENTUM 3 trial, which included 515 HM3 LVAD implanted patients, demonstrated survival outcomes that exceeded those observed in trials or registry experiences.^{7,8} Other studies such as the Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting (ELEVATE) registry suggested excellent 2-year survival; however, the entry criteria were less well controlled and endpoints relied on site-reported, non-adjudicated outcomes.⁹ Once the randomized trial phase of MOMENTUM 3 was completed, a post-pivotal trial continuous access protocol (CAP) was initiated as a single-arm prospective study to assess the reproducibility of HM3 LVAD outcomes among the centres. This initiative included similar entry criteria as the pivotal trial and followed patients carefully through 2 years with independent adjudication of clinical events.¹⁰

We now present the primary 2-year outcomes of the CAP phase of the MOMENTUM 3 trial portfolio. This report was designed to address several objectives: (i) assess if the larger HM3 LVAD experience is associated with reproducible or improved outcomes

by evaluating differences in the principal composite endpoint and overall survival between the early pivotal trial experience and the post-trial experience, (ii) determine if HM3 LVAD survival differs by clinical severity at implant [Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile] or by therapeutic goal based on transplant eligibility [destination therapy (DT)], and (iii) outline the net burden of major adverse events (as well as their individual components) over the course of this clinical experience.

Methods

Device

The HM3 LVAD is a centrifugal, continuous-flow pump, with a friction-free fully magnetically levitated rotor, wide blood flow pathways to decrease destruction of red blood cells, and an asynchronous pulse feature using fixed speed changes, to prevent pump stasis.¹¹ The pump system includes the outflow graft, a modular driveline and an external system controller. This system is intended to support the left ventricle in those with advanced heart failure who are refractory to optimal medical management and have a limited quality and expected length of life.⁴

Patients and study conduct

The MOMENTUM 3 pivotal trial phase enrolled 1028 patients at 69 centres in the United States. Of the 516 patients randomized to the HM3 arm, 515 underwent HM3 implantation between September 2014 to August 2016 and comprise the pivotal cohort in this analysis. Details of the MOMENTUM 3 pivotal trial design, including detailed inclusion/exclusion criteria, have been published previously.¹⁰ After pivotal trial enrolment was completed, CAP enrolment was initiated at the same sites. The study timeline for the MOMENTUM 3 pivotal trial and CAP are shown in online supplementary Figure S1. Inclusion and exclusion criteria for the CAP were the same as the pivotal trial. Starting in October 2017, bridge to transplant (BTT) patients were excluded from CAP enrolment. Shortly after the HM3 pump was approved for long-term use in October 2018, enrolment in the CAP cohort was closed with a total of 1685 patients. All CAP patients had a study outcome (death, heart transplantation, HM3 removal or permanent deactivation, or withdrawal) or reached 2 years of HM3 support by November 2020. The 'pooled cohort' combines the CAP and pivotal cohorts for a total of 2200 patients.

The MOMENTUM 3 trial portfolio, including the pivotal and CAP studies, complied with the Declaration of Helsinki. Study protocols were approved by each institutional review board, and written informed consent was obtained from all patients or their authorized representatives. Study follow-up for the pivotal trial occurred at day 1, day 7, initial discharge, 1, 3, 6, 12, 18, and 24 months post-HM3 implant. The CAP study did not include the 3- and 18-month follow-up visits. The trial was sponsored by Abbott, which provided the devices, selected the sites, and analysed the data. The primary MOMENTUM 3 trial data for the pivotal study have been previously published, and access to its raw data was provided to an independent statistician who validated all primary analyses.^{2–4} In this analysis of the complete trial portfolio, two co-authors (J.C. and C.W.) maintained the raw data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. The utilized data analysis sets were independently validated by two statisticians assigned by the sponsor.

The first author drafted the manuscript, principally contributed to the present study design and analysis plan, and all authors were provided unrestricted access to any requested analyses of the data. All authors read the manuscript, made critical suggestions to the analyses, assisted in the editing of the manuscript and agreed to its submission for publication. All conflicts of interests and disclosures have been provided for each of the authors.

Endpoints

The primary composite endpoint for the study was survival to transplant, recovery or ongoing LVAD support, free of disabling stroke or reoperation to replace or remove a malfunctioning pump, at 2 years post-implant. Disabling stroke was defined as a modified Rankin score (MRS) greater than 3 (scale ranges from 0–6 representing increasing levels of disability with 0 indicating no symptoms, 3 moderate functional limitations and 6 being death). Other secondary endpoints included overall survival and pump replacement. Competing outcomes of death, heart transplantation, HM3 removal or permanent deactivation, and withdrawal were also evaluated through 2 years. These endpoints were compared between the pivotal and CAP cohorts.

Major adverse events were categorized as either haemocompatibility-related or non-haemocompatibility-related events, and these have been previously defined.^{2–4,12,13} Haemocompatibility-related adverse events included suspected pump thrombosis, stroke, and bleeding.¹² Non-haemocompatibility-related adverse events included infection, right heart failure, cardiac arrhythmias, respiratory failure, and renal dysfunction. The protocol specified definitions for each adverse event were previously published.^{2–4,10} An independent clinical events committee adjudicated adverse events for bleeding, infection, neurological dysfunction, suspected device thrombosis and haemolysis. The utilized adverse event definitions and clinical events committee remained the same during the pivotal trial and CAP. The index hospitalization length of stay and all-cause rehospitalizations were evaluated in patients discharged on HM3 support from the initial implant hospitalization.

In addition to comparisons of the overall pivotal and CAP cohorts, outcomes were analysed by the intended goal of therapy as either BTT or bridge to candidacy (BTC) or DT between study cohorts. To evaluate the impact of baseline clinical severity on outcomes, INTERMACS profiles 1–2 (clinically 'unstable' advanced heart failure; profile 1 includes critical cardiogenic shock, and 2 includes progressive decline on inotropic therapy with end-organ failure) were compared to profile 3 (clinically 'stable' but requiring inotropic therapy) and profiles 4–7 (clinically 'stable' ambulatory advanced heart failure) within the pooled cohort.

Statistical methods

Continuous variables are presented as mean and standard deviation and categorical variables are presented as counts and percentages. Comparisons of baseline demographics were performed with the *t*-test for continuous variables and Chi-square test for categorical variables (Fisher's exact test was used when Cochran's rule was not met). For the primary composite endpoint, event-free survival was calculated using the Kaplan–Meier method with data censored for non-fatal outcomes such as elective transplant or LVAD deactivation for myocardial recovery. Withdrawal after LVAD implant, death, disabling stroke, pump replacement, urgent transplant due to pump malfunction and pump deactivation for reasons other than myocardial recovery were failure

events. Hazard ratios (HR) were calculated with Cox proportional hazards modelling and presented with 95% confidence intervals (CI). To account for differences in major baseline demographics, all HR were adjusted for age, sex, race (Caucasian and non-Caucasian), intended goal of therapy (BTT/BTC and DT), and INTERMACS profile (profiles 1–3 and 4–7) unless otherwise specified. Adverse event rates are presented as the percentage of patients or events per patient-year (EPY). The overall 'net burden' of major adverse events was calculated by evaluating the combined EPY rate of the haemocompatibility-related and non-haemocompatibility-related events. All-cause readmission rates for discharged patients are presented in EPY. For adverse event and readmission rate comparisons, rate ratios (RR) with 95% CI from Poisson regression were adjusted for age, sex, race, intended use, and INTERMACS profile. Initial length of stay is presented as median with interquartiles (Q1–Q3) and compared with Wilcoxon rank sum test.

In order to identify independent predictors for specific adverse events [e.g. use of a right ventricular assist device (RVAD)], multivariate logistic regression was utilized. The final model was constructed using stepwise selection (P -value entry <0.05 , P -value stay <0.10). All P -values are two-tailed and were considered significant if $P < 0.05$. Statistical analysis was performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Baseline characteristics in the pivotal and CAP cohorts are shown in Table 1. Demographics including age, body size, sex, race, and ischaemic aetiology of heart failure were similar between groups. Due to the exclusion of BTT patients (after commercial approval of the HM3) midway through CAP enrolment, a higher number of DT patients entered in the CAP vs. pivotal cohorts (75.6% vs. 61.6%, $P < 0.001$). In addition, there was a greater prevalence of intra-aortic balloon pump (IABP) use (16.7% vs. 12.4%, $P = 0.019$) and predominance of 'crashing and burning' INTERMACS profiles 1 (4.1% vs. 2.1%, $P = 0.036$) in CAP compared to the pivotal trial. Other parameters also indicate that the CAP cohort was sicker than the pivotal cohort with worse renal function and reduced use of renin–angiotensin–aldosterone antagonists and beta-blockers (likely due to increased intolerance). There was a lower haematocrit and higher white blood cell count, consistent with increased illness severity in the CAP cohort. The use of cardiac resynchronization therapy was lower in CAP.

Primary composite endpoint and overall survival

Kaplan–Meier estimates of survival free of disabling stroke or reoperation to replace or remove a malfunctioning pump are shown in Figure 1A. At 2 years post-implant, a similar proportion of patients in the CAP vs. pivotal cohorts achieved the composite endpoint [76.7% vs. 74.8%; adjusted HR 0.87 (95% CI 0.71–1.08), $P = 0.21$]. Online supplementary Figure S2 shows the pump replacement component of the composite endpoint. Pump exchange rates were low in both cohorts with 98.4% of the CAP cohort and 96.9% of the

Table 1 Comparison of baseline characteristics between the pivotal and continued access protocol cohorts

Baseline variable	Pivotal cohort (n = 515)	CAP cohort (n = 1685)	P-value*
Age, years	59.2 ± 12.4	59.9 ± 12.2	0.22
BSA, m ²	2.07 ± 0.27	2.08 ± 0.29	0.86
BMI, kg/m ²	29.2 ± 6.3	29.1 ± 6.7	0.84
Male sex	410 (79.6%)	1342 (79.6%)	0.99
Caucasian	341 (66.2%)	1135 (67.4%)	0.60
Ischaemic aetiology of heart failure	216 (41.9%)	760 (45.1%)	0.21
Intended use			
Destination therapy	317 (61.6%)	1274 (75.6%)	<0.001
Bridge to transplant	112 (21.7%)	173 (10.3%)	<0.001
Bridge to candidacy	86 (16.7%)	233 (13.8%)	0.11
Bridge to recovery	0 (0%)	4 (0.2%)	0.58
Rescue therapy	0 (0%)	1 (0.1%)	1.00
IABP	64 (12.4%)	282 (16.7%)	0.019
INTERMACS profile			
1	11 (2.1%)	69 (4.1%)	0.036
2	156 (30.4%)	517 (31.0%)	0.79
3	272 (52.9%)	843 (50.5%)	0.33
4–7	75 (14.6%)	241 (14.3%)	0.88
Diabetes	233 (45.2%)	690 (40.9%)	0.08
Prior stroke	50 (9.7%)	128 (7.6%)	0.12
ACE inhibitor or ARB	158 (30.7%)	338 (20.1%)	<0.001
Beta-blocker	284 (55.1%)	668 (39.6%)	<0.001
Inotropes	444 (86.2%)	1474 (87.5%)	0.45
CRT	188 (36.5%)	407 (24.2%)	<0.001
CABG	102 (19.8%)	320 (19.0%)	0.68
Cardiac index, L/min/m ²	1.96 ± 0.52	1.99 ± 0.59	0.24
RAP, mmHg	10.8 ± 6.5	11.1 ± 8.3	0.34
PCWP, mmHg	23.1 ± 8.6	23.4 ± 8.9	0.57
PAPI	4.14 ± 4.91	3.82 ± 4.37	0.19
RVSWI, mmHg mL/m ²	561 ± 260	569 ± 295	0.60
Total bilirubin, mg/dL	1.00 ± 0.55	1.04 ± 0.56	0.10
BUN, mg/dL	28.3 ± 14.0	29.4 ± 15.4	0.12
Creatinine, mg/dL	1.35 ± 0.43	1.39 ± 0.42	0.08
eGFR, mL/min/1.73 m ²	61.5 ± 23.8	58.8 ± 22.8	0.024
Haematocrit, %	36.5 ± 5.6	35.9 ± 5.6	0.027
WBC count, 10 ³ /mL	7.66 ± 2.55	7.95 ± 2.89	0.034

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CAP, continued access protocol; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; WBC, white blood cell.

* P -values from Chi-square or Fisher's exact test for categorical variable comparisons and t -test for continuous variable comparisons.

pivotal cohort being free of pump replacement at 2 years [adjusted HR 0.53 (95% CI 0.25–1.10), $P = 0.09$]. In the pivotal cohort, 12 pump exchanges were performed for driveline damage or electrical faults ($n = 4$), suspected device thrombosis or elevated lactate dehydrogenase ($n = 3$), outflow graft twist ($n = 2$), infection ($n = 1$), and other reasons ($n = 2$). In the CAP cohort, there were 20 pumps replaced due to infection ($n = 7$), outflow graft twist ($n = 5$), suspected pump thrombosis ($n = 2$), driveline electrical fault ($n = 1$), and other reasons ($n = 5$). Overall rates of outflow graft twist obstruction (including those treated with or without pump replacement) were similar between the pivotal cohort (1.6%, $n = 8$) and the CAP cohort (1.8%, $n = 30$).

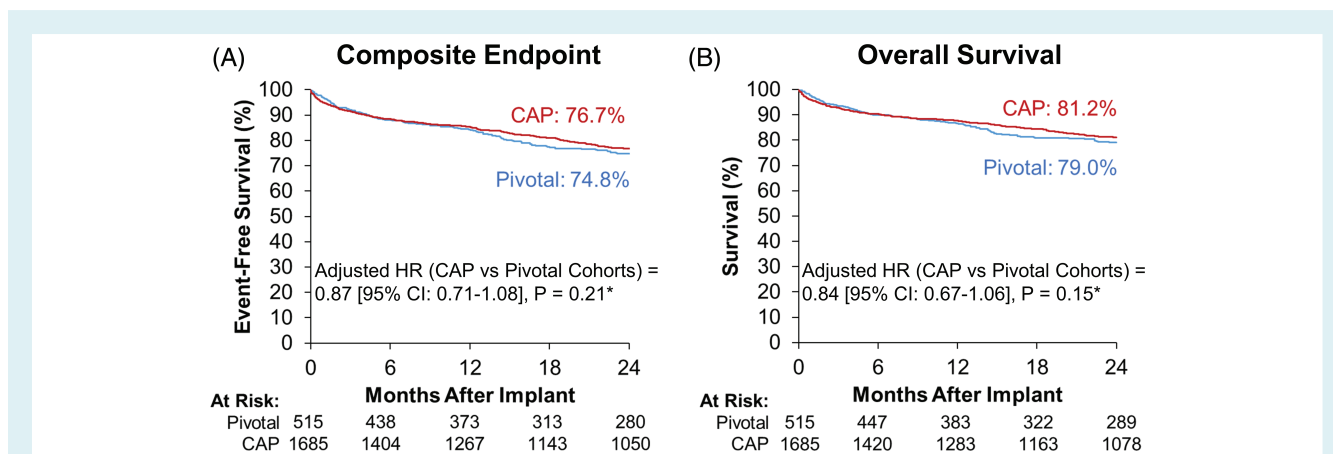


Figure 1 Composite endpoint and overall survival. Comparison of (A) survival free of disabling stroke or reoperation to replace or remove a malfunctioning pump and (B) overall survival between the pivotal and continued access protocol (CAP) cohorts. CI, confidence interval; HR, hazard ratio. *Adjusted HRs and *P*-values are calculated with Cox regression. HRs are presented for CAP vs. pivotal cohorts and adjusted for age, sex, race (Caucasian or non-Caucasian), intended use (bridge to transplant or candidacy, or destination therapy), and INTERMACS profile (1–3 or 4–7).

Overall survival rates at 2 years are shown in *Figure 1B*. In the CAP cohort, survival was 81.2% compared to 79.0% in the pivotal cohort. After controlling for major baseline demographics between the cohorts, the adjusted HR for CAP vs. pivotal cohorts was 0.84 (95% CI 0.67–1.06) (*P* = 0.15). In *Figure 2*, survival was also similar between the CAP and pivotal trial within BTT/BTC patients [adjusted HR 0.70 (95% CI 0.43–1.14), *P* = 0.15] and DT patients [adjusted HR 0.89 (95% CI 0.68–1.16), *P* = 0.38].

Competing outcomes

Online supplementary *Figure S3* shows the cumulative rates of study outcomes in the CAP and pivotal cohorts. The transplant rate was lower compared to the pivotal cohort (16% vs. 23%) and the proportion of patients ongoing on HM3 support was subsequently higher in CAP at 2 years (64% vs. 56%), likely due to the higher number of DT patients in the CAP cohort.

Impact of clinical severity at implant and outcomes

In *Figure 3*, the primary composite endpoint and survival are compared between clinical severity profiles that included INTERMACS profiles 1–2, 3 and 4–7. All groups performed similarly with respect to the composite endpoint. Survival at 2 years was better in INTERMACS profile 3 compared to profiles 1–2 [adjusted HR 0.77 (95% CI 0.62–0.96), *P* = 0.022].

Adverse events

The overall net burden of adverse events (*Figure 4*) was significantly better in CAP [adjusted RR 0.93 (95% CI 0.88–0.98), *P* = 0.006]. This improvement was driven primarily by a decrease in the frequency of non-haemocompatibility-related events

[adjusted RR 0.88 (95% CI 0.82–0.93), *P* < 0.001]. To account for potential bias resulting from a higher transplant rate in the pivotal cohort, rate comparisons between cohorts were also adjusted for transplant occurrence for either haemocompatibility-related events [adjusted RR 1.09 (95% CI 0.99–1.20), *P* = 0.09] or non-haemocompatibility-related events [adjusted RR 0.90 (95% CI 0.84–0.96), *P* < 0.001] and indicated no significant effect.

The 2-year rates for the individual adverse events are shown in *Table 2*. In the CAP cohort, suspected pump thrombosis remained a rare event (1.1%). At 2 years post-implant, freedom from stroke was 89.6% for CAP and 88.6% for the pivotal cohort (online supplementary *Figure S4*). For bleeding, rates were not significantly different between cohorts for gastrointestinal bleeding [adjusted RR 1.07 (95% CI 0.93–1.24), *P* = 0.33] or events requiring surgery [adjusted RR 1.16 (95% CI 0.88–1.55), *P* = 0.29].

Several adverse events demonstrated significant improvements from the pivotal trial to CAP. Infection, specifically localized infections, and cardiac arrhythmias were lower in CAP. Overall right heart failure event rates were similar between cohorts; however, events requiring RVAD placement were more frequent in CAP [adjusted RR 1.68 (95% CI 1.06–2.68), *P* = 0.028]. In both cohorts, over 90% of the RVADs were placed within 30 days of the HM3 implant (online supplementary *Figure S5*).

The pooled cohort was used to identify independent predictors of right heart failure requiring RVAD placement. Covariates included baseline variables such as age, sex, race, intended use, INTERMACS profile, IABP use, and study cohort (CAP or pivotal). Parameters associated with right heart function were also considered (central venous pressure/pulmonary capillary wedge pressure ratio, pulmonary artery pulsatility index, right ventricular stroke work index, estimated glomerular filtration rate (eGFR), total bilirubin, and moderate/severe tricuspid valve regurgitation). The final predictors in the multivariate logistic regression model are shown in online supplementary *Table S1*. IABP use, transplant

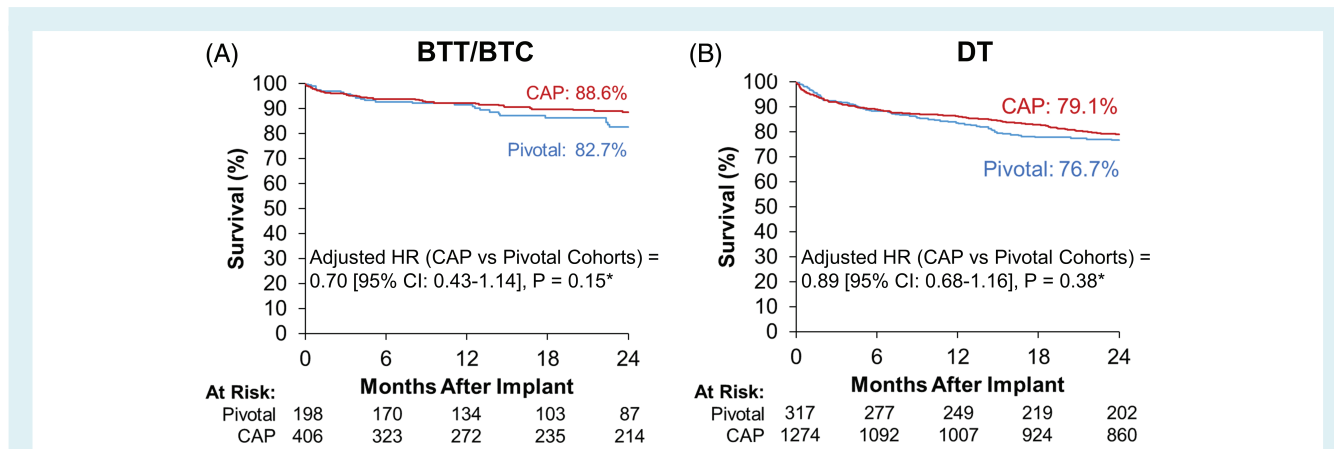


Figure 2 Overall survival by intended goal of implant. Comparison of survival between pivotal and continued access protocol (CAP) cohorts in (A) bridge to transplant or candidacy (BTT/BTC) and (B) destination therapy (DT) patients. CI, confidence interval; HR, hazard ratio. *Adjusted HRs and P-values are calculated with Cox regression. HRs are presented for CAP vs. pivotal cohorts and adjusted for age, sex, race (Caucasian or non-Caucasian), and INTERMACS profile (1–3 or 4–7).

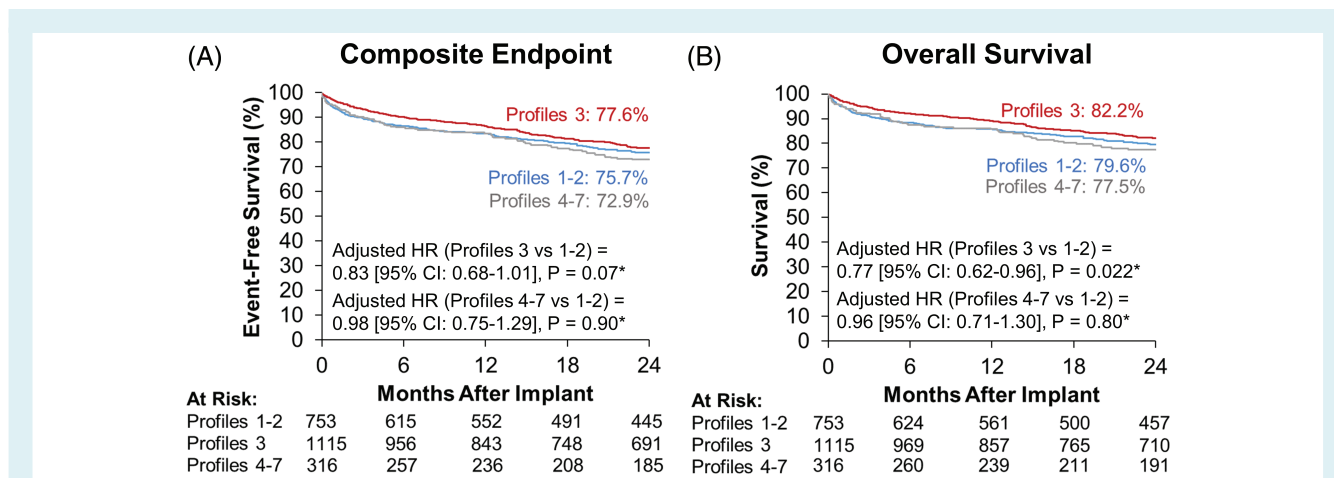


Figure 3 Impact of clinical severity on outcomes. Comparison of (A) the composite endpoint and (B) overall survival between INTERMACS profiles 1–2 ('unstable' advanced heart failure), profile 3 ('stable' on inotropic therapy) and profiles 4–7 ('stable' ambulatory advanced heart failure). CI, confidence interval; HR, hazard ratio. *Adjusted HRs and P-values are calculated with Cox regression. HRs are presented for profiles 3 vs. 1–2 and profiles 4–7 vs. 1–2 and adjusted for age, sex, race (Caucasian or non-Caucasian), and intended use (bridge to transplant or candidacy, or destination therapy).

ineligibility (DT), INTERMACS profiles 1–2, and lower eGFR were independently associated with a higher likelihood of RVAD requirement. Overall survival in patients requiring RVAD was lower than in those without RVAD use (online supplementary Figure S6).

Hospitalizations

In the pivotal cohort, 94.2% of patients (485/515) were discharged from the implant hospitalization on HM3 support with a median length of stay of 19 days (Q1–Q3: 14–25). Similarly, 93.2% of CAP patients (1571/1685) were discharged with a median length of stay of 19 days (Q1–Q3: 14–26, P = 0.74). The all-cause readmission rate was lower in CAP compared to the pivotal trial [2.03 vs. 2.26 EPPY; adjusted RR 0.90 (95% CI 0.86–0.96), P < 0.001].

Discussion

In this primary results report of the MOMENTUM 3 trial portfolio including the pivotal and CAP phase, we present the principal 2-year clinical outcomes in the largest reported prospective series of 2200 consecutively enrolled patients implanted with the HM3 LVAD. The main findings include the following: (i) survival with the HM3 LVAD approaches or exceeds 80% at 2 years, irrespective of clinical severity of advanced heart failure at the time of pump implantation; (ii) outcomes by intended goal of implant based on transplant ineligibility (BTT/BTC or DT) are similar between the pivotal and CAP cohorts, and specifically, survival of transplant ineligible patients is comparable to that reported with heart transplantation¹⁴; (iii) evidence of improving clinical experience is

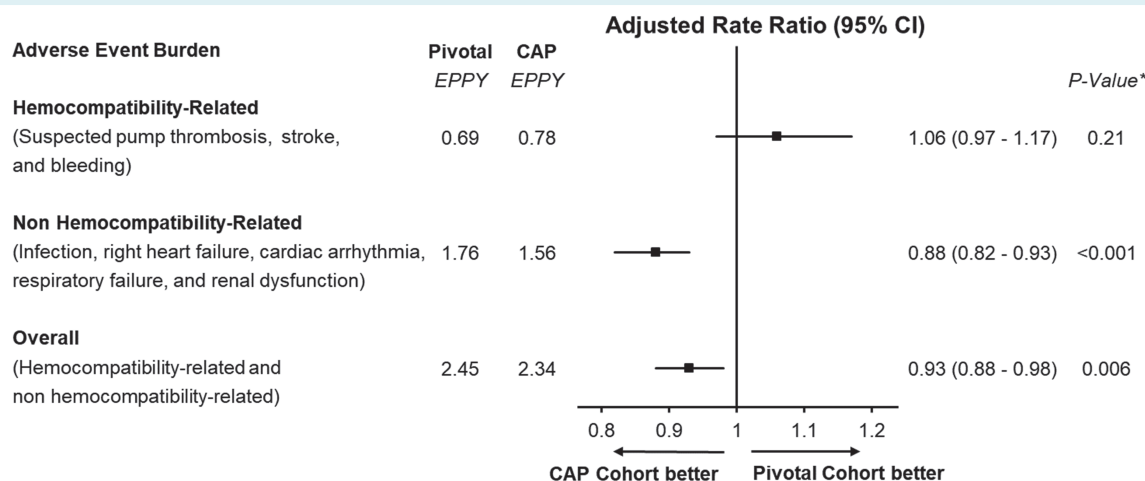


Figure 4 Net burden of adverse events. Comparison of the adverse event burden between the pivotal and continued access protocol (CAP) cohorts. CI, confidence interval; EPPY, events per patient-year. *Adjusted rate ratios and P-values are calculated with Poisson regression. Rate ratios are presented for CAP vs. pivotal cohorts and adjusted for age, sex, race (Caucasian or non-Caucasian), intended use (bridge to transplant or candidacy, or destination therapy), and INTERMACS profile (1–3 or 4–7).

Table 2 Comparison of adverse events between the pivotal and continued access protocol cohorts

Adverse event	Pivotal cohort (n = 515)	CAP cohort (n = 1685)	Pivotal cohort (n = 515) EPPY	CAP cohort (n = 1685) EPPY	Adjusted rate ratio (95% CI)*	P-value*
Suspected pump thrombosis	7 (1.4%)	18 (1.1%)	0.01	0.01	0.74 (0.31–1.81)	0.51
Any stroke	51 (9.9%)	153 (9.1%)	0.08	0.07	0.86 (0.63–1.16)	0.32
Haemorrhagic	25 (4.9%)	74 (4.4%)	0.03	0.03	0.86 (0.55–1.35)	0.51
Ischaemic	29 (5.6%)	87 (5.2%)	0.04	0.04	0.86 (0.57–1.29)	0.45
Disabling	26 (5.0%)	73 (4.3%)	0.04	0.03	0.76 (0.50–1.17)	0.21
Any bleeding	225 (43.7%)	844 (50.1%)	0.61	0.71	1.09 (0.99–1.21)	0.09
Gastrointestinal	126 (24.5%)	488 (29.0%)	0.31	0.36	1.07 (0.93–1.24)	0.33
Requiring surgery	50 (9.7%)	225 (13.4%)	0.08	0.10	1.16 (0.88–1.55)	0.29
Any major infection	300 (58.3%)	968 (57.4%)	0.82	0.73	0.86 (0.79–0.94)	0.001
Driveline	120 (23.3%)	390 (23.1%)	0.23	0.21	0.92 (0.77–1.09)	0.32
Sepsis	78 (15.1%)	259 (15.4%)	0.13	0.13	0.92 (0.74–1.15)	0.48
Localized	210 (40.8%)	620 (36.8%)	0.46	0.39	0.83 (0.73–0.94)	0.003
Any right heart failure	176 (34.2%)	630 (37.4%)	0.27	0.27	1.03 (0.88–1.20)	0.73
Requiring RVAD	21 (4.1%)	125 (7.4%)	0.03	0.05	1.68 (1.06–2.68)	0.028
Cardiac arrhythmia	185 (35.9%)	568 (33.7%)	0.37	0.30	0.82 (0.71–0.94)	0.004
Supraventricular	97 (18.8%)	278 (16.5%)	0.15	0.12	0.76 (0.61–0.95)	0.014
Ventricular	107 (20.8%)	314 (18.6%)	0.20	0.17	0.85 (0.71–1.03)	0.09
Respiratory failure	111 (21.6%)	334 (19.8%)	0.19	0.16	0.83 (0.69–1.01)	0.06
Renal dysfunction	73 (14.2%)	251 (14.9%)	0.11	0.11	0.87 (0.68–1.11)	0.27

CAP, continued access protocol; CI, confidence interval; EPPY, events per patient-year; RVAD, right ventricular assist device.

*Adjusted rate ratios and P-values are calculated with Poisson regression. Rate ratios are presented for CAP vs. pivotal cohorts and are adjusted for age, sex, race (Caucasian or non-Caucasian), intended use (bridge to transplant or candidacy, or destination therapy), and INTERMACS profile (1–3 or 4–7).

noted by a lower 'net burden' of adverse events in the post-pivotal trial cohort, principally driven by non-haemocompatibility-related events, such as infection; and (iv) all-cause hospitalizations are fewer in the CAP cohort (*Graphical Abstract*).

The MOMENTUM 3 trial, which in its pivotal phase was the largest randomized trial of LVAD therapy, extended its experience

with the HM3 pump during the post-pivotal trial phase by enrolling three times more HM3 LVAD patients as in the pivotal trial. The post-pivotal trial cohort applied the same rigor in outcomes assessment as in the pivotal trial phase among the same centres, allowing for adequate between-group comparisons. This analysis replicates the gains in clinical outcomes reported during the pivotal

trial and extends observations to clinically important sub-groups that did not have sufficient sample sizes for assessment in the early trial experience. For example, by pooling the pivotal and CAP cohorts, we can now analyse 753 patients categorized as 'unstable' advanced heart failure in INTERMACS 1–2 profiles.¹⁵ Although 'unstable' INTERMACS profile 1–2 patients demonstrate slightly lower survival when compared with the more stable INTERMACS 3 profile (who also require inotropic therapy), the composite primary endpoint is similar across the severity subsets. These data provide confidence that the HM3 pump performs well throughout the continuum of clinical severity when patients are recruited based upon the inclusion and exclusion criteria of the trial portfolio. Thus, these findings also provide guidance for appropriate selection of patients across a broad range of clinical presentations with predictable principal clinical outcomes.

Generally, advanced heart failure patients tend to segregate among those that are transplant ineligible (DT) or those eligible or possibly convertible into eligible patients for transplantation. Prior studies enforced such a dichotomy and reduced confidence in outcomes with those deemed transplant ineligible due to observations of lower survival in such patient cohorts.^{16,17} The advent of the HM3 pump has led to greater confidence in LVAD use among transplant ineligible patients such that even regulatory authorities in the United States have abandoned the use of such terminology in preference for a single indication of use in patients refractory to pharmacological disease-modifying therapy.^{17,18} We now introduce further certainty that transplant ineligible patients experience excellent survival comparable to rates noted with heart transplantation, at least in the 2-year observation period.¹⁴ Several countries still do not endorse the notion of LVAD implantation beyond a transplant bridge and we believe that reconsideration of this stance is necessary, as many now advocate.¹⁹ Another real-world experience among advanced heart failure patients who are beneficiaries of governmental health insurance and proportionately less eligible for transplantation, has shown a survival advantage to HM3 LVAD use when compared with other commercial LVADs.²⁰

The HM3 LVADs were specifically designed to reduce haemocompatibility-related adverse events including pump thrombosis, strokes and bleeding.¹¹ The pivotal trial phase of MOMENTUM 3 confirmed superiority of the HM3 pump in these domains but non-haemocompatibility-related adverse events were largely unaltered.⁴ The post-pivotal trial experience replicates the benefits regarding haemocompatibility-related adverse events and extends those gains to additional adverse events particularly infections, which have been noted to cumulatively be the most common adverse event encountered during the LVAD patient journey.⁴ A recent analysis of infections in HM3 patients reported that local infections unrelated to pump components were most common followed by driveline-associated infection, suggesting that circulatory changes may confer an immunomodulatory effect predisposing to infection.²¹ The finding of reduced infections suggests that closer attention to LVAD patient care and better surveillance may contribute to ameliorating this adverse event. These observations endorse the importance of effective patient and care provider education as well as multidisciplinary ambulatory care.²² We observed an increased early RVAD requirement in

the post-pivotal trial cohort despite similar rates of right heart failure over time. Our multivariable analysis demonstrates that this reflects the sicker population enrolled and greater preponderance of transplant ineligible patients, a population likely to experience earlier haemodynamic instability.^{23,24} It is not easy to predict the need for RVAD support using haemodynamic parameters or other metabolic indices and the clearest risk for such use is based on the overall clinical severity at time of implantation.²⁵

We recognize that 2-year outcomes may not be sufficient and longer-term follow up is desirable. The MOMENTUM 3 pivotal trial phase has been extended to study 5-year outcomes, even as other smaller multicentre reports surface with longer-term outcomes.²⁶ As we explore longer-term outcomes, we need to stay vigilant for complications that may result from degeneration of peripheral pump components. A rare complication of outflow graft compression has been recognized in some late survivors of LVAD implantation that presents with a decrease in pump flow.²⁷ Continuous reduction of the adverse event burden will be necessary to improve the patient journey and experience in the longer term. Trials to evaluate reduced exposure to anticoagulation regimens or to avoid the use of aspirin are ongoing in an effort to further control bleeding events.^{28,29} Efforts to fully internalize the LVAD system and reduce driveline infections are being actively pursued.¹ These advances are required to improve the overall cost-effectiveness of LVAD therapy with the HM3 pump, especially if this therapy is deemed to replace an established option such as heart transplantation.^{20,30}

In conclusion, accumulating post-pivotal trial experience with the HM3 LVAD suggests a lower adverse event burden, reduced hospitalizations and similar survival free of disabling stroke or reoperation to replace or remove a malfunctioning pump as compared to the pivotal MOMENTUM 3 trial outcomes at 2 years. These beneficial outcomes were noted across the continuum of clinical severity in advanced heart failure and especially among transplant ineligible patients in whom outcomes may now compare favourably with those in transplant eligible patients at 2 years.

Supplementary Information

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

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