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ORIGINAL ARTICLE

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Multicentre clinical trial experience with the HeartMate 3 left ventricular assist device: 30-day outcomes[†]

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Abstract

OBJECTIVES: The objective of this study was to describe the operative experience and 30-day outcomes of patients implanted with the HeartMate 3 Left Ventricular Assist System (LVAS) during the Conformité Européenne (CE) Mark clinical trial.

METHODS: Adult patients met inclusion and exclusion criteria defining advanced-stage heart failure and included the indications of bridge to transplant and destination therapy. Operative parameters, outcomes, adverse events, physical status and quality-of-life parameters were assessed in the first 30 days after LVAS implant.

RESULTS: Fifty patients were implanted with the HeartMate 3 at 10 centres in 6 countries. The 30-day survival rate was 98%. The median operative and cardiopulmonary bypass times were 200 (range: 95–585) min and 84 (range: 47–250) min, respectively. Patients required transfusion with packed red blood cells (3.6 ± 2.3 units), fresh frozen plasma (6.5 ± 5 units) and platelets (2 ± 1 units). Six patients (12%) required reoperation for postoperative bleeding and 10 patients (20%) did not require blood transfusion. The median intensive care time was 6 days (range: 1–112 days) and the total hospital stay was 28 days (range: 14–116 days). The most common adverse events were bleeding (15, 30%), arrhythmia (14, 28%) and infection (10, 20%). There were 2 (4%) strokes.

CONCLUSIONS: The 30-day outcomes following implantation of the HeartMate 3 demonstrates excellent survival with low adverse event rates. The LVAD performed as intended with no haemolysis or device failure.

CLINICALTRIALS.GOV IDENTIFIER: NCT02170363. HeartMate 3™ CE Mark Clinical Investigation Plan (HM3 CE Mark).

Keywords: Advanced heart failure • HeartMate 3 • Magnetically levitated rotor • 30-Day outcomes

INTRODUCTION

Durable mechanical circulatory support with a continuous-flow left ventricular assist device (LVAD) has become an important treatment option for patients with advanced-stage heart failure. Several studies have demonstrated that temporary LVAD support, as a bridge to transplant (BTT) or myocardial recovery, and lifetime support as destination therapy (DT) extends survival with improved quality of life [1–6]. Nevertheless, the combined effects of long-standing heart failure, major surgery for implantation and haematological alterations caused by the device predispose patients to haemorrhagic, thrombotic and infectious adverse events [7]. These serious complications are most prevalent in the first 30 days following implantation, when patients are most vulnerable [8]. Excessive bleeding often requires reoperation and extends intensive care and total hospital time, thereby increasing patients' exposure to infection complications. In addition, damage

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to coagulation factors by the device and the need to change anticoagulation therapy further increase the risk for bleeding and thrombotic events. The interrelationship between these adverse events requires a targeted approach to reduce their occurrence and improve outcomes of patients receiving LVAD support. More specifically, the goals of current clinical research are to lessen the surgery for implantation, eliminate the abdominal pump pocket and improve haemocompatibility.

Current axial and centrifugal continuous-flow LVADs are small, contain a single moving component and are more durable than the previous generation of pulsatile-flow devices [9]. These devices have narrow blood-flow gaps that increase shear stress on blood components. Varying degrees of haemolysis, platelet activation and damage to von Willebrand factor contribute to pump thrombosis, haemorrhagic and thrombotic stroke, surgical bleeding and gastrointestinal bleeding [10–15]. These complications, along with infection, are key limiting factors for LVAD therapy. Design changes that minimize the damage to blood components, lessen the surgery for implantation and provide a biological interface with blood should reduce the frequency of these complications and improve outcomes [16].

The HeartMate 3 Left Ventricular Assist System (LVAS) (St. Jude Medical Inc., St. Paul, MN, USA) is a new, centrifugal-flow device that incorporates a fully magnetically levitated rotor with wide blood-flow paths designed to address the problem of haemocompatibility. The HeartMate 3 LVAS was evaluated for the first time in a prospective multicentre non-randomized trial, designed to assess the safety and performance of the HeartMate 3 for 6 months of support [17]. The purpose of this sub-study was to describe the operative experience and assess the operative (30-day) morbidity and mortality of patients receiving this new device as a bridge to transplantation or for DT.

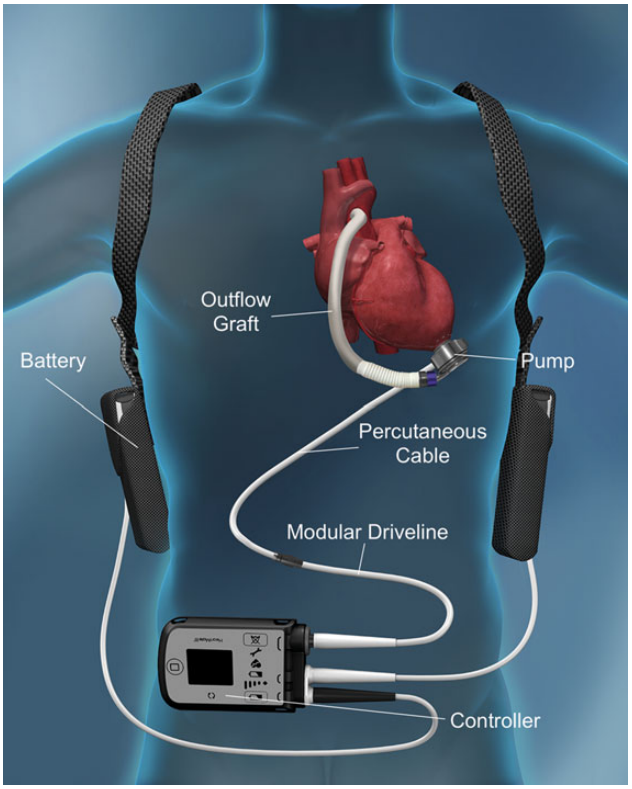

Figure 1: The HeartMate 3 LVAS with the pump in the pericardial space, the inflow conduit within the left ventricle and the outflow graft anastomosed to the ascending aorta. The percutaneous power cable exits the abdominal wall and is connected to a modular cable, a controller and power supply. (St. Jude Medical, Inc.)

MATERIALS AND METHODS

Study design

This prospective, single-arm, non-randomized study was conducted at 10 centres in 6 countries and met the requirements for Conformité Européenne mark designation (ClinicalTrials.gov Identifier: NCT02170363). St. Jude Medical Inc.; the study sponsor, managed the study and analysed the data. Each participating centre sought and obtained approval from their regulatory agencies and ethics committees. All patients gave their written informed consent prior to enrolment. Criteria for study enrolment included adult patients with an ejection fraction ≤25%, cardiac index <2.2 l/min/m^2 while not on inotropes or inotrope-dependent status and who were either on optimal medical management for 45 out of 60 days or listed for heart transplantation. Candidates also were classified as New York Heart Association (NYHA) Class IIIB–IV or American College of Cardiology/American Heart Association Stage D status. The lower limit of the body surface area was 1.2 m^2. Exclusion criteria generally included patients with serious comorbid conditions that would limit survival after implantation.

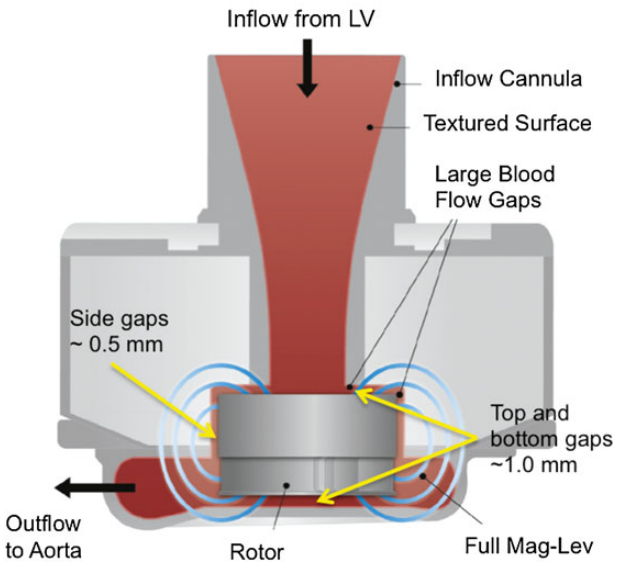

Figure 2: Internal components of the HeartMate 3 blood pump. (St. Jude Medical Inc.)

Device description and implantation

The HeartMate LVAS (Figs 1 and 2) employs a fully magnetically levitated rotor (Full MagLev™) with frictionless movement that eliminates heat generation and wear of the moving component. The device's internal surfaces are textured with titanium microspheres to stimulate adhesion of the patient's cells for the development of a tissue lining. During operation, blood from the left ventricle enters the inflow cannula and pump along a central axis and is propelled through the wide-gap impeller blades of the

rotor and finally out through the outflow graft. The power cable from the pump housing is externalized and connected to a modular cable that is attached to the external system controller and a power supply. With the exception of the HeartMate 3 controller, other external components are the same as the precursor HeartMate II system. The pump receives power from a power module or mobile power unit for AC wall power, or from a pair of 14-V lithium-ion batteries. The pump operates at a rotor speed in the range of 3000–9000 r.p.m. and the maximum flow rate is 10 l/min. The LVAD operates continuously in an artificial pulse mode, where the rotor rapidly changes speed every 2 s to generate pulsatile flow from the pump.

In this trial, the device is implanted through a usual sternotomy approach with standard cardiopulmonary bypass techniques. An apical cuff for securing the pump to the heart is sewn to the epicardium near the apex. Surgeons have the option to core the opening into the left ventricle before placement of the apical cuff (core then sew) or to place the cuff and then core the myocardium (sew then cut). The myocardial core into the left ventricle is created using the standard HeartMate circular knife. The outflow graft is anastomosed end-to-side to the ascending aorta, and the pump is positioned near the apex of the left ventricle. The inflow conduit is inserted into the apical cuff and then secured in place by engaging the slide-lock mechanism on the pump. The pump power cable (driveline) is tunnelled through the abdominal wall to a selected skin site that is opened with a circular knife of the same diameter as the cable. Depending on surgeon preference, the power cable is either looped or fixated with suture internally before it is externalized. The power cable is externalized so that the interface between the subcutaneous tissue and the skin is the silicone portion of the cable. The power cable is then attached to a modular cable that is connected to the system controller. The pump is de-aired through the outflow graft, cardiopulmonary bypass flow is decreased and the pump is turned on at a low speed. The continuous speed setting is assessed with echocardiography and haemodynamic measurements before leaving the operating room.

Postoperative anticoagulation guidelines include intravenous heparin to reach a partial thromboplastin time (PTT) of 45–65 s (1.2–1.8 times control) after chest tube drainage is <50 ml/h for 3 h. On postoperative days 2 and 3, heparin is increased until the PTT is 55–65 s. Once the patient is able to take oral medications, aspirin (81–100 mg daily) and warfarin (or other vitamin K antagonist) are given during the remainder of support, with a target international normalized ratio (INR) of 2.0–3.0.

Data analysis

Operative data, pump performance, survival, adverse event rates, and changes in quality of life and NYHA class after 30 days of LVAD support were analysed. Operative data included concurrent procedures, time of operation, cardiopulmonary bypass time, blood product usage and reoperations. Adverse events occurring within the first 30 days after implant included bleeding, thrombosis, haemolysis, stroke, device-related infection and pump replacement or failure. The INTERMACS registry adverse event definitions (protocol version 3.0, www.intermacs.org) were used. Continuous data are presented as the number of subjects, mean with standard deviation or median and the range where appropriate. Categorical data are reported as frequencies and percentages. Adverse event data are presented as the number and percentage of patients with the event. Change in NYHA class at 30 days when compared with baseline was tested using the McNemar test, whereas the 6-min walk test and quality of life (EQ-5D-5L Visual Analog Scale), from baseline to the 30-day time point, were compared using a paired *t*-test. The 6-min walk test assesses functional status by measuring the maximal distance walked in 6 min. The patient's quality of life was measured by the self-administered EuroQoL-5D-5L questionnaire. Statistical significant status was determined when the *P* value was <0.05. Statistical analysis was performed with SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Fifty patients were enrolled in the study and implanted with the HeartMate 3 between 25 June 2014 and 27 November 2014. All patients were followed to 30 days or outcome. Demographics and pre-implant data are given in Table 1. The majority of patients were men (90%), with 26 (52%) assessed as NYHA Class IIIB and 24 (48%) as Class IV. The indication for LVAD support was divided between BTT (54%) and DT (46%). The majority of patients were determined to be INTERMACS profiles 2–4 (88%) and no patients were from Profile 1 or 7. At the time of implant, no patients were receiving mechanical circulatory support (i.e. intra-aortic balloon pump support), but all were receiving one or more cardiac medications (Table 2). Most patients had one or more cardiovascular

Table 1: Demographics and pre-implant data

Age (years)	58.9 ± 13.5
Male	45 (90)
BSA (m^2)	2.0 ± 0.2
BMI (kg/m^2)	27 ± 4.3
Indication	
BTT	27 (54%)
DT	23 (46%)
INTERMACS profile	
Profile 2	5 (10%)
Profile 3	21 (42%)
Profile 4	18 (36%)
Profile 5	4 (8%)
Profile 6	2 (4%)
Cardiac index ($l/min/m^2$)	1.8 ± 0.5
Left ventricular ejection fraction (%)	19.0 ± 3.7
Central venous pressure (mmHg)	9.9 ± 5.6
Arterial blood pressure (mmHg)	
Systolic	104.7 ± 11.4
Diastolic	64.7 ± 9.4
Mean	78.9 ± 9.4
Pulmonary artery pressure (mmHg)	
Systolic	50.8 ± 18.6
Diastolic	23.6 ± 9.3
Mean	33.7 ± 12.1
Pulmonary capillary pressure (mmHg)	22.4 ± 8.7
Haemoglobin (g/dl)	13.2 ± 2.0
White blood cell count ($\times 10^3/\mu l$)	7.4 ± 2.2
Plasma free haemoglobin (mg/dl)	11.7 ± 15.6
INR	1.3 ± 0.6
Prothrombin time (s)	24.8 ± 28.3
PTT (s)	40.3 ± 11.2
Total cholesterol (mmol/l)	4.5 ± 1.6
Lactic dehydrogenase (U/l)	230 ± 62

BMI: body mass index; BSA: body surface area; INR: international normalized ratio.

Table 2: Pre-implant medications

Medication	*n* (%)
ACE inhibitor	21 (42%)
Angiotensin II antagonist	9 (18%)
β-Blocker	36 (72%)
Anticoagulant/antiplatelet	46 (92%)
Diuretic	49 (98%)
Inotrope	29 (58%)
One inotrope	21 (42%)
Two inotropes	8 (16%)
Antiarrhythmic	22 (44%)

ACE: angiotensin-converting enzyme.

Table 3: Preoperative risk factors

Risk factor	*n* (%)
Valve disease	41 (82%)
Pacemaker/defibrillator	40 (80%)
Hypertension	33 (66%)
Renal insufficiency	19 (38%)
Diabetes	12 (24%)
Prior sternotomy	10 (20%)
Prior cardiac arrest	7 (14%)
Cancer	4 (8%)
Left ventricular aneurysm	4 (8%)
TIA	4 (8%)
Stroke	2 (4%)
Severe COPD	3 (6%)
Peripheral vascular disease	3 (6%)

COPD: chronic obstructive pulmonary disease; TIA: transient ischaemic attack.

risk factors—the most frequent were valvular disease (82%), pacemaker or defibrillator (80%) and hypertension (66%) (Table 3). Ten patients (20%) had prior sternotomy.

Operative data

The core-then-sew apical cuff attachment method was used in 70% of the implant procedures. The slide-lock mechanism, which is unique to the HeartMate 3 device, was easily engaged in 96% of the cases. In two cases, there was difficulty in engaging the mechanism, and in one case, there was a report of a blood leak from the apical cuff. The driveline was exited almost equally as often to the right side versus left side of the abdomen (48 vs 52%, respectively) and in the majority of cases (96%), the driveline was externalized with a silicone-to-skin interface. The median operative and cardiopulmonary bypass times were 200 (95–585) and 84 (47–250) min, respectively. Intraoperatively, patients required transfusion with packed red blood cells (3.6 ± 2.3 units), fresh frozen plasma (6.5 ± 5 units) and platelets (2 ± 1 units). Ten (20%) patients did not require any blood product transfusion during implant. Twenty-one patients (42%) had concurrent cardiac surgical procedures performed during their implant surgery; 9 patients (18%) had more than one procedure (Table 4). The median

Table 4: Concurrent cardiac procedures

Procedure	*n* (%)
PFO closure	5 (10%)
RVAD	2 (4%)
Valve procedures	17 (34%)
Aortic replacement	5 (10%)
Aortic repair	1 (2%)
Mitral repair	6 (12%)
Tricuspid repair	12 (24%)
Other procedure	5 (10%)
Left atrial appendage occlusion	4 (8%)
CRT-D generator exchange	1 (2%)

CRT-D: cardiac resynchronization therapy defibrillator; PFO: patent foramen ovale; RVAD: right ventricular assist device.

operative and cardiopulmonary times for patients undergoing concurrent procedures (*n* = 21) were 279 (174–585) and 110 (76–250) min, respectively, compared with 151 (95–320) and 65 (47–130) min for the patients without concurrent procedures (*n* = 29). Two patients required right ventricular assist device (RVAD) implantation due to failure to wean from cardiopulmonary bypass. In one case, right-sided extracorporeal membrane oxygenation (ECMO) support was used with subsequent removal of the oxygenator after 30 days and continued RVAD support for a total of 103 days. In the other case, a CentriMag RVAD (Thoratec Corporation) supported the patient for 50 days when heart transplant was performed.

Outcomes

At the 30-day follow-up, 49 of the 50 patients remained alive on HeartMate 3 support—a survival rate of 98%. The median intensive care time was 6 days (range: 1–47 days) and the total hospital stay was 28 days (range: 14–116). One patient experienced a stroke on the first postoperative day and then died of cardiac arrest on Day 19.

Pump performance

The mean cardiac index before implant was 1.82 ± 0.46 l/min/m^2; after LVAD support was initiated, the pump flow index was 2.20 ± 0.33 l/min/m^2 ($P < 0.0001$). At 30 days, the mean pump flow was 4.3 ± 0.6 l/min at 5439 ± 303 r.p.m. There were no device failures, thrombosis or exchanges during the 30-day follow-up.

Reoperations

All reoperations, whether device-related or patient-related, were captured in the study. Within the first 30 days post implantation, 13 patients required 20 reoperations. Eight reoperations were due to re-explorations due to bleeding, and other reoperations included delayed chest closure (2), respiratory failure (2), right heart failure (2), wound dehiscence (1), infection (1), lower extremity femoral bypass surgery (1), ECMO cannulation (1), pericardial fluid collection (1) and re-exploration (1). Both reoperations for right heart failure occurred in one of the patients with an RVAD; on

Table 5: Adverse events: Days 0–30

Adverse event	No. of patients	% of patients	No. of events
Bleeding	15	30	19
Requiring surgery	6	12	6
Requiring transfusion	9	18	13
Arrhythmias	14	28	14
Pericardial fluid	1	2	1
Hepatic dysfunction	1	2	1
Hypertension	1	2	1
Any infection	10	20	14
Localized non-device infection	8	16	9
Sepsis	4	8	4
Driveline	1	2	1
Stroke	2	4	2
Neurological dysfunction	2	4	2
Psychiatric episode	1	2	1
Renal dysfunction	5	10	5
Respiratory failure	7	14	7
Right heart failure	4	8	4
Requiring RVAD	2	4	2
Wound dehiscence	2	4	2
Other events	18	36	35

RVAD: right ventricular assist device.

postoperative day 7, the patient underwent re-exploration of the pericardial space and on Day 9 sternal closure. The reoperations for respiratory failure were both tracheostomies in two patients, both on postoperative day 25.

Adverse events

The most common adverse events observed were bleeding (15, 30%), arrhythmias (14, 28%) and infection (10, 20%) (Table 5). Six patients (12%) required reoperations for bleeding and 9 patients (18%) only required transfusion of red blood cells (per bleeding definition ≥4 units within the first 7 days and ≥1 unit after 7 days). Sepsis (positive blood culture and/or hypotension) was the most common infection (4, 8%), and 1 patient (2%) developed a driveline infection. There were two stroke events, with one occurring on the first postoperative day following difficulty in engaging the pump with the apical cuff. This patient's condition deteriorated and he subsequently died of cardiac arrest on postoperative day 19. The second stroke event occurred on postoperative day 23 following anaphylaxis from contrast media for computed tomography. Other neurological events included a seizure and a transient ischaemic attack. There were no reported events of haemolysis, pump thrombosis or pump failure. At 1 week and 1 month of support, the mean plasma free haemoglobin was 9.6 ± 11.6 and 8.9 ± 11.8, respectively, and the lactic dehydrogenase was 376.1 ± 120 and 277.9 ± 90.8, respectively.

Functional status and quality of life

Prior to implant, all patients had an NYHA classification of IIIB or IV, and already at 30 days, 64% of patients were classified as I or II ($P < 0.0001$), with 7 (16%) remaining as IIIB or IV. For patients who were able to complete the 6-min test before implant and at 30 days ($n = 37$), the mean change in the distance was 39.8 m ($P = 0.11$). Quality-of-life assessment by the visual analog score for patients with paired measurements also showed a modest improvement of 5.65 ($P = 0.11$) only 30 days post implantation.

DISCUSSION

In this initial clinical study evaluating the HeartMate 3 LVAS, the 30-day operative survival rate was 98% and the rate of complications was low. Patients had advanced-stage heart failure and were a mix of transplant candidates and non-transplant candidates, a population with high expected morbidity and mortality. These initial results showed lower event rates for bleeding, infection and stroke than in prior clinical trials [1, 3, 5, 18–22]. The majority of patients demonstrated improved physical status already at 30 days post implantation. The LVAS performed as intended and there were no failures or exchanges of the device.

The HeartMate 3 is designed for enhanced haemocompatibility and is implanted with less surgery compared with the HeartMate II (St. Jude Medical Inc.) to help reduce the incidence of haemorrhagic, thrombotic and infectious adverse events. The small size of the device allows for intrapericardial placement, thereby eliminating the need for an abdominal pocket and extensive tissue dissection, which decreases operative time and potential bleeding sites. Although not performed in this study, minimally invasive implantation avoiding sternotomy will be feasible with this device. The rotor of the HeartMate 3 is fully magnetically levitated (Full MagLev™) and has wide blood-flow gaps that allow blood to flow through the device with less shear force. The top and bottom blood-flow gaps are 1.0 mm, and the gaps on the side are 0.5 mm, which are 10–20 times greater than in other devices (Fig. 2). This bearing-less rotor design eliminates friction and the potential for wear of the moving component. The absence of a mechanical bearing should exclude the possibility of thrombus formation as a result of heat generation in mechanical bearings. There were no cases of haemolysis or pump thrombosis during the follow-up time in this study. Full magnetic levitation of the rotor eliminates heat from friction and wear of the moving component. Internal blood-contacting surfaces of the HeartMate 3 are textured with titanium microspheres to attract circulating cells that adhere to the surface, creating a biological tissue layer. Early LVAD studies with HeartMate devices confirmed that a neointimal lining in the pump helps to reduce thrombosis and anticoagulation requirements [23, 24]. The potential advantages of the HeartMate 3 over the HeartMate II are less surgical and gastrointestinal bleeding, fewer thrombotic events and fewer secondary adverse events, such as infection.

Reported rates for bleeding events that require reoperation within 30 days of LVAD implant are in the range of 13–30% [5, 18, 22, 25], whereas 12% of patients in this study required reoperation. Nine patients (18%) required transfusion of red blood cells, which, per the bleeding definition, after 7 days included any transfusion of one or more units. Longer follow-up of infection rates will be required to determine device-related events over time. One stroke event could be attributed to a learning curve with the apical cuff and slide-lock engagement mechanism as the stroke occurred the day after implant during which there was difficulty in engaging the pump with the apical cuff. After this event, the apical cuff and pump slide-lock mechanism engagement was re-reviewed with all of the study investigators and no additional engagement issues were seen. The second stroke was unrelated to

the device and due to a secondary cause—anaphylaxis from contrast media.

The number of patients who converted from NYHA Class IIIB or IV to Class I or II was already significant after 30 days. Despite the fact that the follow-up time was short and VAD patients typically need lengthy rehabilitation times due to long-standing heart failure, the 6-min walk test and visual analog score showed an improving trend already at 30 days post implantation. Longer observation times will be necessary to demonstrate an overall improvement in physical status and quality of life.

The axial flow HeartMate II and centrifugal-flow HeartMate 3 both provide left ventricular unloading and arterial blood flow in proportion to the difference between preload and afterload, or left ventricular and aortic pressure, respectively. There are differences in how flow through each device responds to changing preload and afterload. In the low-flow region about <2 l/min, the HeartMate 3 is more responsive than the HeartMate II to changes in preload and afterload; for flow between ∼2 and ∼5 l/min, the pumps have a similar response; and in the high-flow region about >5 l/min, the HeartMate 3 is less responsive than the HeartMate II. Under conditions of normal preload and afterload, with mean flow rate >4 l/min, the HeartMate 3 typically operates in the range of 5000–6000 r.p.m. and the HeartMate II in the range of 9000–11 000 r.p.m. In this study, the mean pump flow rate was 4.3 ± 0.6 l/min at 5439 ± 303 r.p.m. at 30 days after implant, which provided adequate perfusion as evidenced by the improved physical status for most patients and an excellent survival rate for the group. The set speed of the HeartMate 3 is determined by the centre's team and varies depending on patient conditions. General guidelines for setting the pump speed are to initially maintain a left atrial pressure >10 mmHg and a pump flow rate >3.0 l/min. After stabilization, with echocardiographic guidance, the ventricular septum should be in a midline position with the aortic valve opening approximately once every third heart beat and the left ventricular diastolic dimension near the normal range.

This study was limited by the absence of a control group and it was not randomized. Variations in surgical technique and in perioperative management may vary among the participating centres and cannot be controlled. The study protocol offers guidelines for care, but these are individualized based on patient-specific requirements. This report was on the first 30 days of the HeartMate 3 experience; however, the patients continue to be followed until a final outcome or until reaching 24 months of LVAD support. Comparison of these results to other similar studies should be made carefully, as this study includes a mix of both BTT and DT patients.

CONCLUSION

This early study describing the operative experience and outcomes following implantation of the HeartMate 3 demonstrates an excellent survival rate, with low adverse event rates. Follow-up for this Conformité Européenne mark study continues while studies are ongoing to assess minimally invasive techniques and a randomized controlled trial is in progress in the USA.

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APPENDIX. CONFERENCE DISCUSSION

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Dr A. Simon *(Harefield, UK)*: I have looked at the paper, obviously, and my first question would be how do you explain 34% concomitant valve procedures? I mean, you don't list aortic valve problems as a risk factor or anything, but in 10% aortic valve procedures and the mitral and the tricuspid, is that necessary with this pump or is it a change in your religion in the operating theater?

Dr Zimpfer: That's an excellent question, and that has to be clarified. The decision to proceed or to do concomitant procedures, of course, is done prior to ventricular assist device implantation most of the time in the operating room with the TE in place.

I think what we learned over the last years, and that probably reflects that, is that we are much more aggressive with addressing especially the aortic valves as we know that patients will be on the device for a long time, and we know the problem of aortic valve insufficiency development after ventricular assist device implantation. I think that reflects an overall shift of approach towards this cohort and not a specific trial issue.

Dr Simon: In your paper, you mentioned a significant number of other complications, I think 30%, which were not in your table here. Would you elaborate on that a bit, what that includes?

Dr Zimpfer: That's also, yeah, a good question. As you know, all the CE Mark trials for assist devices, we are basically looking for intermixed predefined complications, and those complications, of course, are explained in the presentation.

Other complications are complications that typically are seen in patients that undergo major cardiac surgery. Its pleural effusion, prolonged ventilation, need for reintubation. So that has not been displayed here because that's not primarily what we are looking for. That's something you see in this cohort because the patients are sick, but that was not the primary focus of the trial, and that's why it's summarized on the other.

Dr Simon: So finally, now we know it works. Why do we need it and what's new about it? What's the upside of implanting that pump?

Dr Zimpfer: Of course, also the six-month data that's still an early experience nowadays. But what we all learned is that mortality is not the only thing we have to look at. We also have to look at strokes. We have to look at GI bleeds, and given the fact that the overall judgment for an assist device, now, this is not only survival but very often event-free survival, we have to do everything possible to develop devices that have low morbidity. Also this device, due to its design, might reduce the incidence of aortic valve insufficiency with this artificial pole feature. It might reduce the incidence of GI bleedings, and it might overall improve the hemocompatibility of devices.

Dr Simon: So to put you on the spot, in Vienna you're now going to stop implanting HeartMate® 2? You don't have to answer that question. It's a bit unfair.

Dr Zimpfer: I can answer this question pretty much straightforward. As soon as we have the CE mark, we will change that. Yeah, we will stop implanting HeartMate® 2 and proceed to HeartMate® 3.

Dr Simon: Okay. Thank you.

Dr W. Awad *(London, UK)*: You had four patients who had occlusion of left atrial appendage. Is this part of your routine again as part of mitral valve surgery or was this as a means of preventing stroke? Also, in your patients who did have stroke, did any of them have this left atrial appendage occlusion?

Dr Zimpfer: That's a very good question. So the decision to proceed for any concomitant procedures was left to the surgeons, so the protocol has no guidelines for additional procedures. What a lot of people nowadays do, they close or amputate the left auricle in order to reduce the stroke rate. And as far as I'm aware, but it's not in the manuscript, the patients that had stroke, one of the strokes was clearly a problem upon connecting the pump to the ventricle, and the other one was after a contrast medium application. So those two strokes are probably not preventable by closing the left auricle.

Dr F. Wagner *(Hamburg, Germany)*: I just noticed that you had basically one-third of your patients with a major bleeding. The question is, is this bleeding, let's say, something that is reported to a very strict protocol of necessity to report bleeding, or is that something that you'll see in your everyday surgery anyway because that to me seems a bit high.

Dr S. Tsui *(Cambridge, UK)*: I noticed the reopening was 10%. So reopening rate was only 10%, and the 30% is transfusion.

Dr Zimpfer: So I think we have to look at that again because that's, of course, an extremely important question. If you look at the definition of bleeding, it's very strict. So if you give more than one red blood cell concentrate after seven days of the operation, that's already a bleeding event.

That, of course, explains the quite high rate of bleeding, but that's what you expect for such a trial because those patients need blood cells sometimes because they are anemic and so on. And the reopening rate was much lower than the overall bleeding rate.