Heart failure is a major cause of death throughout the world, and is associated with a high rate of morbidity and a lower quality of life than that of patients suffering from any other chronic disease. More than 22 million people suffer from heart failure worldwide. Approximately 14 million people in Europe currently suffer from heart failure, and this number is forecast to increase to 30 million by the year 2020 [1].

Heart transplant remains the ‘gold standard’ or preferred treatment option for patients with advanced heart failure. However, the number of transplant candidates far exceeds the donor pool. According to the International Society for Heart and Lung Transplantation Registry Report (2008), the number of heart transplant procedures continues to decrease worldwide, and approximately 3000 transplants were reported in 2006, a 35% reduction compared with the peak number of 4429 in 1994 [4]. Currently, 44% of listed patients receive intravenous inotropes and 23% are supported by left ventricular support devices while waiting for heart transplant, showing a significant increase of necessity of pretransplant support compared with several years ago. Furthermore, many heart failure patients are not eligible for heart transplantation owing to age and other health-limiting factors. Approximately 50% of patients who need a transplant are disqualified owing to age. In addition, opportunistic infection, rejection, malignancy and graft coronary artery disease continue to be limitations of this treatment [5]. These limitations have generated continued interest in the development of a left ventricular assist system (LVAS) that can help patients survive until donor hearts become available, or as an alternative to heart transplantation.
The first generation of implantable LVAS, using pulsatile pump technology, has become an established therapeutic option for advanced heart failure patients. However, there have been technological limitations, which have surfaced as longer term experience was gained [6–11]. These include a high incidence of thromboembolic complications, infection, mechanical failures associated with moving parts and the large size of both the implantable pump and percutaneous cable. In the Randomized Evaluations of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which involved a pulsatile LVAS (HeartMate® VE), sepsis and device failure were the most common causes of death [2]. A total of 29 device replacements were performed in 23 patients. The major causes of device replacement were device failure (62%) and sepsis (19%). Freedom from device replacement was 87% at 1 year and 37% at 2 years [12,13]. Despite the improvement of survival and quality of life, more reliable and safer devices must be realized for widespread LVAS use.

A smaller rotary blood pump emerged as a possible alternative to a large pulsatile pump in the 1990s, eliminating the need for prosthetic valves and the external venting required for implantable pulsatile pumps. The advantages of rotary blood pumps, compared with pulsatile pumps, include small pump size, less invasive surgery and lower infection rate, small percutaneous cable, lower infection rate, low noise, better quality of life, single moving part, extended mechanical durability and longevity, and a wide range of flow capacity, despite a small pump size.

The rotary blood pumps are categorized into either second- or third-generation LVAS based on their technological aspects. Second-generation devices are based on an axial flow pump technology with a blood-immersed bearing or a pivotal bearing [14–19].

The technological advancements that define the third-generation LVAS was the elimination of all mechanical contacts between the impeller and the drive mechanism. This was accomplished by employing either an active magnetic bearing or hydrodynamic bearing technology to levitate the impeller. Magnetic or hydrodynamic levitation enables friction-free rotation of an impeller. The key advantages of a friction-free drive are reduced hemolysis, minimized thrombogenesis and the increased mechanical durability necessary for long-term mechanical circulatory support. Several manufacturers are in various stages of development and clinical application of third-generation rotary blood pumps [20–24].

**DuraHeart™ LVAS**

The DuraHeart™ LVAS (Terumo Heart Inc., MI, USA) is the world’s first third-generation implantable LVAS to obtain market approval (CE-mark). It combines a centrifugal pump and active magnetic levitation designed for long-term circulatory support [25–29]. The DuraHeart LVAS is comprised of three principal implantable components: a blood pump and an inflow and an outflow conduit. The pump connects to the external components with a percutaneous driveline. The primary external components are an externally worn controller and two battery packs (Figure 1A). The DuraHeart pump is an implantable centrifugal pump made of titanium and stainless steel (Figure 1B). The impeller is rotated by a magnetic coupling between the impeller and the motor, and is levitated magnetically by the three electromagnets. The electric current of each electromagnet is controlled by using three position sensors to precisely control the impeller position. DuraHeart is the only pump available that utilizes three-degrees-of-freedom active control of the impeller’s magnetic levitation. The large stable gaps between the impeller (250 m on each side) and the blood chamber walls, in combination with magnetic levitation and centrifugal pump design, translate into reduced shear stress and a corresponding reduction in hemolysis. The large stable gap also provides for improved washout, preventing thrombus formation inside the pump chamber. The pump is housed in a titanium enclosure that hermetically seals the electrical components against any blood or tissue contact. The DuraHeart pump has a diameter of 73 mm, thickness of 45 mm and weighs approximately 540 g. The displacement volume is 196 ml, which is 30–50% smaller than the first-generation pulsatile pumps. The pump is placed in the preperitoneal pocket. The DuraHeart pump is capable of providing 8 l/min of blood flow at 120 mmHg of head pressure with no residual left ventricular function, and is able to generate a wide pressure range from 50 mmHg at 1200 rpm to 180 mmHg at 2400 rpm, a comparable capacity to pulsatile pumps.

The blood-contacting surfaces of the pump and the inlet conduit and outflow conduit connector are made of titanium; they are entirely modified with a stable covalently bound heparin to enhance blood compatibility and reduce the risk of thrombus formation in low-flow areas.

An added feature of the DuraHeart LVAS is the integrated flow-estimation algorithm based on the very stable motor current required to maintain the set rotational speed and viscosity of the blood (as estimated from the measured hematocrit). The DuraHeart LVAS was also designed with additional safety features, such as a hydrodynamic bearing support for back-up in case of failure of magnetic levitation (single-fault recovery mode).

The DuraHeart LVAS received CE-mark in February 2007, and is commercially available in Europe. The pivotal US trial for bridge to transplant (BTT), a multicenter, prospective, nonrandomized study involving 140 patients in up to 40 centers, was initiated in July 2008. A BTT trial in Japan began in October 2008 and enrollment has been completed for Japanese premarket approval.

In May 2009, the one-hundredth patient worldwide was implanted with the DuraHeart LVAS at the Heart and Diabetes Center, North Rhine-Westphalia (NRW), Germany. This patient was the 82nd patient in Europe and the 62nd patient in our institution. The following section reviews the clinical outcome of 82 patients implanted with the DuraHeart LVAS in Europe.

**European clinical experience of the DuraHeart LVAS**

**Methods**

**Study overview: CE-mark study & postmarket study**

The CE-mark study was conducted at four centers in Germany, Austria and France between 15 January 2004 and 7 March 2007 and was a prospective, multicenter, nonrandomized trial designed to characterize the safety and performance of the DuraHeart LVAS in patients eligible for heart transplantation. The primary end point was to evaluate survival of patients either to cardiac transplantation or at 13 weeks (91 days) of device support.
The study protocol and patient informed consent were approved by the Ethics Committee at each investigational site and written informed consent was obtained from all patients. A Clinical Event Committee comprised of study investigators and independent physicians reviewed and adjudicated all adverse events and deaths. The study was conducted in compliance with the Declaration of Helsinki (Tokyo, October 2004), ISO 14155: Parts 1 and 2 (2003) and International Conference on Harmonisation Guideline for Good Clinical Practice.

After CE-mark approval, the postmarket study was initiated in accordance with Medical Devices 2.12.2 (2004), which includes 50 subjects from August 2007.

Study patients
Eligible patients for the CE-mark study were adults with end-stage left ventricular failure at imminent risk of dying. Patients were receiving maximal conventional therapy but remained unresponsive. All patients had to be eligible for cardiac transplantation and fulfilled the inclusion and exclusion criteria. The inclusion criteria were the New York Heart Association (NYHA) functional class IV; a body surface area of at least 1.1 m²; a cardiac index of 2.2 1/min/m² or less, with either a systolic blood pressure of 80 mmHg or less or a pulmonary capillary pressure of 18 mmHg or greater; and patients were receiving optimal medical treatment, including inotropes and/or intra-aortic balloon pump. The eligibility criteria for the postmarket study were similar to those for the CE-mark study, except that there were no hemodynamic criteria in the postmarket study. A complete list of inclusion and exclusion criteria, details of study protocol and adverse event definitions were previously reported [29].

Implant & explant procedures
Implantation and explantation of the DuraHeart LVAS were performed according to the DuraHeart ‘Instructions of Use’, which has been previously reported [29].

Anticoagulation
Postoperative anticoagulation was recommended in the clinical protocol and the DuraHeart ‘Instructions of Use’ [29]. Our institution implemented less intensive anticoagulation with warfarin to maintain an international normalized ratio of 2.0–2.5.

Statistical analysis
Survival analysis for patients continuing on device support was performed using the Kaplan–Meier method, with censoring for heart transplant or device explants. A log-rank statistic was used for comparison. Continuous variables were presented as mean ± standard deviation, median and range, where appropriate. For comparison, a paired t-test or a Wilcoxon rank sum test was used for continuous variables and Fisher’s exact test was used for binary ones. The level of statistical significance was set at p less than 0.05. Adverse events were presented as the percentage of patients who had events and as event rate per patient-year. The Kaplan–Meier method was also used for analysis of freedom from device replacement.

Adverse events were analyzed for CE-mark study patients (n = 33) for extended follow-up periods of at least 15 months at the time of database closure on 15 June 2008, which had been adjudicated by the Clinical Event Committee. The data included the number and percentage of patients with the event, the number of events and event rates per patient-year.
For the postmarket study, only survival, freedom from device replacement, discharge rate and partial preimplant patient characteristics analyses were conducted owing to a limited availability of the data, which had been monitored and adjudicated.

Results

Patients
A total of 82 patients were implanted with the DuraHeart LVAS between January 2004 and May 2009 in Europe. Of those, 33 patients who met the inclusion and exclusion criteria were enrolled in the approval CE-mark study, and 49 patients were implanted after CE-mark. Of the 85 patients, 62 (76%) were enrolled at the Heart and Diabetes Center-NRW, 14 were enrolled at the German Heart Institute Berlin, five were enrolled at the University of Vienna, Austria, and one was enrolled at Pitie Salpetriere Hospital, Paris, France. The preimplant patient characteristics of both groups are shown in Table 1. The majority of patients were rated as NYHA functional class IV. The mean age was 57 ± 11 years (range: 29–74; median: 59) with a mean body surface area of 1.9 ± 0.2 m² (range 1.4−2.4 m²; median: 1.9). In overall groups, 38 patients (46%) were older than 60 years, 22 (27%) were older than 65 years and six (7%) were older than 70 years. Seven (9%) were females and 52% of patients had ischemic etiology for heart failure. There was no significant difference in preimplant characteristics between the two groups in the majority of parameters, including renal and hepatic functions, and levels of intravenous inotropic or mechanical supports prior to implant surgery. Significant differences between the two groups were observed in NYHA classification, cardiac index, pulmonary vascular resistance and serum sodium, which may suggest that the postmarket patients were relatively less ill compared with the trial patients, although other parameters that showed significant differences (lower systemic pressure and hematocrit in postmarket group) did not support this hypothesis. The majority of the patients received intravenous inotropic support, 26% of patients were supported by intra-aortic balloon pumping and 10% were using mechanical ventilation prior to LVAS implantation. A total of 53% of the patients had an implantable cardioverter-defibrillator, and 37% had a biventricular pacemaker.

Outcomes
Patient outcomes were analyzed for 82 patients as of August 2009, when all of the patients either completed the study end point or had at least 13 weeks of follow-up with ongoing device support. At the time of data analysis, 72 patients (88%) completed the 6 months follow-up or study end point, and 68 patients (83%) completed the 1-year follow-up or study end point. The patients were censored at the time of heart transplantation and device explantation owing to recovery. The patients who were replaced with a second DuraHeart device and kept alive were included as survivors in the survival analysis, whereas the patient who was replaced with a different type of device was withdrawn from the study.

A total of 23 patients (28%) received heart transplantation, with a median time to heart transplantation of 157 days (range: 43–497 days). The majority of the patients (87%) received heart transplantation within 1 year of device support, while fewer patients (13%) received transplantation after 1 year. The median age of the patients who received heart transplantation was 52 years (range: 29–68), while the median age of the patients with ongoing device support was 60 years (range: 30–73), with 12 patients (31%) over 65 years and four patients (11%) over 70 years (p = 0.009).

In total, 20 (24%) patients died on support with a median time to death of 167 days (range: 17–1066 days). The majority of the patient deaths (70%) occurred within 1 year of support. Two patients recovered and the devices were removed at 283 and 344 days of support. The median duration of device support was 261 days (range: 17–1494 days), with a cumulative duration of 78 patient-years.

At 1 year, only 20 patients (29%) received heart transplantation, while 31 patients (46%) remained on device support with median support duration of 1.5 years; 14 patients (21%) died, two patients (3%) recovered and underwent device explantation and one patient (2%) was withdrawn from the study after the original device was replaced with another type of device (Figure 2). As of August 2009, 36 patients (45%) were alive using device support, with a median duration of 442 days, with a longest duration of 4.1 years.

Overall Kaplan–Meier survival for the patients who continued on device support was 90% (95% CI: 81–95) at 13 weeks end point, 85% (95% CI: 75–92) at 6 months, 79% (95% CI: 67–87) at 1 year and 58% (95% CI: 37–74) at 2 years (Figure 3). Overall survival for 62 patients (76% of all patients) implanted at the Heart and Diabetes Center-NRW showed a better survival outcome of 85% (95% CI: 71–92) at 12 months and 69% (95% CI: 48–84) at 24 months than the other centers (log-rank p = 0.05 at 12 months; p = 0.0365 at 24 months) (Figure 3).

The average pump flow rate was maintained over 5 l/min and the average pump index was over 2.7 l/min/m² at an average motor speed of 1700 rpm throughout the support duration. Table 2 shows average values for end-organ functions measured by creatinine, blood urea nitrogen, total bilirubin, glatamic pyruvic transaminase, glutamic oxaloacetic transaminase, lactate dehydrogenase and hemolysis parameters at baseline, 3 months and 6 months. By approximately 2 weeks postimplant, the average values for renal and hepatic functions decreased to nearly normal ranges for the duration of the study period, except that the serum creatinine value did not change significantly. The lactate dehydrogenase value increased after implantation, then rapidly decreased during the first postoperative week and leveled off near the upper normal limit for the duration of the study period. Average plasma-free hemoglobin values remained within normal ranges throughout the study period. These data suggest that clinically significant hemolysis did not occur as a result of implantation of the DuraHeart LVAS. Anticoagulation with warfarin maintained an average international normalized ratio of 2.4 ± 0.9 (median: 2.5) throughout the implant periods.

In total, 66 patients (80%; 86% of the patients who survived >30 days) were discharged from the hospital with the LVAS, with a median hospital stay after implantation of 36 days (range: 20–147 days). The median time of out of hospital was 260 days (range: 29–410).
Causes of death
Of the 20 deaths, 13 were adjudicated by the CEC. Of the 13 adjudicated deaths, the primary causes of death were cerebrovascular accident (CVA) in six patients (four hemorrhagic; two ischemic) and sepsis in three patients. Other causes included nontraumatic subdural hematoma, accidental fall, acute myocardial infarction and unknown. Owing to a high incidence of fatal intracerebral bleeding and other bleeding complications observed in the initial 11 patients (three hemorrhagic strokes and one subdural hematoma), the anticoagulation and antiplatelet regimen was reviewed and the investigators agreed to follow a less intensive anticoagulation/antiplatelet regimen recommended in the protocol for the remainder of the study.

Adverse events
All adverse events for the 33 CE-mark trial patients were monitored and adjudicated by the CEC as of 15 June 2008 after extended follow-up periods with a median duration of 201 days.
The highest bleeding. Three events of sudden temporary flow interruptions occurred in eight patients (24%). Four events (two failure and the patient later died of multiorgan failure. Bleeding resolved within a few days. One patient (3%) had chronic renal failure. These patients were observed 11 times in ten patients (30%), and one patient (3%) required a right ventricular assist device with the Thoratec PVAD™ (Thoratec Corp., CA, USA).

A total of 11 neurological events occurred in ten patients (33%), six were CVA and five were transient ischemic attacks. Of these six CVAs (four hemorrhagic and two ischemic), five were determined to be the cause of death. One intracerebral bleeding that followed an accidental fall was resolved without permanent neurological deficit. In the initial 11 patients, five CVAs were reported (1.05/patient-year), whereas only one CVA was reported in the last 22 patients (0.04/patient-year) after implementing less intensive anticoagulation and antiplatelet therapy. Five CVAs occurred within the first 3 months and only one hemorrhagic CVA occurred at 549 days postimplant. Perioperatively four patients developed acute renal dysfunction (12%); however, all events resolved within a few days. One patient (3%) had chronic renal failure and the patient later died of multiorgan failure. Bleeding events occurred 11 times in eight patients (24%). Four events (two cardiac tamponades and two pump pocket bleedings) required surgical interventions. Three patients (9%) had gastrointestinal (GI) bleeding. Three events of sudden temporary flow interruption occurred in two patients (6%). In each case, the pump was subsequently restarted; however, the decision was made at the site to electively replace the pump at 40 and 108 days after implantation. The patients did not experience any adverse clinical consequence related to the temporary flow interruption or pump replacement. The returned pumps were fully functional without any sign of mechanical failure upon engineering analyses. The root cause of the temporary flow interruption was identified as the distortion of the motor back electromotive force (EMF) waveform that could result in incorrect motor winding commutation timing by the controller. This commutation error on a rare occasion did lead to stopping and restarting of the motor rotation. Since such a distortion is caused by combination of the rotor magnet positioning and electromagnetic noise, manufacturing process improvement measures were implemented to assure the back EMF motor waveform was not distorted. Specifically, the tolerances of the rotor magnet position were tightened and a 100% motor back EMF test was introduced to ensure the absence of any distortion in the back EMF waveform. The clinical experience to date has shown no pump malfunctions for the patients with improved motors. The freedom from pump replacement for all 82 patients was 97% (97% CI: 90–99) at 3 months, 96% (95% CI: 87–99) at 6 months and there was no additional pump replacement thereafter up to 4 years of support duration.

Event rates of major adverse events and deaths were plotted at specific intervals of device support (0–30 days, 31–90 days, 91–180 days and >180 days) as shown in Figure 4. The highest rates of adverse events and deaths were observed within 30 days, and significantly lower levels of adverse events and deaths were observed after 1 month, which further decreased over time during late follow-up periods (91–180 days and >180 days).

**Discussion**

In this study, we evaluated the safety and performance of the DuraHeart LVAS, a third-generation rotary pump LVAS combined with magnetic levitation technology and a centrifugal pump. The results demonstrated that the DuraHeart LVAS was safe and performed as intended for mechanical circulatory support for patients at imminent risk of death due to end-stage left ventricular failure, and eligible for cardiac transplantation. The DuraHeart LVAS provided effective hemodynamic support for a wide range of body sizes, fast recovery of end-organ functions, improved functional status and a survival benefit to the patients both inside and outside the hospital.

Although there has been no randomized comparison between different implantable LVAS for BTT application or between LVAS and optimal medical therapy in patients awaiting heart transplantation, historical data from the BTT studies of the first-generation pulsatile LVAS have shown survival benefit with an...
improved quality of life in advanced heart failure patients. In the studies with pulsatile LVAS, overall survival to transplantation or survival on LVAS support was approximately 70% at 6 months and 50–60% at 1 year [6–9,11,30,31]. In the present study with the DuraHeart LVAS, overall survival was 79% at 1 year, 73% at 18 months and 58% at 2 years, which demonstrated significantly improved survival compared with that of pulsatile devices for BTT application, and superior to that of REMATCH trial and post-REMATCH [33] with a pulsatile LVAS for destination therapy (DT; 23 and 31%, respectively, at 2 years). Other second- and third-generation rotary blood pump LVAS also demonstrated improved survival comparable with the current study [17–19,23,24]. High mortality rate within 90 days of support due to CVA, sepsis or multiorgan failure may reflect the patient selection and timing of LVAS implantation, as shown in other studies [32–34]. The combination of new LVAS technologies with the improvements in patient selection and earlier introduction of LVAS may further improve the outcomes of LVAS therapy.

Event rates for major adverse events during DuraHeart support were acceptable in comparison with the first-generation pulsatile [6] and the second-generation axial flow LVAS [17]. The event rate of bleeding requiring surgery (0.14 per patient-year) was considerably lower in the DuraHeart than the first- and second-generation LVAS (1.47 and 0.78, respectively). There were three GI bleedings (9%; 0.10 per patient-year) at 197, 275 and 113 days after implantation. None required intervention or resulted in death. Recent studies demonstrated that the patients with rotary blood pump LVAS had significantly higher rates of GI bleedings than those with pulsatile LVAS (0.63 vs 0.07 per patient-year; p = 0.0004) [35] and suggested that this may be associated with acquired von Willebrand disease, possibly caused by high shear stress of rotary blood pumps [36]. In the present study, the patients implanted with the DuraHeart LVAS showed a lower rate of GI bleedings compared with those reported previously with other rotary blood pumps (0.10 vs 0.63) and comparable to pulsatile pumps. The flow characteristics and the pattern and magnitude of shear stress depend largely on the design of each blood pump; therefore, further study will be necessary to define the flow characteristics of each pump design and their relatedness with GI bleedings.

### Table 2. End-organ function and hemolysis during support.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Preimplant (n = 82)</th>
<th>3 months (n = 55)</th>
<th>6 months (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dl)</td>
<td>36.9 ± 22.0</td>
<td>26.5 ± 16.6</td>
<td>31.8 ± 26.4</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.5 ± 0.7</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.4 ± 1.1</td>
<td>0.7 ± 0.4</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>GOT (U/l)</td>
<td>71.2 ± 191.3</td>
<td>31.3 ± 10.0</td>
<td>35.2 ± 24.3</td>
</tr>
<tr>
<td>GPT (U/l)</td>
<td>83.1 ± 286.9</td>
<td>28.0 ± 11.7</td>
<td>26.9 ± 14.4</td>
</tr>
<tr>
<td>Free hemoglobin (mg/dl)</td>
<td>12.4 ± 12.5</td>
<td>11.7 ± 7.8</td>
<td>17.6 ± 10.3†</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>371.9 ± 287.7</td>
<td>262.3 ± 61.1</td>
<td>248.5 ± 60.5</td>
</tr>
</tbody>
</table>

†Higher plasma free hemoglobin values were likely caused by blood drawing at out-patient setting, while LDH values were kept low.
BUN: Blood urea nitrogen; GOT: Glutamic oxaloacetic transaminase; GPT: Glutamic pyruvic transaminase; LDH: Lactate dehydrogenase; SD: Standard deviation.
### Table 3. Incidence of serious adverse events of 33 CE-mark trial patients for extended duration of support.

<table>
<thead>
<tr>
<th>Serious adverse event</th>
<th>Overall (n = 33)</th>
<th>0–30 days</th>
<th>&gt;30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>Number of patients (%)</td>
<td>Event rate</td>
</tr>
<tr>
<td>All serious adverse events</td>
<td>114</td>
<td>31 (94)</td>
<td>3.96</td>
</tr>
<tr>
<td>Local, nondevice related infection</td>
<td>14</td>
<td>14 (42)</td>
<td>0.49</td>
</tr>
<tr>
<td>Driveline infection</td>
<td>7</td>
<td>5 (15)</td>
<td>0.24</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>1</td>
<td>1 (3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6</td>
<td>6 (18)</td>
<td>0.21</td>
</tr>
<tr>
<td>Right heart failure requiring RVAD</td>
<td>1</td>
<td>1 (3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Right heart failure extended inotropes</td>
<td>10</td>
<td>9 (27)</td>
<td>0.35</td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>2</td>
<td>2 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hemorrhagic CVA</td>
<td>4</td>
<td>4 (12)</td>
<td>0.14</td>
</tr>
<tr>
<td>TIA</td>
<td>5</td>
<td>5 (15)</td>
<td>0.17</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>8</td>
<td>8 (24)</td>
<td>0.28</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5</td>
<td>5 (15)</td>
<td>0.17</td>
</tr>
<tr>
<td>Total bleeding</td>
<td>11</td>
<td>8 (24)</td>
<td>0.38</td>
</tr>
<tr>
<td>Bleeding requiring surgery</td>
<td>4</td>
<td>4 (12)</td>
<td>0.14</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4</td>
<td>4 (12)</td>
<td>0.14</td>
</tr>
<tr>
<td>Pump replacement</td>
<td>2</td>
<td>2 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>2</td>
<td>2 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other; total</td>
<td>34</td>
<td>21 (63)</td>
<td>1.18</td>
</tr>
</tbody>
</table>

*Events/patient-year.*

CVA: Cerebrovascular accident; RVAD: Right ventricular assist device; TIA: Transient ischemic attack.

Driveline or pocket infection rate was reduced by 90% compared with the pulsatile device (0.27 vs 3.49) and was comparable to the small axial flow devices (0.27 vs 0.34). The rate of CVA was 50% less than that of a pulsatile device (0.21 vs 0.44) and comparable to an axial flow LVAS (0.21 vs 0.19). There was a high incidence of cardiac and subdural hematoma among patients who died of CVA with massive intracerebral bleeding and other bleeding complications. Also, the rate of CVA was 50% less than that of a pulsatile device (0.21 vs 0.44) and comparable to an axial flow LVAS (0.21 vs 0.19). There was a high incidence of cardiac and subdural hematoma among patients who died of CVA with massive intracerebral bleeding and other bleeding complications. Also, the rate of CVA was 50% less than that of a pulsatile device (0.21 vs 0.44) and comparable to an axial flow LVAS (0.21 vs 0.19).
received transplantation in the present study was closer to that of DT patients who are younger than 65 years (20%) [10]. In the present study, the median age of the patients was 59 years, which was older than the patient cohort in most of the BTT studies (median age was typically 50 years and younger) and showed similar age distribution to that of DT patients. The median age of the patients who continued on device support at late follow-up periods was 60 years, which was significantly older than the patients who received transplantation (52 years; p = 0.009). Some of these ongoing patients had been converted to DT owing to patient preference, delisted from transplantation owing to absence of device–related complications, or less donor availability for the older-age patients. Lower rate of transplantation at late follow-up periods prolonged the time to heart transplantation in the present study. Historical data from the BTT studies with pulsatile LVAS have shown 1–3 months of average support duration to heart transplantation or recovery [6–9], whereas the median time to transplantation of the present study was 157 days (range: 43–497), which was twice as long as that with a pulsatile LVAS and 50% longer than that of the most recent clinical study (97 and 108 days) with an axial flow LVAS for BTT application in the USA [17,19]. Recent data from the Interagency Registry for Mechanical Assisted Circulatory Support demonstrated that there was no significant difference in survival between the patients (n = 382) implanted with a LVAS for BTT and the patients who received a LVAS (n = 69) for DT (p = 0.53) at 1 year [31]. The clinical outcomes of the present BTT study, having a similar age distribution to the DT cohort with extended support duration over 1 year, may simulate the outcome for DT.

Significantly lower rates of major adverse events and deaths at late follow-up periods (>180 days) were observed in the present study, while the majority of adverse events and death occurred within 3 months of LVAS implantation, with the highest rates within 30 days. The reduction in adverse events and deaths during late follow-up periods in the present study suggested that the DuraHeart LVAS was able to provide safe and reliable long-term support; an appropriate selection of the patients and an appropriate timing of LVAS implantation may further improve both early and late clinical outcomes.

**Conclusion**

A third-generation DuraHeart LVAS combined with a centrifugal pump and active magnetic levitation provided adequate circulatory support with improved survival and reduced adverse event rates during extended follow-up periods for the patients who are eligible for transplantation with an older patient cohort similar to DT. Better survival outcomes, reduced adverse event rates and long-term device reliability in the present study with the DuraHeart LVAS compared with the first-generation pulsatile LVAS would set a new standard for LVAS therapy for advance heart failure patients. The device may have significant potential for long-term circulatory support for both BTT and DT. However, the limitations of the present study include a limited clinical experience with 82 patients, with few patients supported beyond 2 years, and lack of a direct, randomized comparison with other LVAS, including second- and third-generation LVAS or optimal medical therapy. Further clinical investigation will be necessary to evaluate whether the DuraHeart LVAS continues to provide safe and reliable operation and survival benefit with an improved quality of life to the patients with advanced heart failure.

**Five-year view**

As we gain clinical experiences of a newer generation rotary pump LVAS for long-term support, and the device continues to provide reliable and safe circulatory support for advanced heart failure patients, LVAS therapy may be able to apply to less advanced heart failure patients of NYHA Class III, which would further improve the clinical outcomes of LVAS therapy comparable to heart transplantation. Although the risk of device-related infections associated with a percutaneous cable and a pump pocket has been reduced in a new-generation LVAS, driveline/pocket infection remains a concern for LVAS therapy. In order to eliminate LVAS-related infection, several manufacturers have been working on developing a further miniaturized implantable pump and a totally implantable system using a transcatheter energy/information transmission...
system that eliminates a percutaneous cable, and offers a 'tether-free' better quality of life to the patients. Furthermore, a miniaturized pump will provide surgeons with an option of minimally invasive pump implantation with/without off-pump procedure, which will facilitate a patient’s recovery from surgery and shorten the time of hospitalization. The refinement of the system, including a physiological control algorithm and remote monitoring capability, will further enhance the quality of life of the patient.

**Key issues**

- Heart failure is a major cause of death throughout the world, and is associated with a high rate of morbidity and a lower quality of life than that of patients suffering from any other chronic disease.
- Heart transplant remains the ‘gold standard’, or preferred treatment option, for patients with advanced heart failure. However, the number of transplant candidates far exceeds the donor pool.
- The first generation of implantable left ventricular assist systems (LVAS) using a pulsatile pump technology has become an established therapeutic option for advanced heart failure patients for both bridge-to-transplant or destination therapy. However, there have been technological limitations, which include a high incidence of infection, mechanical failures, thromboembolism associated with moving parts and the large size of both the implantable pump and percutaneous cable.
- A smaller rotary blood pump emerged as a possible alternative to a large pulsatile pump, which eliminates the need for prosthetic valves and the external venting required for implantable pulsatile pumps.
- The newest design of rotary blood LVAS that define the third-generation LVAS was the elimination of all mechanical contacts between the impeller and the drive mechanism, while second-generation LVAS have a mechanical bearing with contact points. This was accomplished by either an active magnetic bearing or hydrodynamic bearing technology to levitate the impeller. The key advantages of a friction-free drive are reduced hemolysis, minimized thrombogenesis and the increased mechanical durability necessary for long-term mechanical circulatory support.
- The DuraHeart™ LVAS is the world’s first third-generation implantable LVAS to obtain market approval (CE-mark); it combines a centrifugal pump and active magnetic levitation technology designed for long-term circulatory support.
- The initial clinical experience of the DuraHeart LVAS with 82 patients in Europe demonstrated that the device provided adequate circulatory support with significantly improved survival, reduced adverse event rates and long-term device reliability over the first-generation pulsatile LVAS during extended follow-up periods for the patients who are eligible for transplantation, and an older patient cohort similar to destination therapy.
- Further refinement in system designs with a tether-free configuration would be necessary to make LVAS therapy a true alternative to transplantation.

**References**

DuraHeart™ for advanced heart failure patients

Device Profile


Website

101 Study on Heart Failure Awareness and Perception in Europe
www.heartfailure-europe.com

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