Background: The DuraHeart left ventricular assist device (LVAD) is the world’s first approved magnetically levitated implantable centrifugal pump. We report our initial experience with the DuraHeart as a bridge to heart transplantation.

Methods and Results: Between 2008 and 2011, 23 patients (17 males; mean age 35 years, range 16–53 years) with endstage heart failure underwent implantation with the DuraHeart LVAD at Osaka University Hospital. Of those, 7 underwent conversion surgery from a Nipro paracorporeal LVAD to the DuraHeart. There were no deaths during the mean support period of 559±241 days (176–999 days). In total, 17 patients (74%) remain with the LVAD and 5 (22%) underwent heart transplantation after 580±302 days (176–982 days) of support. Major adverse events included 8 (34%) driveline/pocket infections, 4 (17%) cerebrovascular accidents, 4 (17%) right heart failures requiring mechanical support, and 3 (13%) mechanical device failures (magnetic levitation failure caused by driveline fracture). Of the 5 patients who developed pump pocket infection, 3 underwent previous conversion surgery from the Nipro LVAD.

Conclusions: Our initial experience with the DuraHeart LVAD in Japan demonstrated excellent long-term survival with acceptable rates of adverse events. With refinement of the system, including mechanical durability, this pump will further enhance the quality of life for patients who require long-term mechanical circulatory support. (Circ J 2013; 77: 1736–1741)

Key Words: Cardiomyopathy; Heart failure; Transplantation; Ventricular assist device
ity, and reduced device-related complications. In 2011, implantable continuous-flow LVADs were approved for commercial use in Japan, such as the DuraHeart LVAD (Terumo Heart Inc, MI, USA), which is the world’s first approved third-generation continuous-flow pump. This device has no mechanical contacts between the impeller and drive mechanism, and combines a centrifugal pump with active magnetic levitation for long-term circulatory support. Since acquiring the CE mark in 2007 in Europe, the DuraHeart has shown favorable clinical results as a bridge to transplantation. We report our initial experience with the DuraHeart as a bridge to transplantation.

Methods

Patients
Between October 2008 and October 2011, 25 patients with endstage HF underwent implantation of a DuraHeart LVAD at Osaka University Hospital as a bridge to heart transplantation; 2 patients who underwent biventricular assist device implantation using 2 continuous-flow pumps, a Jarvik 2000 (Jarvik Heart Inc, NY, USA) and the DuraHeart, were excluded from this study. Thus, 23 patients were analyzed, including 2 who participated in a multicenter clinical trial in Japan and 12 participants in a clinical trial supported by Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan. The baseline patient characteristics are shown in Table 1. Their mean age was 35 years (range 16–57 years) and mean body surface area was 1.58 m² (1.39–1.80 m²); 17 patients (73.9%) were male and only 3 (13.0%) had ischemic etiology for HF; 9 (39.1%) had undergone previous open heart surgeries, including 7 (30.4%) who were initially implanted with a Nipro LVAD and then underwent conversion to the DuraHeart LVAD. The 13 patients who never received Nipro LVAD support were rated as New York Heart Association (NYHA) functional class IV, with a mean left ventricular ejection fraction of 22±7% and a mean left ventricular end-diastolic diameter of 68±8 mm. Three patients were also receiving mechanical support including extracorporeal membrane oxygenation (ECMO). Most (82.6%) were categorized as interagency registry for mechanically assisted circulatory support (INTERMACS) level 2 or 3 at the time of implantation with the DuraHeart LVAD.

Surgical Procedures
The surgical techniques used for DuraHeart implantation have been previously described by several groups. Briefly, the device is implanted through a median sternotomy under cardiopulmonary bypass (CPB) with beating heart. An abdominal pocket is created in the preperitoneal space. After initiation of CPB, the left ventricular apex is cored and the inflow cuff sutured onto it using pledgetted mattress sutures placed in a circumferential manner. The inflow cannula is then inserted into the left ventricle through the cuff and firmly secured with heavy sutures, and the Vascutec outflow graft is anastomosed to the ascending aorta. The device is then deaired and the pump is started while CPB is gradually discontinued.

The 7 patients with previously implanted Nipro paracorporeal LVADs underwent conversion to the DuraHeart LVAD. Conversion surgery comprised a repeat sternotomy and conventional CPB. The Nipro inflow/outflow cannulae were dissected freely and their skin exit sites completely trimmed off to minimize the risk of late pocket infection. After initiation of CPB, the inflow cannula was removed from the left ventricle and any mobile wedge thrombi were carefully excised. The Nipro inflow cuff was left in place and re-used for the inflow to the ascending aorta. The device is then deaired and the pump is started while CPB is gradually discontinued.

Results
The mean duration of DuraHeart support was 559±241 days (176–999 days, median 472 days), with a cumulative duration of 35 patient-years. At the time of data analysis, 22 (96%) patients had completed 6-month follow-up, 19 (83%) 1-year follow-up, and 6 (26%) 2-year follow-up examinations. Patients who underwent replacement with a second DuraHeart LVAD were included in the analysis, although 1 patient who received a different type of device as replacement was withdrawn from the study.

Table 1. Preoperative Patient Characteristics (n=23)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (mean±SD)</th>
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<tbody>
<tr>
<td>Mean age in years at implantation (range)</td>
<td>35.1±11.2 (16–57)</td>
</tr>
<tr>
<td>Males (%)</td>
<td>73.9</td>
</tr>
<tr>
<td>Mean BSA in m² (range)</td>
<td>1.58±0.11 (1.39–1.80)</td>
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<tr>
<td>Heart disease</td>
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<tr>
<td>ICM</td>
<td>3</td>
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<tr>
<td>DCM</td>
<td>11</td>
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<tr>
<td>dHCM</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>Previous procedures</td>
<td></td>
</tr>
<tr>
<td>Nipro LVAD implantation</td>
<td>7</td>
</tr>
<tr>
<td>Mitral annuloplasty</td>
<td>4</td>
</tr>
<tr>
<td>CABG</td>
<td>1</td>
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<tr>
<td>LVES (%)</td>
<td>21.9±6.6*</td>
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<tr>
<td>LVEDD (mm)</td>
<td>68±8*</td>
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<tr>
<td>INTERMACS level</td>
<td></td>
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<tr>
<td>1</td>
<td>4</td>
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<tr>
<td>2</td>
<td>11</td>
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<tr>
<td>3</td>
<td>8</td>
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<tr>
<td>Mechanical support prior to implant surgery</td>
<td></td>
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<tr>
<td>Nipro LVAD</td>
<td>7</td>
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<tr>
<td>ECMO</td>
<td>3</td>
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</table>

Data are mean±SD, number or percentage.
*Echocardiographic data for 13 patients without mechanical support.
BSA, body surface area; CABG, coronary artery bypass grafting; DCM, dilated cardiomyopathy; dHCM, dilated phase of hypertrophic cardiomyopathy; ECMO, extracorporeal membrane oxygenator; ICM, ischemic cardiomyopathy; INTERMACS, the interagency registry for mechanically assisted circulatory support; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVES, left ventricular ejection fraction.

DuraHeart, because the inflow cannulae of both devices are virtually the same diameter. The DuraHeart outflow graft was then anastomosed end-to-end to the previous Nipro outflow graft. A direct aortic valve closure was added in 1 patient suffering from progressive HF symptoms secondary to severe aortic insufficiency (AI).

For the postoperative anticoagulation regimen, coumadin was administered to maintain an international normalized ratio (INR) of 2.0–2.5, together with 100 mg of aspirin daily, once the patient was able to take oral medication. An intravenous administration of heparin was not used for the initial 15 patients, considering the risk of bleeding. However, it was added to the protocol after a perioperative stroke occurred in 1 patient. Heparin was started at 12 h after surgery with an activated prothrombin time of 50–70 s unless significant bleeding occurred.
Operative Results

There were no hospital deaths among the 23 patients implanted with the DuraHeart LVAD. The mean CPB time was 133±78 min (39–318 min), including patients who underwent conversion from the Nipro to DuraHeart LVAD, whose mean CPB time was shorter (90±60 min). In 3 cases (13.0%), chest re-exploration for bleeding was required, 2 of which were conversion cases, and 5 patients required temporary RVAD support for refractory right ventricular failure, of whom 3 were successfully weaned from RVAD after a mean support period of 21±7 days, while the other 2 did not show sufficient recovery of right ventricular function and underwent conversion to a Nipro RVAD. The mean duration of ICU stay was 3.5±2.3 days (1–11 days) for patients who did not require temporary RVAD support and 39.5±16.7 days (19–60 days) for those with RVAD support.

Late Survival

There were no deaths during the support period. Five patients successfully underwent heart transplantation after 580±302 days (176–982 days) of DuraHeart support (total LVAD support including Nipro LVAD 768±188 days). One patient was withdrawn from the study after the original device was replaced with another type of device. The other 17 patients are currently on DuraHeart support. All except 2 patients who required Nipro RVAD implantation were discharged from the hospital with DuraHeart support and rated as NYHA class I or II.

Pump Performance

The average pump flow rate was 4.5±0.8 L/min with a flow index of 2.9±0.6 L/min⁻¹·m⁻² and an average motor speed of 1,686±88 rpm throughout the duration of support. Table 2 shows average values for end-organ functions, as determined by blood urea nitrogen, creatinine, total bilirubin aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase (LDH) levels measured at baseline, and 1, 6, and 12 months after implantation. The average values for renal and hepatic functions decreased to nearly normal ranges by 1 month after DuraHeart implantation. The LDH value remained at the upper limit of normal for the duration of the support period, suggesting that clinically significant hemolysis did not occur as a result of implantation of the DuraHeart LVAD.

Echocardiographic Findings

Echocardiographic follow-up examinations were performed for all patients to monitor recovery of left ventricular function and development of AI. The left ventricular end-diastolic/systolic diameter decreased from 70±11/64±11 mm before surgery to 57±16/53±16 mm after 1 year, but there was no improvement in left ventricular ejection fraction (21.1±7.6% preoperatively, 23.3±9.2% at 1 year).

The severity of AI was graded according to color-flow Doppler findings and characterized as none or trace (0), mild (1), mild to moderate (2), moderate (3), or severe (4). Overall progression of AI over time was seen (0.18±0.5 preoperatively, 1.7±0.8 at 6 months, 2.1±0.8 at 1 year). Although none of the patients developed grade 4 AI, grade 2 or greater de novo AI was seen in 17 of 19 (89%) after 1 year. In most patients, there was no opening of the aortic valve recognized during echocardiography. Furthermore, none of the present cohort showed significant HF symptoms related to progression of AI.

Adverse Events

During the support period, there were 4 CVAs (3 hemorrhagic, 1 ischemic) in 4 patients (17%). The INR values were within the therapeutic range in all patients except 1, who had not been on intravenous heparin postoperatively and had an INR value that was subtherapeutic (1.8), and who had an embolic stroke 4 days after LVAD implantation. After this event, we changed our anticoagulation protocol to the current regimen in which administration of intravenous heparin begins 12 h after surgery unless significant bleeding continues. All patients were discharged from the hospital without significant neurological deficits except 1 who suffers from mild residual dysarthria.

A total of 8 patients (34%) experienced device infections, including 3 driveline and 5 pump pocket infections. The driveline infections were treated with meticulous local care of the driveline exit site wound, whereas the pump pocket infections required aggressive surgical treatments, including an omental flap procedure in all 5 patients and a musculocutaneous flap procedure in 3 patients for recurrent infection. All patients with a pocket infection had previously undergone either conversion surgery (n=3) or long-term paracorporeal RVAD implantation (n=2). Each of these patients, except the 2 who required long-term RVAD support, were discharged from the hospital.

In the late postoperative period, 4 patients experienced recurrent low-flow alarms. Chest radiography showed altered position of the inflow cannula in some patients, directed toward the lateral wall of the left ventricle (Figure). No serious symptoms were encountered by adjustment of the pump flow rate under echocardiographic guidance.

There were 3 (13.0%) device mechanical failures that occurred at 211, 258, and 283 days, respectively, after implantation, during which failure of the magnetic levitation system occurred and the device went into a hydrodynamic bearing rotation mode. Although none of these patients experienced any adverse clinical consequences, a device exchange was performed in the first 2 cases through a subcostal approach without a repeat sternotomy. Detailed investigations of the explanted devices by the manufacturer identified a fracture of a position sensor wire in the percutaneous cable of each. The

<table>
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<tr>
<th>Table 2. Laboratory Data During Support</th>
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<tr>
<td>BUN (mg/dl)</td>
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<td>Cr (mg/dl)</td>
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<td>TB (mg/dl)</td>
</tr>
<tr>
<td>AST (U/L)</td>
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<tr>
<td>ALT (U/L)</td>
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<tr>
<td>LDH (U/L)</td>
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Data are mean±SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; LDH, lactate dehydrogenase; TB, total bilirubin.
DuraHeart LVAD

third patient is being carefully followed in hydrodynamic bearing mode, and has not shown any compromised clinical status or abnormal laboratory data indicating significant hemolysis during more than 9 months of support since the failure.

**Discussion**

Implantable continuous-flow LVADs are categorized as either second- or third-generation devices based on their technological features. Second-generation devices, such as the Jarvik 2000 and HeartMate II (Thoratec Corp, CA, USA), are based on axial flow pump technology and equipped with a blood-immersed or pivotal bearing. Third-generation devices eliminate all mechanical contacts inside the blood chamber by using either magnetic or hydrodynamic bearing technology to levitate the impeller. Potential advantages of frictionless impeller rotation obtained with such technology include reduced hemolysis, reduced potential pump thrombosis, and increased mechanical durability.

The DuraHeart is the world’s first third-generation continuous-flow LVAD equipped with an active magnetic levitation system. This device was first implanted in clinical trials in Europe starting in 2004 and received the CE mark in 2007. The largest number of DuraHeart implantations was reported in clinical results presented by Morshuis et al. Between 2004 and 2009, they implanted the DuraHeart LVAD in 82 patients, including 33 being treated as part of a European multicenter clinical trial and 49 treated during the post-trial period. The median support duration was 261 days (17–1,494 days), with a cumulative duration of 78 patient-years. In total, 36 patients (45%) remain ongoing, 23 (28%) were transplanted with a median time to heart transplantation of 157 days (43–497 days), 2 underwent explantation, and 20 (24%) died during support with a median time to death of 167 days. The Kaplan-Meier survival rate during support was 85% at 6 months, 79% at 1 year, and 58% at 2 years. In their study, adverse events in 33 CE mark trial patients were analyzed. During the median support duration of 201 days (17–1,077 days), device infections occurred in 6 (18%) patients, including 1 pump pocket infection. Also, CVA was reported in 6 (18%), 5 in the initial 11 patients (0.05/patient-year) and only 1 among the final 22 patients (0.04/patient-year), after implementing less intensive anticoagulation/antiplatelet therapy. Two patients experienced device malfunctions and underwent pump replacement. No mechanical failures were identified by the manufacturer’s investigation of explanted devices.

Long-term survival in our series was superior to other reports of continuous-flow LVAD use. In a DuraHeart-CE/post-CE mark study reported by Morshuis et al, the 1-year survival rate was 79%, and a post-FDA study of the HeartMate II, the most popular second-generation axial flow pump, reported a 1-year survival rate of 85% while receiving device support. In our series, there were no mortalities during the mean support period of 559 ± 241 days (176–999 days, median 472 days). Despite the small number of patients, our results show that this device is safe and useful as a bridge to transplantation in Japan, where the average waiting time on LVAD support exceeds 2 years.

In terms of major adverse events, our results are comparable to the DuraHeart-CE and HeartMate II post-FDA studies. The rate of CVA (0.11/patient-year) in the present study was lower than that in the DuraHeart-CE (0.21) and similar to the HeartMate II (0.08) studies. As previously noted, because most occurrences of CVA in the DuraHeart-CE study were in the initial 11 patients, probably associated with excessive anticoagulation therapy, the actual CVA rate of the DuraHeart is comparable to that of the HeartMate II.

In addition, the driveline or pocket infection rate (0.22/patient-year) in our series was comparable to that in the DuraHeart-CE (0.27) and HeartMate II (0.34) studies. It is important to note that only patients who underwent either implantation with a Nipro RVAD (n=2) or conversion from a Nipro to DuraHeart LVAD (n=3) developed a pump pocket infection. In the present study, an RVAD was used in 5 patients (3 temporary centrifugal, 2 long-term Nipro) after implantation of the DuraHeart LVAD. A pump pocket infection occurred in 2 of the Nipro RVAD cases, and none was seen in the temporary RVAD cases. Of the 7 LVAD conversion cases,
3 (43%) developed a pump pocket infection. We previously reported that a limited local infection or even minor erosion at the skin exit site of the Nipro cannulae can cause a serious pocket infection following conversion surgery.\textsuperscript{12} Although all of the present patients survived this serious complication by undergoing aggressive surgical treatment, such as an omental and/or musculocutaneous flap procedure, a pump pocket infection associated with an implantable LVAD is often fatal. Meticulous local care must be taken to prevent a driveline infection and careful consideration is required regarding the indications for conversion surgery.

It has been shown that requirement of an RVAD is a significant risk factor for mortality after LVAD implantation.\textsuperscript{4} Considering the poor results of long-term BiVAD therapy, a reasonable strategy is use of a temporary centrifugal RVAD for severe right HF at LVAD implantation, followed by an attempt to wean RVAD support when the patient becomes stabilized. We previously reported that there was no significant difference regarding survival between patients who underwent isolated LVAD support and those who were initially implanted with a temporary BiVAD and then underwent RVAD removal.\textsuperscript{13} In the present study, 5 patients required temporary RVAD at the time of DuraHeart LVAD implantation. The preoperative diagnoses for these patients were DCM in 2, Becker type muscular dystrophy in 1, arrhythmogenic right ventricular cardiomyopathy (ARVC) in 1, and myocardial infarction in 1. The temporary RVAD was successfully weaned in 3 patients (DCM, muscular dystrophy, ARVC) who were relatively stable and had normal end-organ function at the time of DuraHeart implantation. The reasons for using a temporary RVAD were prophylactic placement for ARVC and unexpected right HF because of severe pulmonary edema after prolonged CPB support. However, we were unable to wean 2 patients (DCM, MI) from the temporary RVAD and they required conversion to long-term extracorporeal RVAD. Both were already receiving ECMO support at the time of DuraHeart implantation (INTERMACS level I), and showed severe right HF symptoms including ascites and liver dysfunction. Because preoperative ECMO support and end-organ dysfunction have been shown to be significant risk factors for RVAD requirement,\textsuperscript{4} the indications regarding an implantable LVAD for such critical cases should be carefully considered.\textsuperscript{17–19}

The other important long-term complication following LVAD implantation is the development of AI. The incidence of significant AI after HeartMate II implantation has been reported to be 52%, with a median time to AI development of 187 days.\textsuperscript{20} Another report noted that 78% of patients with continuous-flow LVAD developed AI of grade 2 or greater.\textsuperscript{21} In our series, there was overall progression of AI over time and 89% of the patients developed de novo AI within 1 year. As for clinical influence, Toda et al found that survival was significant worse when de novo AI developed in patients supported with a pulsatile LVAD (mostly Nipro LVADs),\textsuperscript{22} whereas another study found no negative effect of AI on survival of patients supported with a continuous-flow LVAD (HeartMate II).\textsuperscript{23} In the present study, none of our patients showed significant HF symptoms. As compared with the Nipro VAD, the DuraHeart has a greater flow capacity and may be able to compensate for the hemodynamic influence caused by AI. When considering that increasing numbers of patients requiring long-term LVAD support, careful attention and monitoring of the development of AI will be necessary. Adjustment of LVAD flow to avoid complete closure of the native aortic valve may be useful for some patients, as such closure is a significant risk factor for AI development.\textsuperscript{21}

As for technical considerations, implantation of the DuraHeart requires special attention to maintaining correct device configuration.\textsuperscript{17} Alignment of the inflow cannula is important, as it is made from titanium, which is an inflexible material. The ideal orientation of the inflow cannula should be decided before the connection is tightly fixed to the blood pump, because adjustment after placing the device into the pump pocket and restoration of heart beat is difficult. If the pump flow of the DuraHeart is not sufficient on weaning from CPB, the orientation of the inflow cannula should be rechecked using transesophageal echocardiography and adjusted by rotating the inflow cannula, if necessary. It should be also noted that malposition of the inflow cannula can develop late after device implantation because of reverse ventricular remodeling.\textsuperscript{23–25}

The recurrent low-flow alarms experienced in 4 patients were attributable to inflow obstruction partly caused by a positional change of the device late after implantation. In our series, device mechanical failures occurred in 3 patients from 6 to 12 months after DuraHeart implantation. In each, failure of the magnetic levitation system occurred and the pump converted to hydrodynamic bearing rotation mode. In a normally functioning DuraHeart, the impeller is levitated magnetically by 3 electromagnets and its position is precisely controlled by 3 position sensors. If the active levitation system fails, mostly because of position sensor error, the pump is still able to function by automatically converting to the hydrodynamic back-up mode, in which the impeller is levitated by hydrodynamic force. However, because of the lack of active positional control, the bearing gap between the impeller and pump housing becomes narrower (10–20 μm) than normal (250 μm), resulting in increased risk of hemolysis and thrombus formation. For these reasons, urgent device replacement was performed in our first 2 patients, though they did not show any adverse clinical consequences. Details of those operative procedures have been previously described.\textsuperscript{13} Briefly, an abdominal midline incision was made along the prior operative incision and extended to the subcostal area. After opening the pump pocket, the device was freely dissected, including the connector nuts of both the inflow and outflow conduits. Next, CPB was established by femoral access, and the malfunctioning pump was separated from both conduits by loosening the connectors and replaced with a new pump. During the procedure, the patient was kept in the Trendelenburg position and the operative field was flooded with carbon dioxide. A pig-tail catheter was placed in the ascending aorta through the femoral artery, connected to the CPB, and used as an intra-aortic venting cannula.\textsuperscript{26} The postoperative course was uneventful in both patients, though 1 later developed a pump pocket infection, requiring omental and musculocutaneous flap procedures. After noting the stable hemodynamic support provided in those 2 patients and the increasing risk of future pocket infection, the third has been carefully followed in hydrodynamic bearing mode for more than 9 months. That patient has been well supported and no laboratory values indicating significant hemolysis or end-organ dysfunction have been noted. Investigation of the explanted pumps by the manufacturer revealed that the failure of the magnetic levitation system was caused by a fracture of a position sensor wire in the percutaneous cable of each, and no mechanical failure was identified in the pump housing. Additional investigations are currently ongoing and Terumo Heart Inc has decided to temporarily refrain from distributing this device until effective countermeasures are developed.

In conclusion, our initial results demonstrated that the DuraHeart LVAD is safe and provides adequate circulatory
support, as well as excellent survival and acceptable adverse event rates for patients eligible for heart transplantation. Pump pocket infection is avoidable by careful consideration of operative indication, especially in cases of conversion from a paracorporeal LVAD. Although issues remain to be solved, especially in terms of mechanical durability, the DuraHeart is expected to be an effective option for improving the prognosis of severe HF patients by enabling reliable long-term circulatory support.

Disclosures

This study was financially supported by Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan. None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the report or any other conflicts of interest to disclose.

References