http://www.jhltonline.org

Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) – First ReportFirst J-MACS report

Takeshi Nakatani, Kazuhiro Sase, Hiroaki Oshiyama, Masatoshi Akiyama, Masao Horie, Kan Nawata, Tomohiro Nishinaka, Yoshihisa Tanoue, Koichi Toda, Masao Tozawa, Shunichi Yamazaki, Masanobu Yanase, Hiroshi Ohtsu, Michiko Ishida, Ayaka Hiramatsu, Kensuke Ishii, Soichiro Kitamura

PII: S1053-2498(17)31947-2
DOI: http://dx.doi.org/10.1016/j.healun.2017.08.002
Reference: HEALUN6581

To appear in: *Journal of Heart and Lung Transplantation*

Cite this article as: Takeshi Nakatani, Kazuhiro Sase, Hiroaki Oshiyama, Masatoshi Akiyama, Masao Horie, Kan Nawata, Tomohiro Nishinaka, Yoshihisa Tanoue, Koichi Toda, Masao Tozawa, Shunichi Yamazaki, Masanobu Yanase, Hiroshi Ohtsu, Michiko Ishida, Ayaka Hiramatsu, Kensuke Ishii and Soichiro Kitamura, Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) – First ReportFirst J-MACS report, *Journal of Heart and Lung Transplantation,* http://dx.doi.org/10.1016/j.healun.2017.08.002

Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) – First Report

(Short title: First J-MACS report)

(Key words: assist device, bridge to transplantation, mechanical circulatory support, registry, severe heart failure)

Takeshi Nakatani, MD, PhD (1), Kazuhiro Sase, MD, PhD (2), Hiroaki Oshiyama (2), Masatoshi Akiyama, MD, PhD (3), Masao Horie (3), Kan Nawata, MD, PhD (3), Tomohiro Nishinaka, MD, PhD (3), Yoshihisa Tanoue, MD, PhD (3), Koichi Toda, MD, PhD (3), Masao Tozawa (3), Shunichi Yamazaki (3), Masanobu Yanase, MD (3), Hiroshi Ohtsu, MS (4), Michiko Ishida, PhD (5), Ayaka Hiramatsu (5), Kensuke Ishii, PhD (5), Soichiro Kitamura, MD, PhD (6); on behalf of the J-MACS investigators.

(1) Principal investigator, Chair, J-MACS Operating Committee

(2) Co-principal investigator, J-MACS Operating Committee

(3) Investigator, J-MACS Operating Committee

(4) National Center for Global Health and Medicine

(5) Pharmaceuticals and Medical Devices Agency

(6) Chair, J-MACS Steering Committee

Abstract

Background

In Japan, ventricular assist devices (VADs) have been used for patients with severe heart failure as a bridge to transplantation (BTT) since 1992. However, it was not until 1997, when the Organ Transplant Law was enacted, that medical devices received approval by the national health insurance system for that use. To encourage research and development of innovative medical devices, the Pharmaceuticals and Medical Devices Agency has established a public-private partnership in collaboration with academic societies, hospitals, and manufacturers.

Methods

The Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) is a prospective registry designed to be harmonized with the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS). Participation in J-MACS is mandatory for device manufacturers to meet the conditions of approval as well as for hospitals to obtain authorization for reimbursement from the national health insurance system.

Results

From June 2010 to April 2015, 476 patients were registered at 31 hospitals. Of those, analysis of primary VAD patients (n=332) revealed that their overall 360-day survival was 91% (implantable, 93%; extracorporeal, 84%).

Conclusions

This initial report from J-MACS focuses on patient demographics, device types, survival, competing outcomes, adverse events, and successful examples of system failure detection.

Background

In Japan, the Organ Transplant Law enacted in 1997 paved a path for patients with severe heart failure to be officially listed for heart transplantation.[1, 2, 3] Although ventricular assist devices (VADs) continue to undergo evolutionary refinements, their use and development remain challenging for both healthcare providers and device manufacturers, due to the typically long waiting period for qualified patients to undergo heart transplantation.[4, 5]

The Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)[6] was established in 2009 and is the first national registry designed to be harmonized with the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS).[7]

Goals of the J-MACS registry

The primary aims of J-MACS are to utilize VAD data collected by the J-MACS registry to improve clinical assessments and management, as well as treatments and related technologies for patients with severe heart failure. In addition, by clarifying associated risks and benefits, the data obtained are used to establish appropriate safety measures and promote development of next generation technology.

J-MACS design, structure, and organization

J-MACS is a public-private partnership that includes 7 different academic societies, as well as participating hospitals and relevant VAD manufacturers, and is funded by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan (Figure 1). A Steering Committee (SC) and Operating Committee (OC) have been established for management of J-MACS, with the SC consisting of representatives from the academic societies, along with experts from the participating hospitals and manufacturer associations, while the OC consists of a principal investigator (PI) and co-PIs, as well as experts from the participating hospitals and VAD manufacturers. In addition, the Observational Study Monitoring Board (OSMB) and Adverse Event and Adjudication Committee (AEAC) have been established as independent and impartial organizations. The OSMB oversees the registry, while the AEAC investigates major adverse events (device malfunction, bleeding, neurological dysfunction, infection) and death in registered cases.

J-MACS routinely and/or immediately provides prospectively obtained clinical data, including patient demographics, operative surgery information, postoperative follow-up findings, and adverse events, via the J-MACS web-based data entry system. It should be noted that VAD manufacturers are allowed to utilize J-MACS data for reporting medical device malfunctions and conducting post-marketing surveillance, as required under the Pharmaceutical Affairs Law (PAL) and Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular

Therapy Products, Gene Therapy Products, and Cosmetics of Japan.

The present study design, including data elements, follow-up schedule, and adverse event definitions, was implemented so as to harmonize with INTERMACS[7] through the U.S.-Japan Medical Device Harmonization by Doing (HBD) program.[8-10]

Requirement for site participation and auditing system

Membership in J-MACS is one of the essential conditions for an authorized hospital to use an implantable LVAD and receive national medical insurance coverage. As of January 2015, 40 hospitals in Japan were authorized by relevant academic societies to utilize an implantable VAD for BTT in qualified patients. A primary investigator has been established at each participating site and is responsible for data entry via the J-MACS web-based data entry system.

With the aim to enhance the quality of the registry, J-MACS conducts site visits for auditing. The audit committee consists of supervisory physicians experienced in VAD therapy and works with the data-coordinating center (DCC). Members of the committee periodically visit selected hospitals to examine data integrity, including confirmation of entered data and documentary records. The DCC also urges participating hospitals to input all eligible patient data based on reports (e.g., number of implanted devices) provided by VAD manufacturers. The committee makes a report of the auditing results and submits that to the OC. After confirming the report, the OC informs the SC regarding its contents.

Device types

Table 1 shows a list of VADs included in the J-MACS registry. When the J-MACS system was launched in June 2010, an extracorporeal pulsatile flow device was the only type available for BTT. Thereafter, 2 implantable continuous flow devices were approved for use in Japan in December 2010.

Patient population

Patient inclusion criteria for J-MACS are as follows: 1) a durable VAD approved for use in Japan, as noted in Table 1, has been implanted, 2) the VAD implantation was performed at a hospital authorized by the cooperating academic societies, and 3) an informed consent form for inclusion in the registry has been signed by the patient and/or a family member. In addition, patients who have applied to receive an extracorporeal type of LVAD at an authorized hospital as BTT and provided informed consent for inclusion are also included in the J-MACS registry.

Between June 2010 and April 2015, 476 patients from 31 participating hospitals were enrolled. In the early stage, only patients with an extracorporeal type of LVAD were included. However, since introduction of implantable continuous flow devices in December 2010, the number of enrolled patients has dramatically increased (Figure 2). For this first report, we analyzed 332 patients who met all of the selection criteria (primary LVAD population), which are as follows: 1) assisted only by an LVAD, 2) never used any VAD prior to the time of enrollment, and 3) over 18 years old. The cutoff date for data collection was July 8, 2015. The rates for compliance of data entry

regarding follow-up examinations were 92% at 1 month, 92% at 12 months, and 91% at 24 months.

Male gender accounted for 79% of the patients (implantable, 81%; extracorporeal, 73%) (Table 2). The majority of patients with an implantable type ranged from 30 to 59 years old, while younger patients more often received an extracorporeal type. The primary disease in the majority of patients was dilated cardiomyopathy.

The main strategy for receiving an implantable VAD in the majority of patients was use as BTT, with 67% with an implantable type listed with the Japan Organ Transplant Network as a candidate for heart transplantation (Table 3). In contrast, 39% of patients with an extracorporeal type received that as BTT and only 8% were listed in the registry as a heart transplant candidate. Nearly half (49%) of patients with an extracorporeal device were in critical cardiogenic shock (INTERMACS patient profile level 1), whereas the majority of those with an implantable device were level 2 (53%) or 3 (41%).

Survival

Actuarial survival rate, determined using the Kaplan-Meier method, for the entire cohort was 91.2% at 360 and 88.7% at 720 days after implantation (Figure 3). Patients are censored at the time of transplantation, device explantation (because of recovery or switch to an implantable type in those with the extracorporeal type), or at the time of the last observation. Actuarial survival rates for patients with the implantable and extracorporeal type were 92.6% and 84.0%, respectively, at 360 days, and 89.8% and

84.0%, respectively, at 720 days (Figure 4). When stratified by INTERMACS patient profile, 360-day survival was 87.4% for level 1, 92.4% for level 2, and 90.8% for level 3. Patients at level 1 showed significantly worse survival as compared to those at level 2 or 3 (Figure 5).

Competing outcomes

The likelihood of BTT patients to undergo heart transplantation was 1.0% within 360, 7.8% within 720, and 38.8% within 1080 days in the implantable group (Figure 6), as compared with 0%, 1.6%, and 13.7%, respectively, in the extracorporeal group (Figure 7). When patients with an extracorporeal type as BTT received official approval to become a candidate for heart transplantation, the majority were switched to an implantable type. Approximately 63.8% of patients with an extracorporeal type underwent explantation within 360 days, mainly because of switch to implantable type due to the above-mentioned reasons (Figure 6). Death within 1080 days after receiving the implantable type occurred in 16.8% of those cases.

Cause of death

The primary causes of death are listed in Table 4. Infection, neurologic event, and multi-organ failure were the major events occurring in patients with an implantable device.

Adverse events

The numbers of patients affected by each of the 4 types of major adverse events, infection, neurologic dysfunction, device malfunction, and bleeding, before and 30 days after implantation are shown in Table 5. Infection was the most common adverse event seen in the patients regardless of device type, with device-related infection seen in 22 cases (18%) with the implantable type and 10 (32%) with the extracorporeal type. In those with the implantable type, infection of the cable exit site was found to be the primary cause of infection. Neurologic dysfunction was the second most common adverse event seen in patients with both types of devices, and its diagnosis was obtained based on brain CT findings and clinical course at each hospital. Specifically, hemorrhage stroke, ischemic stroke, and transient ischemic attack (TIA) were seen in 35 (40%), 27 (31%), and 21 (24%), respectively, of the 87 patients with the implantable type, and 9 (41%), 5 (23%), and 5 (23%), respectively, of those with the extracorporeal type. As for device malfunction, the rate was higher in extracorporeal type cases as compared to implantable type. In the registry, a 'pump exchange due to thrombus formation' event is reported as a device malfunction, as is malfunction of the device-line in an implantable device. Regarding bleeding, many of the cases were reported to have a surgical cause and required an operation, whereas gastrointestinal bleeding was not so frequent in patients with either type of device. Most device-related infections occurred after 30 days in both types and hemorrhagic stroke was also more frequent after 30 days in each type. In contrast, bleeding was more frequent prior to 30 days in cases with the implantable type. Rates for major adverse events within the first

12 months after implantation are presented in Table 6. There was an approximately 2-fold greater number of adverse events experienced by patients with the extracorporeal type as compared to those with the implantable type.

The AEAC noted successful detection of failure, including thrombosis formation of an inflow cannula[11] and malfunction of the drive-line,[12] as part of their observations. Notably, thrombosis formation of an inflow cannula was detected by reviewing the high rate of ischemic stroke in a single device. According to the results of their reviews, the AEAC gives advice to the appropriate regulatory agency. Fortunately, in cooperation with relevant academic societies, the VAD manufacturers have promptly improved the design of their devices based on that information.[13]

Discussion

This is the first report of the Japanese registry for mechanical circulatory support, J-MACS, in which we focus on patient demographics, device type, survival, competing outcomes, and adverse events. Thanks to the leadership of the International Society for Heart and Lung Transplantation (ISHLT) in establishing the International registry for Mechanically Assisted Circulatory Support (IMACS),[14, 15] J-MACS is now an important part of the larger community together with INTERMACS (since 2006)[7, 16] and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS, since 2012).[17]

Our investigation of acquired data shows that Japanese patients are experiencing longer waiting times for heart transplantation while being supported by a primary LVAD as compared to those in other counties. According to our analysis of competing outcomes with the implantable type, the number of transplant cases was clearly increased in cases supported from 720 to 1080 days. In spite of such an extended time with LVAD support, the results of heart transplantation in these BTT cases are good, as approximately 90% survive for more than 10 years after the transplant.[3] Thus, many patients in Japan with severe heart failure express their desire to be listed as a candidate for heart transplantation and undergo implantation of an implantable LVAD as BTT. Our detailed examination of those cases showed the importance of exploring better ways to control infection, neurological dysfunction, and bleeding to improve patient quality of life. Furthermore, alternative options for patients who are not candidates for heart transplantation are needed due to the good quality of life offered by use of an implantable LVAD.

In regard to the aspect of support duration, Japanese patients with an LVAD as BTT might be comparable to those in other countries receiving LVAD support as destination therapy. However, a randomized trial of LVADs is an enormously complex and difficult task, especially when undertaken for an extended trial period.[18] Thus, prospective registries that contain high-quality data collection are becoming more important for regulatory agencies in this era of real-world evidence.[19] We think that our database is an important source of safety information, especially for long-term use cases. On the other hand, this initial investigation of available data has also revealed some

local patterns specific to Japan. For example, some patients initially received an extracorporeal device before being switched to an implantable one. Such cases are a reflection of the reimbursement policy of the Japanese national health insurance system, which limits use of implantable devices to those who have been officially 'listed' or 'approved' as heart transplant candidates.

Among the cases analyzed, device malfunctions such as thrombus formation were reported as ischemic stroke related to neurologic dysfunction by the AEAC. Careful assessment of adverse events is crucial to clarify important issues and points that require improvement, and reduce the number of similar events in the future. Furthermore, a quick response to the cause of an adverse event is important to provide an opportunity to effectively treat affected patients who need a new device.

Presently, we are continuing analyses of our accumulated data in greater detail, including quality of care and device durability, with special focus on patients who receive support for longer periods. Those findings will be reported in the near future.

Conclusion

J-MACS is the first internationally harmonized registry for mechanical circulatory assist devices in Japan. Presently, the 1-year survival rate for patients with an implantable LVAD is approximately 90%. When stratified by INTERMACS patient profile, survival in the present study after 360 days was 87.4% for level 1, 92.4% for level 2, and 90.8% for level 3. For patients who have received implantable LVAD support for BTT, the likelihood of transplantation within 720 days is presently 7.8%.

Detection of device failures and adverse events by the AEAC has facilitated prompt actions by regulators as well as manufacturers.

Disclosure statement

H. O., M. T., M. H., and S. Y. are employees of Terumo Heart K.K, Century Medical, Inc., NIPRO CORPORATION, and Sun Medical Technology Research Corp., respectively. T.N. was supported by the Intramural Research Fund (25-4-1) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center and K.S. by a JSPS KAKENHI Grant (no. 25350585). None of the other authors has a financial relationship with a commercial entity, personal interest in any subject presented in the manuscript, or other conflicts of interest to disclose.

The J-MACS registry is a pilot project of the PMDA established for gathering and evaluating data regarding the use of medical devices. It is funded by post-marketing safety measure contributions from authorized marketing holders and also sponsored by Terumo Heart K.K, Century Medical, Inc., NIPRO CORPORATION, and SUN MEDICAL Technology Research Corp. for use in post-marketing surveillance. Those companies had no influence on the design of the present study nor data collection, analysis, and interpretation.

Acknowledgements

We thank all of the participating hospitals (Appendix 1), J-MACS project members (Appendix 2), and cooperating academic societies (Appendix 3) for their advice and help with data collection.

We express our gratitude to Dr. Bram D. Zuckerman and Dr. Eric A. Chen for their support as part of the U.S. - Japan Harmonization by Doing program. We are also grateful for the support and encouragement of Dr. James K. Kirklin, Dr. David C. Naftel, and the INTERMACS investigators.

References

1. Nakatani T. Heart Transplantation. Cir J 2009; Suppl A: A-55-A-60.

2. Nakatani T, Fikushima N, Ono M, Saiki Y, Matsuda H, Yozu R, Isobe M. The registry report of heart transplantation in Japan (1999-2013). Cir J. 2014; 78: 2604-09.

3. Kitamura S. Heart transplantation in Japan: a critical appraisal for the results and future prospects. Gen Thorac Cardiovasc Surg 2012; 60: 639-644.

4. Yamane, T, Kyo, S, Matsuda, H, et al. Japanese Guidance for Ventricular Assist Devices/Total Artificial Hearts. Artificial Organs 2010; 34:699-702.

5. Tatsumi E, Nakatani T, Imachi K, et al. Domestic and foreign trends in the prevalence of heart failure and the necessity of next -generation artificial hearts: a survey by the Working Group on Establishment of Assessment Guidelines for Next-Generation Artificial Heart Systems. J Artif Organs 2007; 10:187-194.

6. J-MACS: Japanese registry for Mechanically Assisted Circulatory Support.

(Japanese) (http://www.pmda.go.jp/safety/surveillance-analysis/0009.html, Accessed March 1, 2017)

7. Kirklin JK, Naftel DC, Stevenson LW, et al. INTERMACS Database for Durable Devices for Circulatory Support: First Annual Report. J Heart Lung Transplantat, 2008; 27:1065–72.

8. Sapirstein W, Chen E, Zuckerman B. US FDA perspective on regulatory issues affecting circulatory assist devices. Expert Review of Medical Devices. 2006; 3, 749-753.

9. U.S. Food and Drug Administration. US/Japan Regulatory Collaboration. (http://www.fda.gov/MedicalDevices/InternationalPrograms/USJapanRegulatoryCollaboration/default.htm, Accessed June 1, 2016)

10. Sase K. US-Japan Harmonization by Data (HBD) – Initial Experience with a Post-Marketing Follow-up Study of Mechanical Circulatory Assist Devices (J-MACS), and Ongoing Collaboration with Academic Research Consortiums -. Pharmaceutical and Medical Device Regulatory Science. 2012; 43: 339-346. (Japanese)

11. Saito S, Yamazaki K, Nishinaka T, et al. J-MACS Research Group: Post-approval study of a highly pulsed, low-shear-rate, continuous-flow, left ventricular assist device, EVAHEART: a Japanese multicenter study using J-MACS. J Heart Lung Transplant 2014;33: 599-608.

12. J-MACS Adverse Event and Adjudication committee. The First Report on Adverse Event for Mechanically Circulatory Support. December, 2012. (http://www.pmda.go.jp/files/000147200.pdf, Accessed June 1, 2016)

13. Ad Hoc Committee of DuraHeart for adverse events and exceptional clinical use. Report of improvement of post-market DuraHeart. Jinko Zoki, 2013;42:262-274 (Japanese).

14. Kirklin JK, Mehra MR. The dawn of the ISHLT Mechanical Assisted Circulatory Support (IMACS) Registry: Fulfilling our mission. J Heart Lung Transplant, 2012; 31: 115-116.

15. Kirklin JK, Cantor R, Mohacsi P, et al. First Annual IMACS Reoprt: A global International Society for Heart and Lung Transplantation Registry for Mechanical Circulatory Support. J Heart Lung Transplant. 2016; 35:407-412.

16. Acker MA, Pagani FD, Stough WG, et al. Statement regarding the pre and post market assessment of durable, implantable ventricular assist devices in the United States. J Heart Lung Transplant, 2012; 31: 1241-1252.

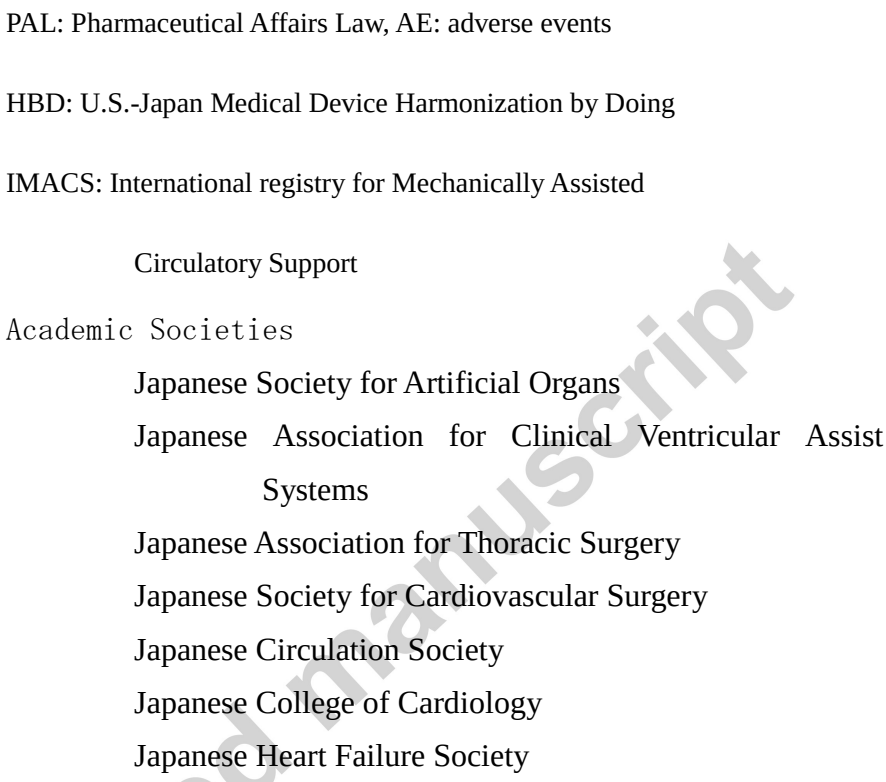
17. De By T, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, et al. The European Registry for patients with mechanical circulatory support (EUROMACS): first annual report. Eur J Cardiothorac Surg, 2015;47:770-776.

18. Hetzer R and Delmo Walter EM. Mechanical Circulatory Support Devices – In Progress. N Engl J Med. 2017; 376:487-9.

19. Sherman RE, Anderson SA, Dal Pan GJ et al. Real-World Evidence – What Is It and What Can It Tell Us? N Engl J Med. 2016; 375:2293-7.

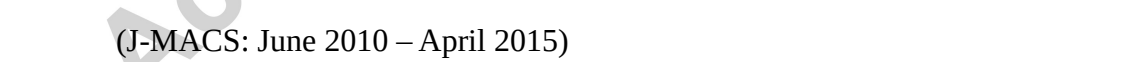
Figures

1. Organization of Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)

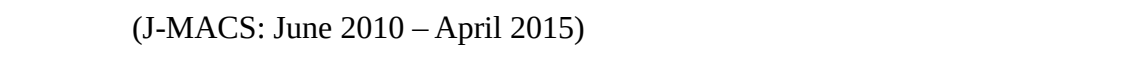


2. Patients enrolled in J-MACS

3. Actuarial survival for entire primary LVAD population registered with J-MACS.



4. Actuarial survival stratified by implantable and extracorporeal type for primary LVAD population (implantable/extracorporeal)



5. Actuarial survival stratified by INTERMACS patient profile for primary LVAD cases (patient profiles).

(J-MACS: June 2010 – April 2015)

6. Analysis of competing outcomes following implantation of implantable type in primary LVAD population. Death, died with device; Explanted, device explantation performed; Alive, device in place. At all points in time, the sum of the probabilities of each outcome event total 100%.

   (J-MACS: June 2010 375)– April 2015: implantable type: n=259)

7. Analysis of competing outcomes following implantation of extracorporeal type device in primary LVAD population. Death, died with device; Explanted, device explantation performed; Alive, device in place. At all points in time, the sum of the probabilities of each outcome event total 100%.

   (J-MACS: June 2010 – April 2015: extracorporeal type: n=73)

Tables

1. Device list
2. Patient demographics
3. Pre-implant patient profiles and device strategies
4 Primary causes of death
5. Adverse events (J-MACS: April 2010 - June 2015)
6. Rates of adverse events (patients affected/100 patients-months) within first 12 months after implantation (J-MACS: April 2010 - June 2015)

Table 1. Device list

Device	Type	Approval date
EVAHEART	Implantable & continuous	December 2010
DuraHeart	Implantable & continuous	December 2010
Heartmate II	Implantable & continuous	November 2012
Jarvik 2000	Implantable & continuous	November 2013
Nipro-Toyobo	Extracorporeal & pulsatile	April 1990

Table 2. Patient demographics

J-MACS (June 2010 – April 2015)	Implantable (%) n=259	Extracorporeal (%) n=73	Total (%) n=332
Gender			
Female	49 (19)	20 (27)	69 (21)
Male	210 (81)	53 (73)	263 (79)
Age at implant in years			
10~19	6 (2)	1 (1)	7 (2)
20~29	32 (12)	18 (25)	50 (15)
30~39	59 (23)	20 (27)	79 (24)
40~49	70 (27)	17 (23)	87 (26)
50~59	72 (28)	14 (19)	86 (26)
60 ~69	19 (7)	3 (4)	22 (7)
70~79	1 (0)	0 (0)	1 (0)
Mean ± SD	43.4±12.2	38.9±12.1	42.4±12.3
Height (cm)	167.7±8.0	168.0±7.9	166.5±8.5
Body Mass Index (BMI) (kg/m²)	20.7±3.6	20.7±3.3	20.8±4.7
Body Surface Area (BSA) (m²)	1.65±0.18	1.66±0.16	1.63±0.22
Pre-implant cardiac diagnosis (primary)			
Congenital heart disease	4 (2)	1 (1)	5 (2)
Coronary artery disease	26 (10)	10 (14)	36 (11)
Hypertrophic cardiomyopathy	32 (12)	7 (10)	39 (12)
Valvular heart disease	0 (0)	1 (0)	1 (0)
Dilated cardiomyopathy	184 (71)	52 (71)	236 (71)
Others	13 (5)	2 (3)	15 (5)

Table 3. Pre-implant patient profiles and device strategy

J-MACS (June 2010 – April 2015)	Implantable (%) n=259	Extracorporeal (%) n=73	Total (%) n=332
Pre-Implant INTERMACS patient profile			
Level 1: Critical cardiogenic shock	8 (3)	36 (49)	44 (13)
Level 2: Progressive decline	136 (53)	35 (48)	171 (52)
Level 3: Stable but inotrope dependent	106 (41)	2 (3)	108 (33)
Level 4: Recurrent advanced HF	9 (4)	0 (0)	9 (3)
Level 5: Exertion intolerant	0 (0)	0 (0)	0 (0)
Level 6: Exertion limited	0 (0)	0 (0)	0 (0)
Level 7: Advanced NYHA Class III	0 (0)	0 (0)	0 (0)
Pre-Implant device strategy			
Bridge to transplant, listed	174 (67)	6 (8)	180 (54)
Bridge to transplant, applied	54 (21)	1 (1)	55 (17)
Bridge to transplant, pre-application	29 (11)	22 (30)	51 (15)
Long-term support without transplant	2 (1)	0 (0)	2 (1)
Post-ADHF*	0 (0)	9 (12)	9 (3)
Pre-ADHF	0 (0)	2 (3)	2 (1)
Others	0 (0)	33 (45)	33 (10)

*ADHF: acute decompensated heart failure requiring VAD support as INTERMACS patient profile level 1-2

Table 4. Primary cause of death

J-MACS (April 2010 – June 2015	Implantable (n=23)		Extracorporeal (n=8)	
Primary cause of death	No.	%	No.	%
Infection	7	30.4	6	75.0
Neurologic event	7	30.4	0	0.0
Multi-organ failure	3	13.0	1	12.5
Right ventricular (RV) failure	2	8.7	0	0.0
Bleeding	1	4.4	0	0.0
Device malfunction	1	4.4	0	0.0
Others	2	8.7	1	12.5
Total	23	100.0	8	(100.0)

Table 5. Adverse events (J-MACS: April 2010 - June 2015)

Adverse event	Implantable (n=259)			Extracorporeal (n=73)		
	≤30 days	>30 days	Total	≤30 days	>30 days	Total
Infection	32	90	122	10	21	31
device-related	1	21	22	0	10	10
non-device-related	31	69	100	10	11	21
Neurologic dysfunction	24	63	87	9	13	22
hemorrhagic stroke	5	30	35	1	8	9
ischemic stroke	9	18	27	4	1	5
TIA	8	13	21	2	3	5
others	2	2	4	2	1	3
Device malfunction	16	64	80	19	18	37
Bleeding	34	19	53	9	9	18
non-GI bleeding	33	16	49	8	9	17
GI bleeding	1	3	4	1	0	1

(TIA: transient ischemic attack, GI bleeding: gastrointestinal bleeding. Values indicate number of patients affected.)

Table 6: Adverse events rates (patients affected/100 patient-months) in first 12 months after implant (J-MACS: April 2010 - June 2015)

Adverse event	Implantable (n=259)		Extracorporeal (n=73)	
	No. affected	rate	No. affected	rate
Infection	104	6.24	30	11.5
Neurologic dysfunction	75	3.97	19	6.29
Device malfunction	66	3.36	32	11.85
Bleeding	48	2.38	14	4.21

Fig1

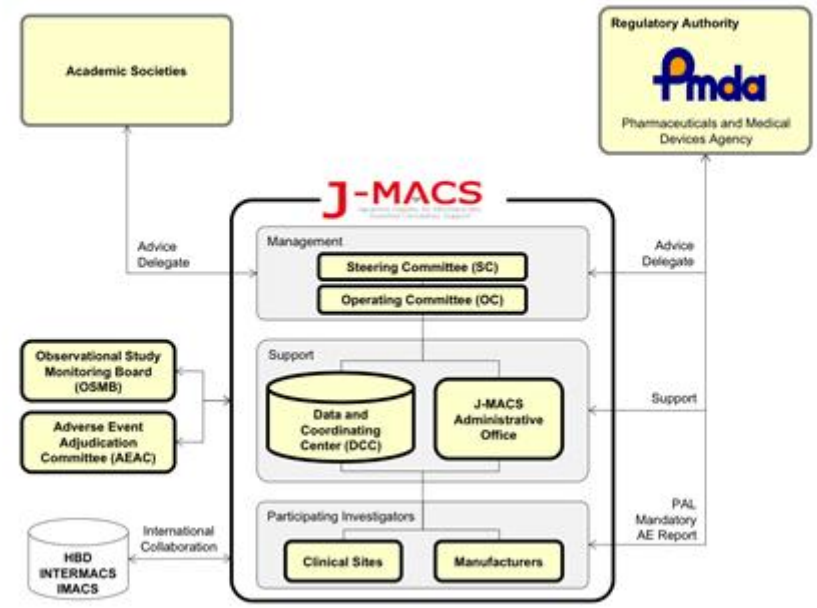


Figure 2

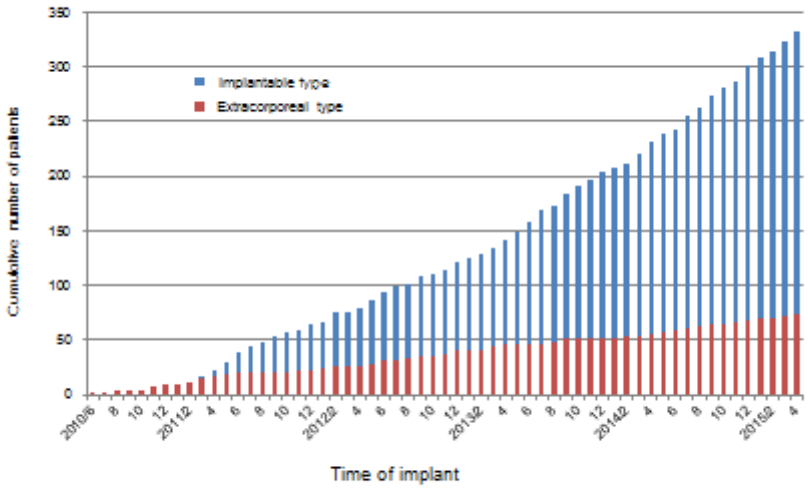


Figure 3

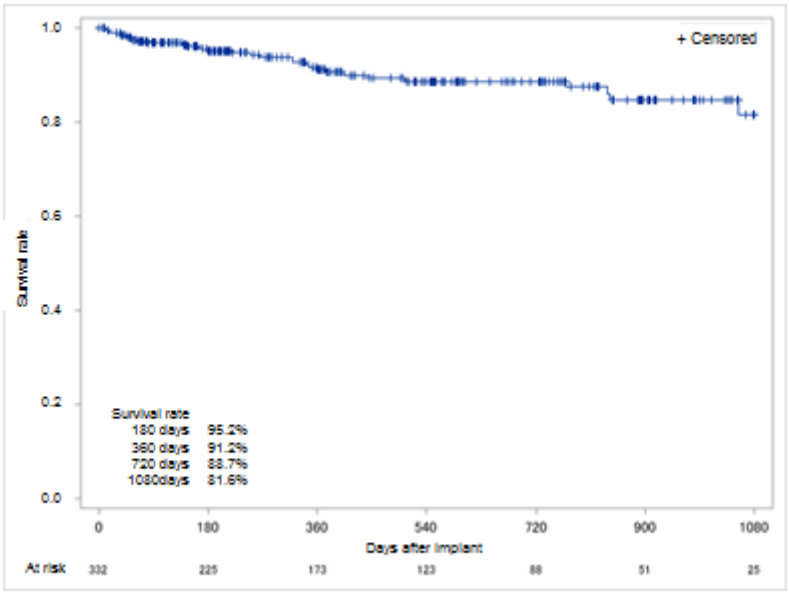


Figure 4

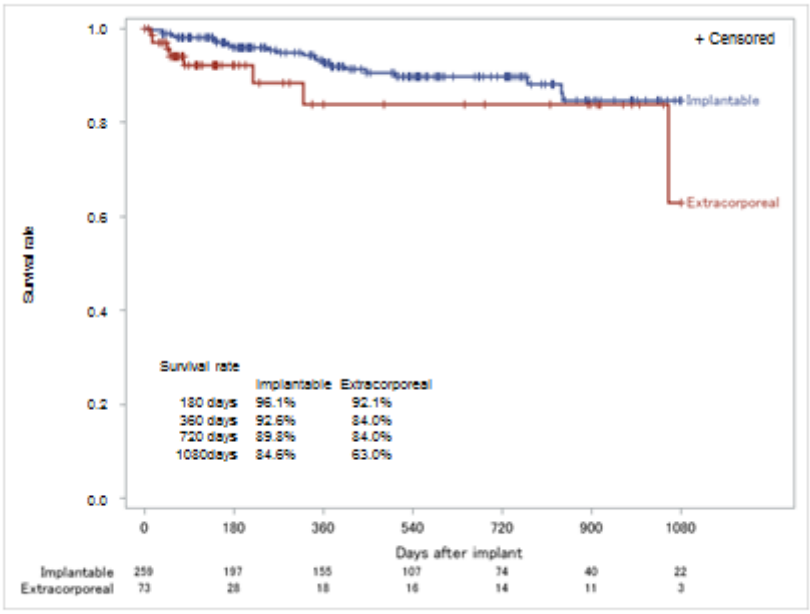


Figure 5

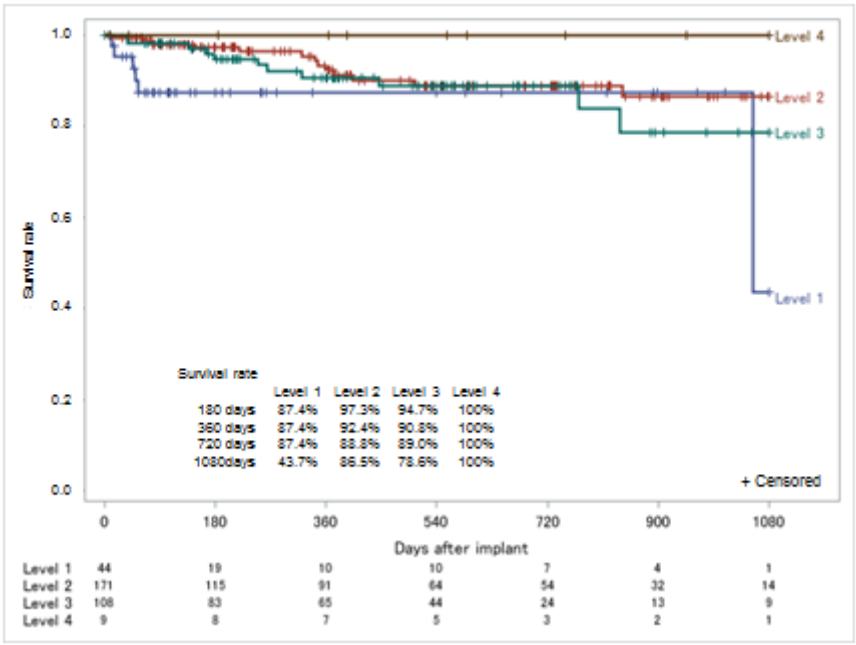


Figure 6

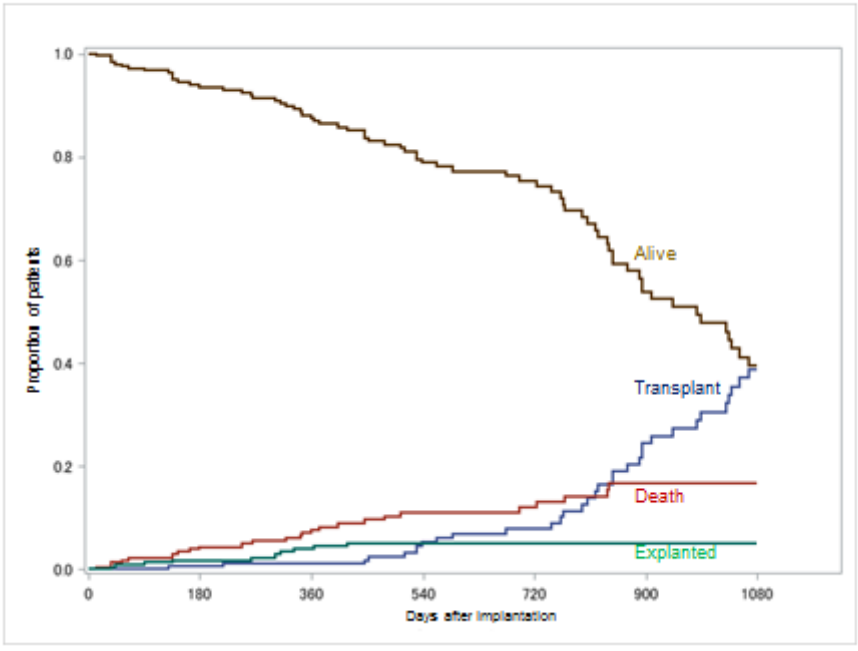


Figure 7