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ORIGINAL CLINICAL SCIENCE

Second annual report from the ISHLT Mechanically Assisted Circulatory Support Registry

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KEYWORDS:
mechanical circulatory support;
International Society for Heart and Lung Transplantation;
IMACS;
ventricular assist devices;
risk factors;
adverse events;
outcomes

The second annual IMACS registry report includes over 14, 000 patients from 35 countries. Survival, adverse events, and an updated risk model is presented. Continuous flow pumps continue to dominate the world's experience. One and Two-year survival remains at 80% and 70%. Congenital heart disease and biventricular support are the most dominant risk factors. The database is poised for major novel analyses.

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The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry represents a global database for patients receiving durable mechanical circulatory support (MCS) devices. The stated mission focuses on acquisition of international MCS patient data and generation of analyses and publications that benefit the field.[1,2] This second annual report focuses on an updated survival analysis, adverse events, and risk modeling.

Since the initiation of patient enrollment in January 2013, 14,062 patients have been enrolled through

1053-2498/
https://doi.org/10.1016/j.healun.2018.01.1294

Table 1 IMACS Participating Countries, January 1, 2013 to December 31, 2016 ($n = 14,062$)

Australia	Denmark	Israel	Singapore
Austria	Egypt	Italy	Slovakia
Azerbaijan	Finland	Japan	Spain
Belarus	France	Kazakhstan	Sweden
Belgium	Germany	Netherlands	Switzerland
Brazil	Greece	New Zealand	Turkey
Canada	Hong Kong	Norway	UK
Colombia	Hungary	Poland	USA
Czech Republic	Ireland	Saudi Arabia	

IMACS; International Society for Heart and Lung Transplantation Mechanical Circulatory Support Registry

December 31, 2016, representing 35 countries (Table 1). Data sources include individual hospitals and the following collectives (large databases that have collected MCS data for entire countries or regions): the European Registry for Patients with Mechanical Circulatory Support (EUROMACS, Europe)[3]; the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS, USA)[1]; the Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS, Japan)[4]; and the UK Registry (UK). Collective data downloads occur in December of each year and are merged into one comprehensive IMACS data set for analysis.

Patients' demographics and device types

Among device types represented in this database, left ventricular assist devices (LVADs) accounted for 13,102 (93%) implants, of which 99% were continuous-flow (CF) pumps. Total artificial hearts (TAHs) represented 2% (279 devices) of the experience and biventricular support 5% (refer to Supplementary Material Figure S1, available online at www.jhltonline.org/).

Patients' demographics indicate 79% males, with 60% of patients between 50 and 60 years of age (Table 2). At the time of implant, 51% of patients were in rapid decline or cardiogenic shock (Table 3). Only 16% of patients had ambulatory heart failure (Patient Profile 4 to 7). Nearly 60% of patients were actively listed or considered candidates for heart transplantation, whereas 41% received devices as long-term destination therapy (Table 4). The device strategies among various patient profiles[1] at implant are listed in Table 5.

Table 2 Age Distribution at Implant, IMACS, January 1, 2013 to December 31, 2016 ($n = 14,062$)

Age at implant	Number	Percent
19 to 29 years	713	5%
30 to 49 years	3,248	23%
50 to 60 years	8,447	60%
70^{+} years	1,654	12%
Total	14,062	100%

IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support.

Survival

Among all patients, survival at 1 and 2 years continued to be 79% and 70%, respectively (Supplementary Material Figure S2 online).[5] The 3-year survival with CF durable devices (Figure 1) was just over 60%. Figure 1 shows hazard function[6] had a rapidly decreasing risk, which merged with a constant phase at about 3 months. Survival was clearly superior for patients receiving isolated left ventricular support compared with biventricular support (Figure 2). The 1-year survival for isolated CF LVAD support was 81% vs 53% for biventricular support and about 48% for TAH. The rate of transplantation was rather low, 28% at 1 year, among patients with a CF LVAD listed for transplant (Supplementary Material Figure S3 online). The transplant rate was higher for listed patients requiring biventricular support (36% at 1 year), and highest for TAH patients (50% at 1 year) (Supplementary Material Figures S4 and S5 online). Patients implanted with a strategy of destination therapy continued to show worse survival compared with a strategy of bridge to transplant or transplant candidacy (Figure 3).

Causes of death

The most frequent primary causes of death were multisystem organ failure (21% of mortality), cardiovascular causes (primarily right heart failure) (20%), and stroke (19%) (Supplementary Material Table S1 online).

Table 3 Patient Profile Distribution at Implant, IMACS, January 1, 2013 to December 31, 2016 ($n = 14,062$)

Patient profile at time of implant	Number	Percent
1. Critical cardiogenic shock	2,405	17%
2. Progressive decline	4,714	34%
3. Stable but inotrope dependent	4,558	32%
4. Resting symptoms	1,817	13%
5. Exertion intolerant	298	2%
6. Exertion limited	87	0.6%
7. Advanced NYHA Class III	66	0.5%
Unspecified	117	0.8%
Total	14,062	100%

IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

Table 4 Device Strategy, IMACS, January 1, 2013 to December 31, 2016 ($n = 14,062$)

Device strategy	N	%
Listed for transplant	3,984	28%
Bridge to candidacy	4,072	29%
Destination therapy	5,724	41%
Other	282	2%
Total	14,062	100%

IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support.

Adverse events

Infection and bleeding affected the most patients, occurring in 40% and 35% of patients, respectively; 19% had neurologic events (Table 6). Bleeding was the most frequent adverse event during the first 3 months post-implant, followed by infection (Table 7). During the later phase (beyond 3 months), infection and internal bleeding had the highest incidence. Among patients with CF devices, freedom from first infection was 68% at 6 months (Supplementary Material Figure S6). The likelihood of stroke (ischemic or hemorrhagic) was 14% at 6 months and 19% at 12 months (Supplementary Material Figure S7 online). The risk of respiratory failure was highest during the first month (Supplementary Material Figure S8 online).

Risk factors for mortality

A detailed multivariable analysis identified risk factors for early and midterm mortality for patients receiving CF devices (Table 8). The 2 most dominant risk factors for early mortality were a diagnosis of congenital heart disease (hazard ratio [HR] 5.2) and the need for biventricular support (HR 3.4). The adverse effect of congenital heart disease was only evident during the first 2 months, after which patients with congenital heart disease did as well as those with other diagnoses (Figure 4).

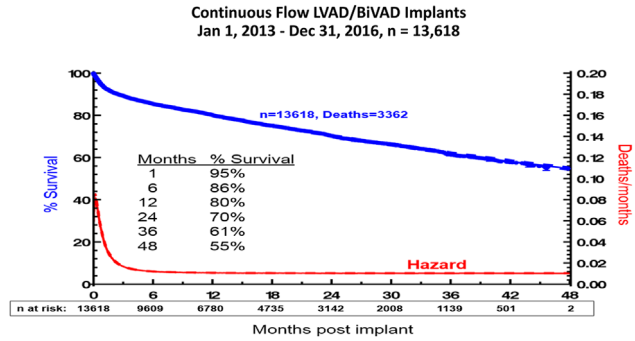


Figure 1 Parametric survival curve and associated hazard function with 70% confidence limit for survival after implantation of a continuous-flow left ventricular assist device (LVAD) or biventricular assist device (BiVAD), January 1, 2013 to December 31, 2016 ($n = 13,618$). The number of patients at risk during each time interval is indicated below the diagram.

Older age was a risk factor both in the early and constant phases, particularly in patients >50 years old (Figure 5). Among patients 30 to 50 years old, the 2-year survival was 79% compared with 58% for patients >70 years old ($p < 0.0001$). The increased vulnerability of elderly patients is especially magnified when they are critically ill at implant or require biventricular support (Figures 6 and 7).

This global analysis quantifies the importance of increased risk among patients who are critically ill (Profile 1 or 2) at the time of implant (Figure 8). Compared with stable but inotrope-dependent patients (Patient Profile 3) those presenting in cardiogenic shock had a 1-year survival of 71% vs 84% ($p < 0.0001$), respectively. The stratified Kaplan–Meier depiction in Figure 8 also shows the midterm survival benefit of patients who were less ill (Levels 5 to 7) at the time of implant. If this trend continues, and depending on associated post-implant morbidity in less ill patients, this may have implications regarding patient selection. A strategy of destination therapy was only a risk factor in the constant phase, with HR 1.14 (Figure 3 and Table 8). Concomitant surgeries also increased risk (Table 8, and Supplementary Material Figure S9 online).

Table 5 Device Strategy by Patient Profile, IMACS, January 1, 2013 to December 31, 2016 ($n = 14,062$)

	Device strategy at time of implant							
	Listed for transplant		Candidacy to transplant		Destination therapy		Other	
Patient profile at time of implant	*n*	%	*n*	%	*n*	%	*n*	%
1. Critical cardiogenic shock	526	13.2%	865	21.2%	885	15.4%	129	45.7%
2. Progressive decline	1,478	37.0%	1,315	32.2%	1,828	31.9%	93	32.9%
3. Stable but inotrope dependent	1,313	32.9%	1,212	29.7%	2,005	35.0%	28	9.9%
4. Resting symptoms	468	11.7%	534	13.1%	799	13.9%	16	5.6%
5. Exertion intolerant	107	2.6%	71	1.7%	115	2.0%	5	1.7%
6. Exertion limited	32	0.8%	23	0.5%	28	0.4%	4	1.4%
7. Advanced NYHA Class III	22	0.5%	20	0.4%	23	0.4%	1	0.3%
Unknown	38	0.9%	32	0.7%	41	0.7%	6	2.1%
Total	3,984	100.0%	4,072	100.0%	5,724	100.0%	282	100.0%

IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

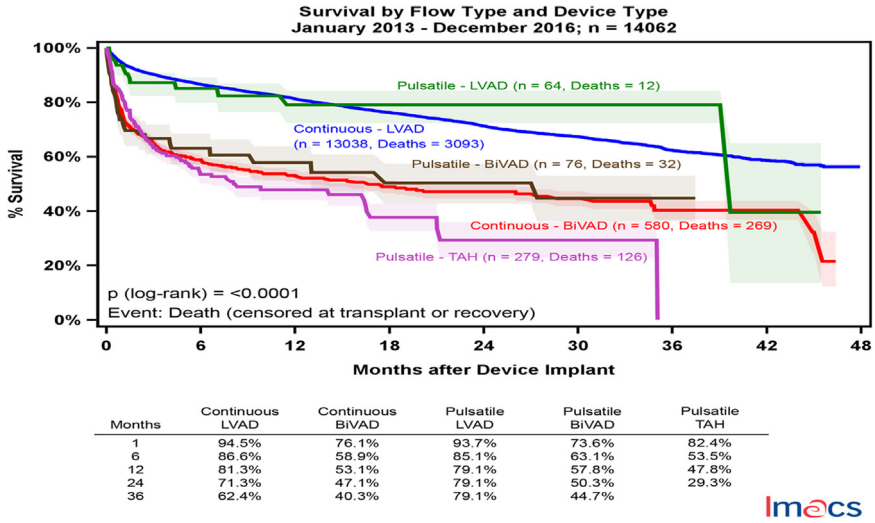


Figure 2 Actuarial survival curve for primary implants, stratified by flow type and device type, January 1, 2013 to December 31, 2016 (n = 14,062). The shaded areas indicate ±1 standard error. BiVAD, biventricular assist device; LVAD, left ventricular assist device; TAH, total artificial heart.

Pre-implant renal function had a dominant effect on survival (Table 8). Patients requiring dialysis within 2 days before implant had a high early mortality (Supplementary Material Figures S10 and S11 online), and higher blood urea nitrogen (BUN) (Supplementary Material Figure S12 online) and creatinine impacted early and later survival. Signs of hepatic dysfunction and tricuspid regurgitation as risk factors likely reflect worsening right heart failure. Poor nutritional status (lower albumin) impacted both early and longer term survival (Table 8).

Summary

1. The IMACS database now includes >14,000 patients with global representation.
2. CF pumps currently constitute 97% of device implants.
3. Patients with ambulatory heart failure account for only 16% of durable device implants.
4. Overall 1- and 2-year survival have continued at 80% and 70%, respectively, in this international database.
5. For the first time, we have identified a more favorable midterm survival among patients with ambulatory heart failure.
6. Among the elderly, survival is particularly poor among patients critically ill at implant or if biventricular support is required.
7. Bleeding and infection remain the most common adverse events.
8. The most dominant risk factors early after implant are a diagnosis of congenital heart disease and the need for biventricular support.
9. Peripheral vascular disease is a major predictor of midterm mortality.
10. The IMACS database is poised to generate impactful analyses in the international MCS arena.

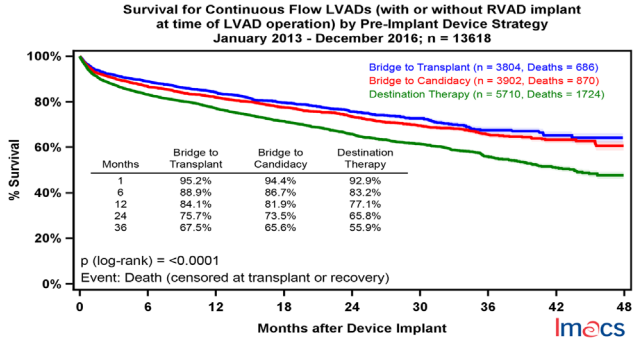


Figure 3 Actuarial survival curve for continuous-flow LVADs and BiVADs, stratified by pre-implant device strategy, January 1, 2013 to December 31, 2016 (n = 13,618). The shaded areas indicate ±1 standard error. BiVAD, biventricular assist device; LVAD, left ventricular assist device.

Table 6 Major Adverse Events, Continuous-flow LVAD/BiVAD, IMACS, January 1, 2013 to December 31, 2016 (n = 13,618)

Adverse event type	Patient experiencing event	Percentage of all patients
Infection	5,439	40%
Bleeding	4,745	35%
Neurologic dysfunction	2,638	19%
Respiratory failure	2,205	16%
Device malfunction	233	2%
Arterial non-CNS thromboembolism	159	1%

BiVAD, biventricular assist device; CNS, central nervous system; IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

Table 7 Adverse Event Rates, Continuous-flow LVAD/BiVAD, IMACS, January 1, 2013 to December 31, 2016 ($n = 13,618$)

Adverse event type	Early event (<3 months) count (n)	Early event (<3 months) rate (per 100 patient-months)	Late event (≥3 months) count (n)	Late event (≥3 months) rate (per 100 patient-months)	p-value
Bleeding	5,074	13.78	4,845	2.88	<0.0001
Infection	4,664	12.66	5,891	3.51	<0.0001
Respiratory failure	2,242	6.09	641	0.38	<0.0001
Neurologic dysfunction	1,536	4.17	1,943	1.16	<0.0001
Device malfunction	99	0.27	241	0.14	<0.0001
Arterial non-CNS thromboembolism	112	0.30	54	0.03	<0.0001

BiVAD, biventricular assist device; CNS, central nervous system; IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

Table 8 Continuous-flow LVAD/BiVAD, IMACS, January 1, 2013 to December 31, 2016 ($n = 13,618$)

	Early hazard		Constant hazard	
Pre-implant risk factors for death	Hazard ratio	p-value	Hazard ratio	p-value
Demographics				
Older age (unit: 10 years)	1.44	<0.0001	1.23	<0.0001
Female	1.28	0.003	1.18	0.008
Higher BMI (unit: 5 kg/m^2)	1.12	<0.0001	1.04	0.021
Destination therapy strategy at time of implant			1.14	0.014
Not blood type O			0.89	0.013
Surgical complexities				
History of CABG	1.31	0.002	1.20	0.004
Concomitant surgery	1.34	<0.0001		
BiVAD	3.42	<0.0001		
Clinical status				
Patient Profile 1	1.77	<0.0001		
Patient Profile 2	1.51	<0.0001		
Not patient Profile 4 to 7			0.85	0.014
Primary diagnosis—congenital	5.23	0.002		
Peripheral vascular disease			1.41	<0.01
Intervention 48 hours pre-implant—ventilator	1.32	0.003		
BUN (unit: 10 mg/dl) higher	1.06	<0.0001	1.04	<0.0001
Creatinine (unit: 1 mg/dl) higher			1.08	0.004
Intervention with 48 hours pre-implant—dialysis	1.92	<0.0001		
Albumin (unit: 1 g/dl) lower	0.85	0.001	0.86	<0.0001
Sodium (unit: 10 mEq/liter) lower			0.86	0.004
AST (unit: 10 U/liter) higher	1.13	<0.0001		
ALT (unit: 10 U/liter) lower	0.94	<0.01		
Total bilirubin (unit: 5 mg/dl) higher	1.18	<0.0001		
Tricuspid regurgitation: moderate/severe	1.37	<0.0001		
Implantable cardioverter-defibrillator			1.21	0.004

CNS-Central Nervous System; LVAD-left ventricular assist device; BiVAD-biventricular assist device; CABG-Coronary Artery Bypass Graft; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bi-VAD, biventricular assist device; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronoary bypass artery graft; IMACS, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

- Age: calculated risk factor for 10 year range
- BMI-Body Mass Index (kg/m^2): 5 unit increase
- Total Bilirubin (mg/dL): 5 unit increase
- Sodium (mEq/L): 10 unit decrease
- BUN-Blood Urea Nitrogen (mg/dL): 10 unit increase
- Aspartate Aminotransferase/AST (u/L): 10 unit increase
- Alanine Aminotransferase/ALT (u/L): 10 unit decrease

[a]None.

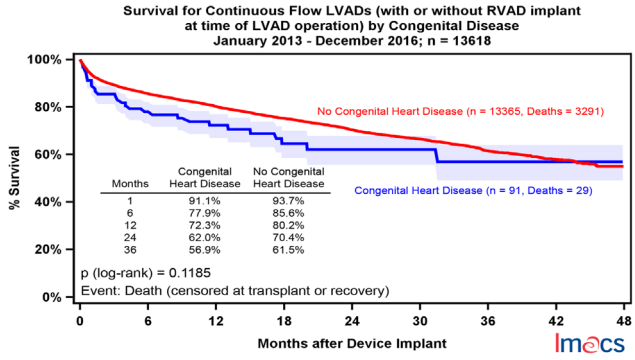


Figure 4 Actuarial survival curve for continuous-flow LVADs and BiVADs, stratified by pre-implant history of congenital heart disease, January 1, 2013 to December 31, 2016 ($n = 13,618$). The shaded areas indicate ±1 standard error. BiVAD, biventricular assist device; LVAD, left ventricular assist device.

Disclosure statement

J.K.K. received partial support as principle investigator of the INTERMACS NHLBI-sponsored Registry for U.S. mechanical circulatory support (funding paid through institution) and is chair of the DSMB for a Xeltis Clinical Trial of a bioprosthetic heart conduit (receiving at 1-time fee of $2,500). J.C. received $5,000 for research-related travel support from Abbott and Medtronic and is on the steering committee for Medtronic and Abbott, Institutional Clinical Trial Support. S.S. works as a proctor and consultant for Medtronic. D.G. is an Abbott consultant and received travel expenses related to role as national principal investigator in the MOMENTUM 3 clinical trial and is a consultant for Ethicon, Inc. The remaining authors have no conflicts of interest to disclose.

IMACS acknowledges the dedicated commitment of all hospitals and collectives participating in IMACS. The data supplied by each hospital contributes to our mission of advancing the field of mechanical circulatory support and generating scientific publications for the ISHLT.

INTERMACS® is a registered trademark of the U.S. Department of Health and Human Services (HHS), which provided the original funding for the INTERMACS Registry. HHS does not endorse any products or services.

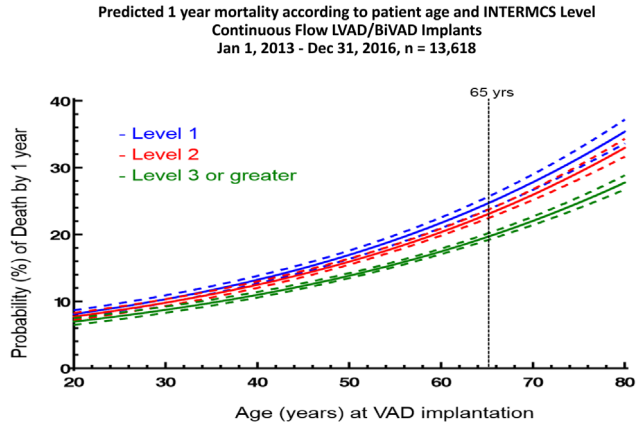


Figure 6 Nomogram showing the solution to the multivariable equation for death by 1 year, depicting the interaction between patient age and patient profile level at implant for continuous-flow LVADs and BiVADs, January 1, 2013 to December 31, 2016 ($n = 13,618$).

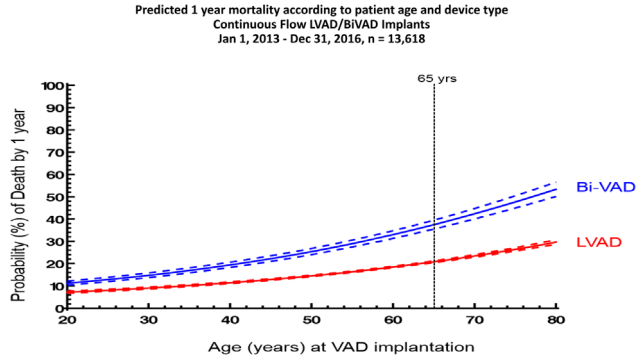


Figure 7 Nomogram showing the solution to the multivariable equation for death by 1 year, depicting the interaction between patient age and device type at implant for continuous-flow LVADs and BiVADs, January 1, 2013 to December 31, 2016 ($n = 13,618$).

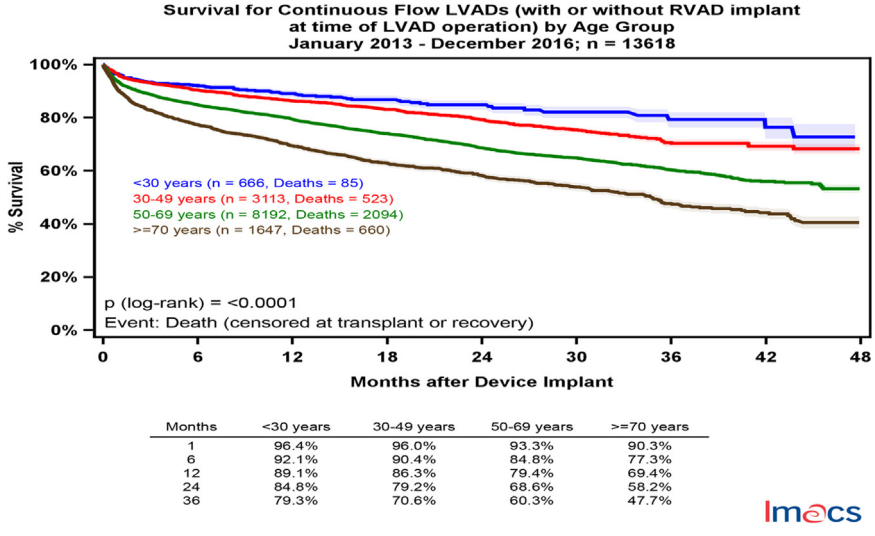
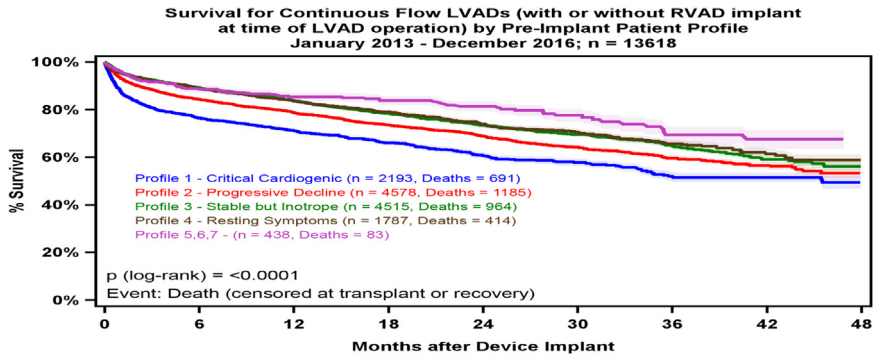


Figure 5 Actuarial survival curve for continuous-flow LVADs and BiVADs, stratified by pre-implant age group, January 1, 2013 to December 31, 2016 ($n = 13,618$). The shaded areas indicate ±1 standard error. BiVAD, biventricular assist device; LVAD, left ventricular assist device.



Months	Profile 1 Critical Cardiogenic	Profile 2 Progressive Decline	Profile 3 Stable but Inotrope	Profile 4 Resting Symptoms	Profile 5,6,7 All Others
1	87.9%	93.4%	96.0%	95.5%	96.1%
6	76.6%	84.4%	89.3%	88.9%	88.7%
12	71.2%	78.8%	83.8%	83.6%	85.5%
24	60.7%	68.9%	73.4%	73.9%	81.5%
36	52.0%	59.7%	64.9%	65.7%	69.4%

Figure 8 Actuarial survival curve for continuous-flow LVADs and BiVADs, stratified by pre-implant patient profile, January 1, 2013 to December 31, 2016 ($n = 13,618$). The shaded areas indicate ±1 standard error. BiVAD, biventricular assist device; LVAD, left ventricular assist device.

Appendix A. Supplementary material

Supplementary data associated with this article can be found online version at www.jhltonline.org.

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