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## INTERMACS ANNUAL REPORT

### **Eighth Annual INTERMACS Report: Special Focus on Framing the Impact of Adverse Events**

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#### **KEYWORDS:**

**advanced heart failure;**

**destination therapy;**

**INTERMACS;**

**mechanical support;**

**ventricular assist device**

## ABSTRACT

The eighth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) updates the first decade of patient enrollment. The database now includes over 20, 000 patients from more than 180 hospitals. In the current era, greater than 95% of implants are continuous flow devices. Overall survival continues to remain above 80% at one year and 70% at 2 years. Review of major adverse events shows minimal advantage for patients with ambulatory heart failure pre-implant. Stroke, major infection, and continued inotrope requirement during the first 3 months have a major effect on subsequent survival. Greater application of durable devices to patients with ambulatory heart failure will mandate more effective neutralization or prevention of major adverse events.

## INTRODUCTION

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)<sup>(1)</sup>, a public-private partnership between the National Heart, Lung and Blood Institute (NHLBI), the U.S. Food and Drug Administration (FDA), Centers for Medicaid and Medicare Services, hospitals, and industry, has completed a decade of data collection. This annual report provides an update on many aspects of basic registry data as well as a focus on the impact of adverse events. The pediatric aspects of INTERMACS (PEDIMACS) are detailed in a separate report.

## PATIENT AND SITE ENROLLMENT

Between June 23, 2006 and December 31, 2016, 22,866 patients who received a US Food and Drug Administration (FDA)-approved mechanical circulatory support (MCS) device were entered into the INTERMACS database (Figure 1). Of the 185 participating hospitals, the rate of patient enrollment has continued at a pace exceeding 2,500 implants per year, with a decrease noted during 2016, likely related to increased enrollment of patients with pumps implanted within clinical trials. INTERMACS captures only FDA approved MCSDs. During 2016, an important clinical trial investigating a non-FDA approved device (HeartMate 3; Abbot Laboratories, Abbot Park, IL) was actively enrolling subjects. These devices are not captured in INTERMACS. Of the 18,987 primary left ventricular assist device (LVAD) implants, greater than 90% have been continuous flow devices. Since 2013, both centrifugal and axial flow pumps have been utilized (Supplemental Figure 1)\*. The Heartmate II (Abbott Laboratories, Abbott Park, IL) axial-flow pump was approved as bridge-to-transplant (BTT) therapy in 2008 and for Destination Therapy (DT) in 2010. The HeartWare HVAD (Medtronic Inc., Minneapolis, MN) centrifugal flow pump was approved for BTT in November 2012. It should be noted that the total numbers and trends for durable device implantation do not include patients enrolled in the investigational arm of new device clinical regulatory trials. FDA approved devices used as a control comparator in clinical regulatory trials are recorded in INTERMACS.

## DEVICE STRATEGY

The proportion of LVADs implanted for DT has progressively increased over the past decade. By 2015, nearly 50% of continuous flow device implants were implanted with a strategy of DT (Table 1). Patients listed for transplantation comprised 26% of implants in the recent era, and bridge to candidacy 23%.

## PATIENT PROFILES

The INTERMACS patient profiles 1-6 indicate the various clinical stages of NYHA Class IV<sup>2</sup>. The proportion of patients implanted with cardiogenic shock has stabilized at 14-16% since 2008. (Table 2) Of note, the largest and proportionately increasing

category are those patients in Profile 3 (stable but inotrope dependent), now representing nearly 38% of implants. Patients in Profiles 4-7 are considered to have ambulatory heart failure. The proportion of patients in this category has actually decreased since 2012-2014, 18.2% vs. 12.8% (2015-2016).

## **SURVIVAL**

The overall survival of patients receiving continuous flow LVADs +/- RVAD, since 2008 is 81% at 12 months and 70% at 24 months (Figure 2). The hazard analysis identifies three separate phases of risk: an early rapidly falling hazard phase merges with a constant phase at about 3 months. A gradually increasing late hazard phase becomes manifest at about 84 months. (Supplemental Figure 2) An era effect has been identified, which is most apparent when comparing the early era of 2008-2012 with the more recent eras (Figure 3). The overall survival curve has remained essentially unchanged since 2013. The negative survival impact of re-operations (most commonly for pump exchange<sup>3,4</sup>) is highlighted in Figure 4.

## **COMPETING OUTCOMES**

Among patients listed for cardiac transplantation, just over 30% of VAD patients underwent cardiac transplantation within the first year (Figure 5). Of importance, actual mortality on a device is just over 10% at 1 year. Among patients who are candidates for transplantation but not actually listed, less than 20% are actually listed and transplanted within the first year (Supplemental Figure 3).

## **CAUSES OF DEATH**

Early after device implant, multisystem organ failure, right heart failure, and strokes (ischemic or hemorrhagic) pose the greatest risk. Between 6 months and 4 years, stroke dominates as the major cause of death (Figure 6). The cumulative risk of fatal strokes out to 6 years is depicted in Figure 7.

## **RISK FACTORS FOR MORTALITY**

A detailed multivariable pre-implant risk factor analysis is presented in Table 3. Device type (axial vs. centrifugal flow) was not a risk factor for early or later mortality.

Older age continues to be a risk factor both early and later; female gender is an important risk early. More critically ill patients increase the risk of early mortality (Figure 8). The interaction between INTERMACS Profile and age is such that patients above about 65 years at are particularly high risk when their circulatory state is rapidly deteriorating (Profile 1 and 2) (Supplemental Figure 4). Patients undergoing implant with a strategy of long-term support (DT) continue to have somewhat worse survival than those considered for cardiac transplantation (Figure 9). The Kaplan Meier 5 year survival estimate for DT is approximately 35%.

Among noncardiac system comorbidities, chronic pulmonary disease, peripheral vascular disease, and renal dysfunction, as well as the overall nutritional state, continue to impact survival in either the early or late phase (Table 3). The biggest contributor to early mortality is the need for right ventricular assist device (BiVAD) support at the original operation, with a hazard ratio of 3.76 (Supplemental Figure 5). The next largest risk factor identified is pre-implant dialysis, with a hazard ratio 3.29. As expected, increased surgical complexity, either through previous cardiac surgery or concomitant cardiac procedures at the implant operation, increases early risk.

In the quality of life domain, patients who were too sick to complete the EQ-5D Questionnaire had a higher risk of early mortality, likely reflecting a more critically ill INTERMACS Profile of 1 or 2.

## **TOTAL ARTIFICIAL HEART EXPERIENCE**

A total of 373 total artificial hearts from a limited number of centers have been entered into the INTERMACS database. Since these are patients who generally need biventricular support, the survival more closely approximates the BiVAD cohort (Figure 10). The 12 month survival remains less than 60%.

## **MAJOR ADVERSE EVENTS**

Bleeding as an adverse event reflects predominately surgical bleeding during the early phase and gastrointestinal bleeding after the first 3 months (Table 4). After bleeding, infection is the most frequent adverse event during the first 3 months and the most common thereafter. The risk of stroke persists as an important adverse event

throughout the first year following implant. When adverse events are examined according to INTERMACS profiles, severe right heart failure is highly correlated with patient profile, with those in cardiogenic shock having a two-fold or greater propensity for severe right ventricular failure compared to other patient profiles (Figure 11). When comparing ambulatory heart failure patients to those more critically ill, there is no difference in the time to first pump related infection (Figure 12), stroke (Figure 13), or time to first re-hospitalization (Figure 14). In a composite event of multiple adverse events, INTERMACS levels 2-7 had somewhat greater freedom compared to those patients in cardiogenic shock at implant (Figure 15).

## **QUALITY OF LIFE**

On average, important improvement in quality of life is noted in the first 3 months and is maintained out to at least 24 months post implant. The quality of life outcomes are similar for the domains of self-care (Supplemental Figure 6), usual activities (Supplemental Figure 7), and visual analog score (Supplemental Figure 8). When patients are queried about whether they are satisfied with their decision to have VAD therapy, approximately 80% of responding patients have a favorable impression of their VAD experience during the first 2 years (Supplemental Figure 9).

## **IMPACT OF ADVERSE EVENTS ON SUBSEQUENT SURVIVAL**

Adverse events during MCS are known to profoundly impact life satisfaction and often survival. However, the quantitative impact of such events compared to pre-implant risk factors has not previously been analyzed. Table 5 lists the risk factors identified among continuous flow LVAD patients who have survived at least 3 months post-implant. In addition to the preoperative variables examined in Table 3, major adverse events occurring within the first 3 months were also included, as were the quality of life indicators at 3 months. Compared to the risk factors identified in the pre-implant model, only 4 were retained in the 3 month model which included post-implant adverse events (Table 5). A constant phase of hazard was identified, in which the presence of ascites, the need for continuous inotropic support, and the number of strokes during the first 3 months carried the highest hazard ratio for subsequent mortality. The negative impact of

stroke on subsequent survival is apparent in Figure 16. When multiple major adverse events occur, the effect is particularly severe.

## SUMMARY

- Over 22,000 patients have been entered into the INTERMACS database over the past decade.
- The proportion of patients receiving devices with ambulatory heart failure has decreased slightly over the past 2 years.
- Overall Kaplan-Meier survival during support is 81% at 1 year and 70% at 2 years.
- InterMACS profiles 1 and 2, as well as renal dysfunction and right heart failure, continue to be important risk factors for early mortality.
- Early post-implant, multisystem organ failure, right heart failure, and stroke pose the greatest risk for death.
- After the first 6 months, stroke remains the major cause of death out to 4 years.
- Important improvement in quality of life is, on average, maintained out to at least 2 years post-implant.
- About 80% of responding patients have a favorable impression of their VAD experience during the first 2 years.
- The occurrence of major adverse events within the first 3 months has a major impact on subsequent survival.

## CONCLUSION

Despite incremental improvements in survival, the rate of adoption and dissemination of MCS therapy using FDA approved devices has appeared to plateau during the most recent era. Extension of durable devices to a greater proportion of ambulatory heart failure patients will require more effective neutralization or prevention of major adverse events. Greater emphasis on patient reported outcomes in addition to traditional assessments of outcomes is needed to understand the totality of the benefit and risk of MCS therapy.



## ACKNOWLEDGEMENTS

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## DECLARATIONS

Lynne Warner Stevenson, M.D., received research support from Abbot Laboratories, Abbot Park, IL.

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## FIGURE LEGENDS

**Figure 1:** Summary of INTERMACS implants between June 2006 and December 2016. VAD, ventricular assist device; R, right; L, left; TAH, total artificial heart.

**Figure 2:** Parametric survival curve and associated hazard function for continuous flow implants, including both isolated left ventricular assist devices (LVADs) and biventricular support (BiVAD). The dashed lines indicate the 70% confidence limits (CL).

**Figure 3:** Kaplan-Meier survival following continuous flow VAD implant, stratified by Era at the time of implant. LVAD, left ventricular assist device; BiVAD, biventricular assist

device. \*One patient was implanted with a continuous flow device before 2008 and was excluded from this depiction.

**Figure 4:** Actuarial survival stratified by whether the VAD implant represented the original operation (blue curve), the second operation (first pump replacement) (red curve), or the third operation (second pump replacement) (green curve). Depiction is as in Figure 3.

**Figure 5:** Competing outcomes depiction for continuous flow left ventricular assist devices (CFLVADs) in patients who are listed for heart transplantation (BTT). At any point in time, the sum of the proportions for each outcome equals 1.

**Figure 6:** Hazard function curves indicating the instantaneous risk of death overtime for the major causes/modes of death. RHF, right heart failure; MSOF, multiple system organ failure.

**Figure 7:** Cumulative hazard function for major causes/modes of death. RHF, right heart failure; MSOF, multiple system organ failure.

**Figure 8:** Kaplan-Meier survival curves, stratified by INTERMACS profile at the time of implant. Depiction is as in Figure 3.

**Figure 9:** Kaplan-Meier survival curves, stratified by device strategy and era. The depiction and abbreviations are as in Figure 3.

**Figure 10:** Kaplan-Meier survival curves, stratified by era and biventricular support (CFBiVAD) vs total artificial heart (TAH).

**Figure 11:** Freedom from severe right heart failure (RHF) (Kaplan-Meier), stratified by INTERMACS profile at implant. RVAD, right ventricular assist device; BiVAD, biventricular assist device.

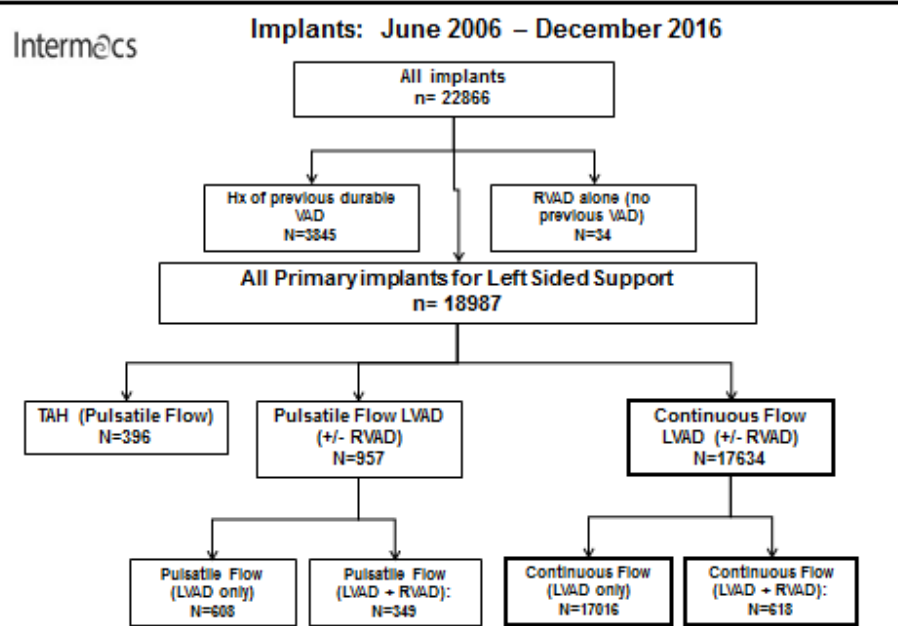
**Figure 12:** Freedom from pump-related infection (PRI), stratified by INTERMACS profile. The depiction is as in Figure 11.

**Figure 13:** Freedom from first stroke, stratified by INTERMACS profile. The depiction is as in Figure 11.

**Figure 14:** Freedom from first readmission, stratified by INTERMACS profile. The depiction is as in Figure 11.

**Figure 15:** Freedom from the combined major event of first infection, bleeding, device malfunction, stroke, or death. The depiction is as in Figure 16.

**Figure 16:** Solution to the multivariable equation for risk of death after 3 months, conditional upon 3 months survival. The dashed lines indicate the 70% confidence limits.



Intermedics Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633

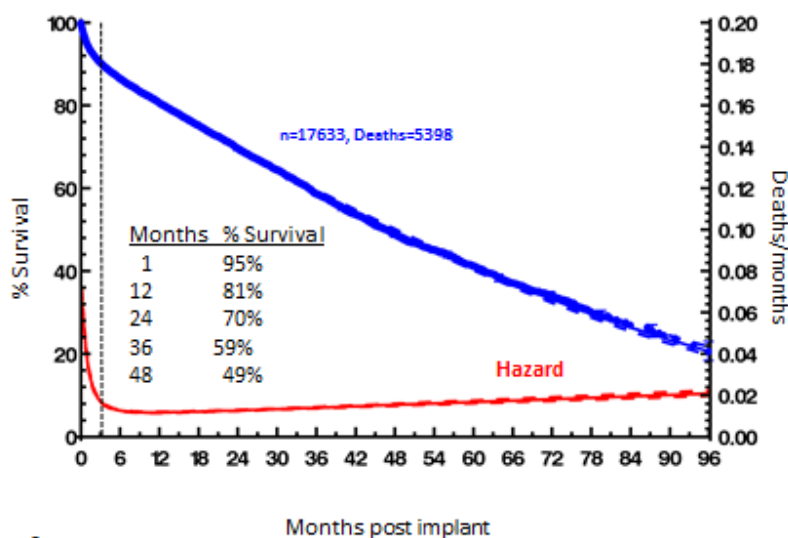


Figure 2

Intermedics Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633\*

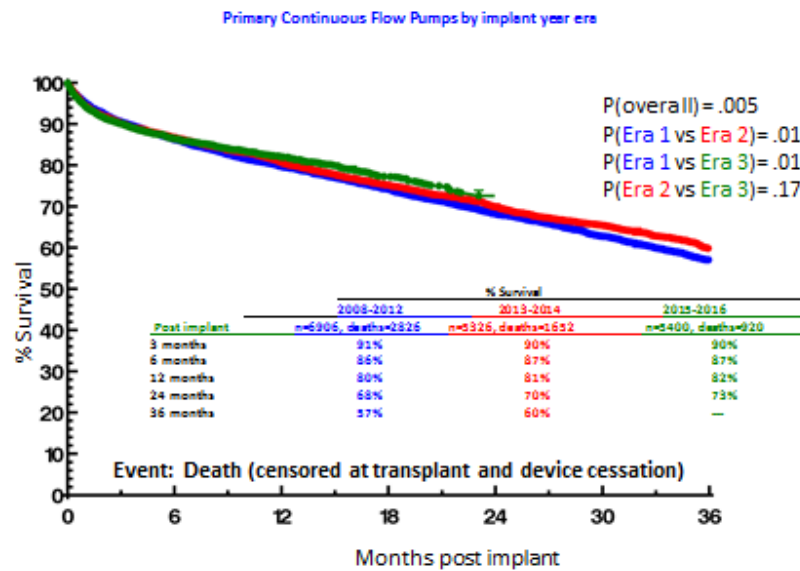


Figure 3

3

Intermedics Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633

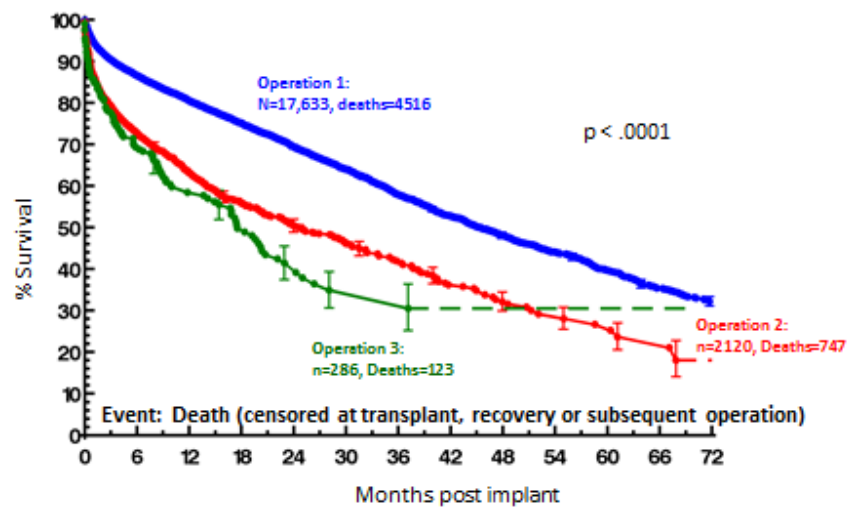


Figure 4

4

Intermecs Implants: June 2006 – December 2016, n=18987

BTT: Listed CFLVADs implants 2015-2016, n=1375

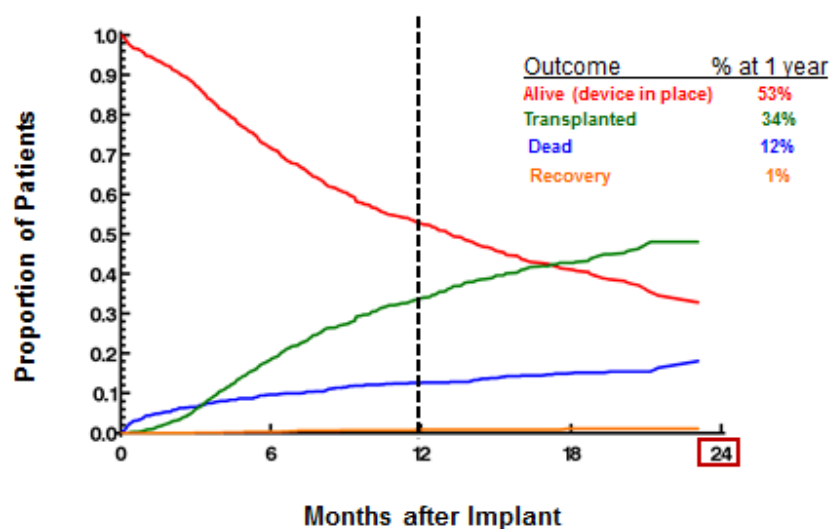


Figure 5

3

Intermecs Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633

Instantaneous Death Rate (Hazard) for selected causes

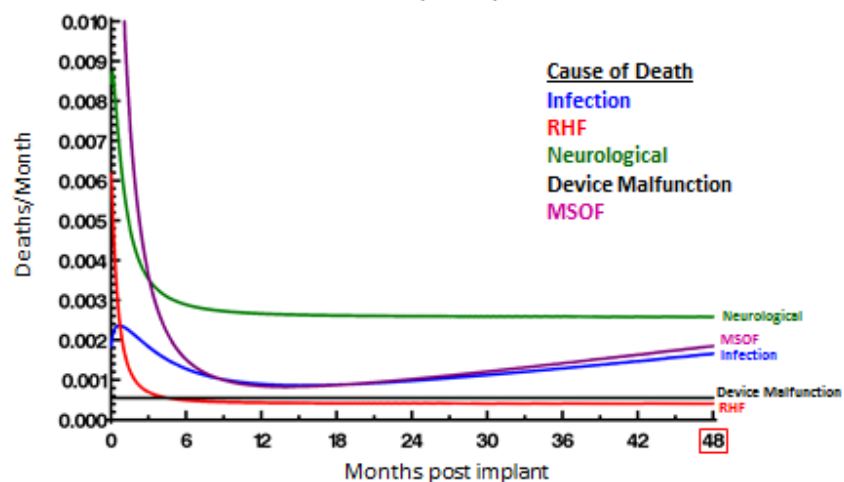


Figure 6

6

Intermacs Continuous Flow LVAD/BiVAD Implants: 2008 – 2016, n=17633

Cumulative Death Rate (Hazard) for selected causes

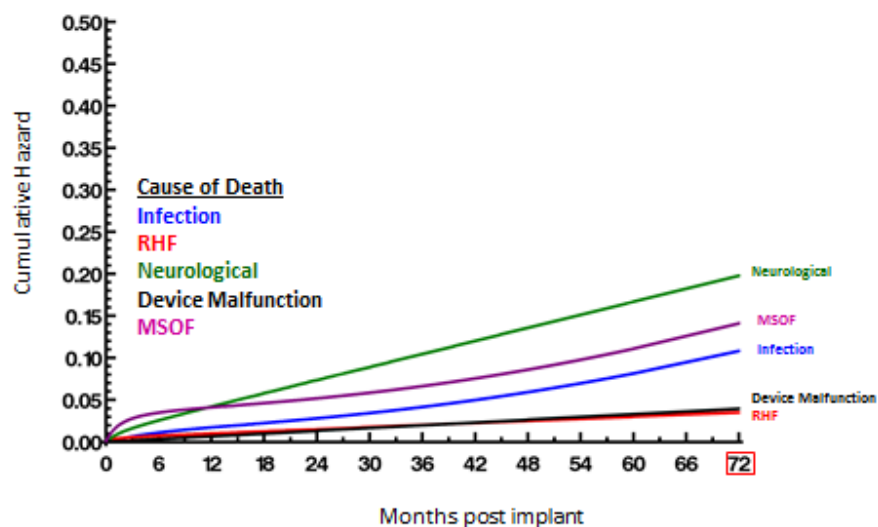


Figure 7

Intermacs Continuous Flow LVAD/BiVAD Implants: 2013 – 2016, n= 10,726

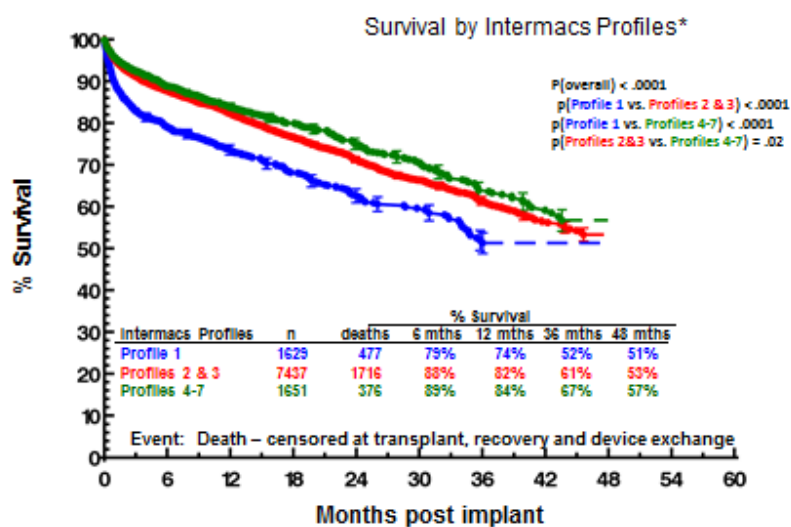


Figure 8

\* 9 patients with unspecified Patient Profile at time of implant

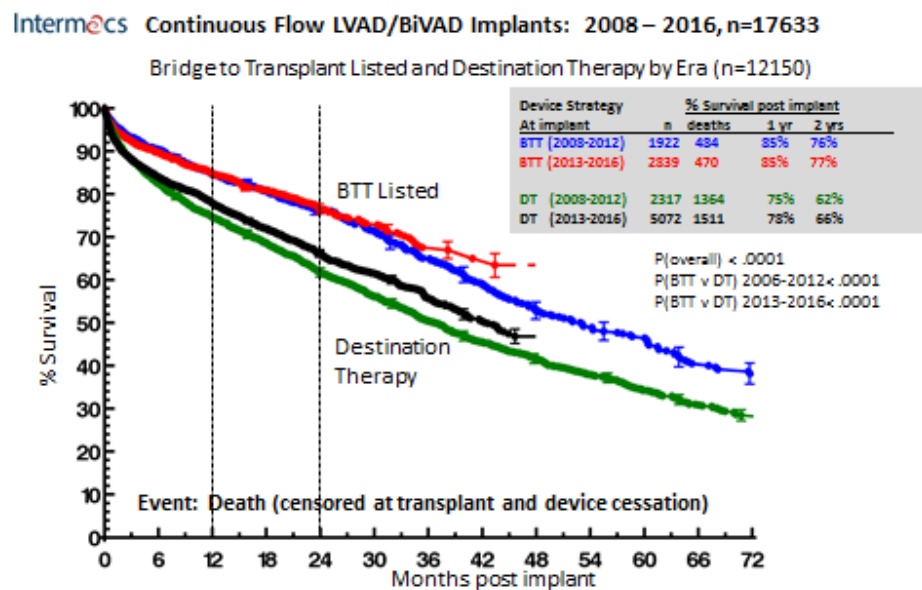


Figure 9

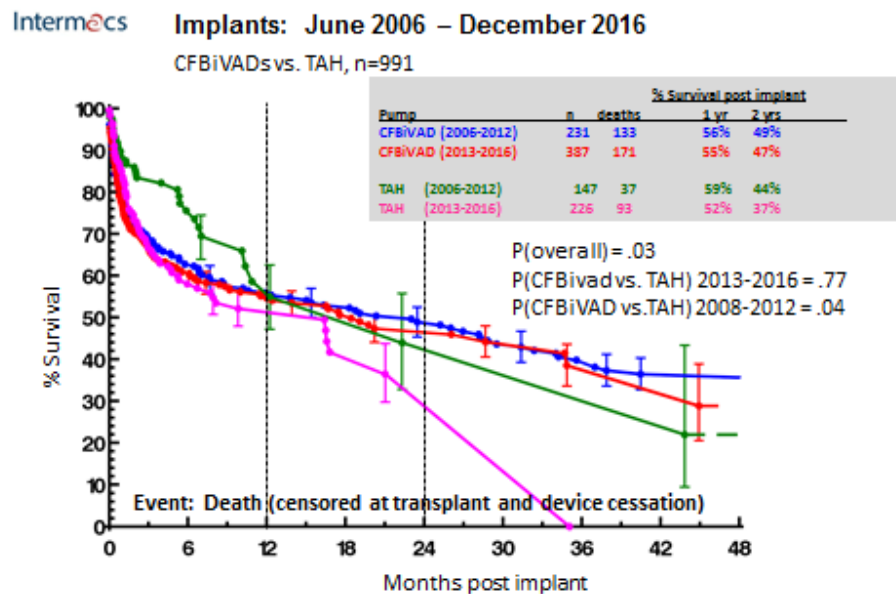


Figure 10

Intermacs CF-LVAD/BiVAD Implants: 2012 – 2016, n=10953

Placement of RVAD at time of LVAD (Bi-VAD) or subsequent

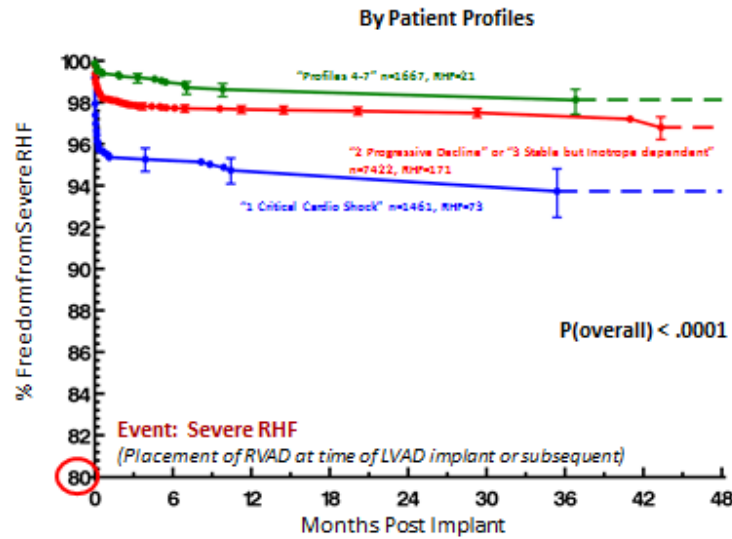


Figure 11

11

Intermacs CF-LVAD/BiVAD Implants: 2012 – 2016, n=10953

Time to First Pump Related Infection (PRI)

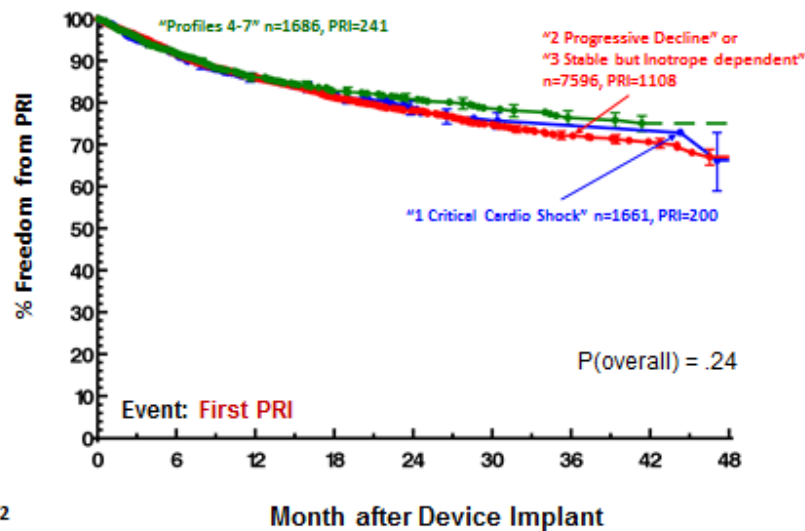


Figure 12

12



Intermacs CF-LVAD/BiVAD Implants: 2012 – 2016, n=10953

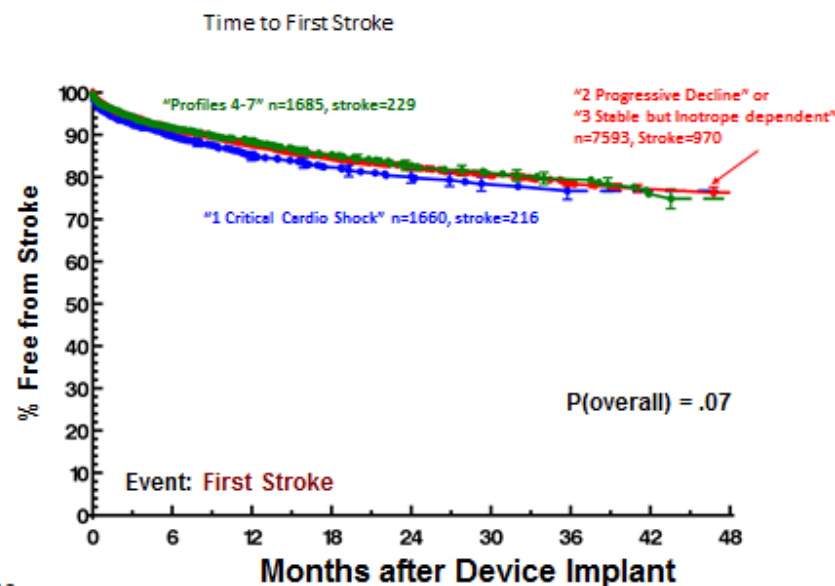


Figure 13

Note: 10 patients with INTERMACS Profile “not specified”

13

Intermacs CF-LVAD/BiVAD Implants: 2012 – 2016, n=10953

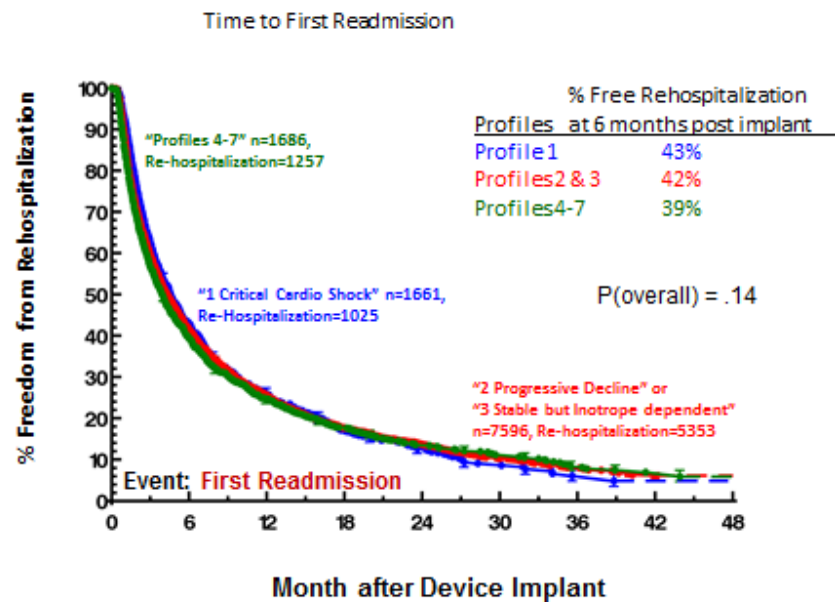


Figure 14

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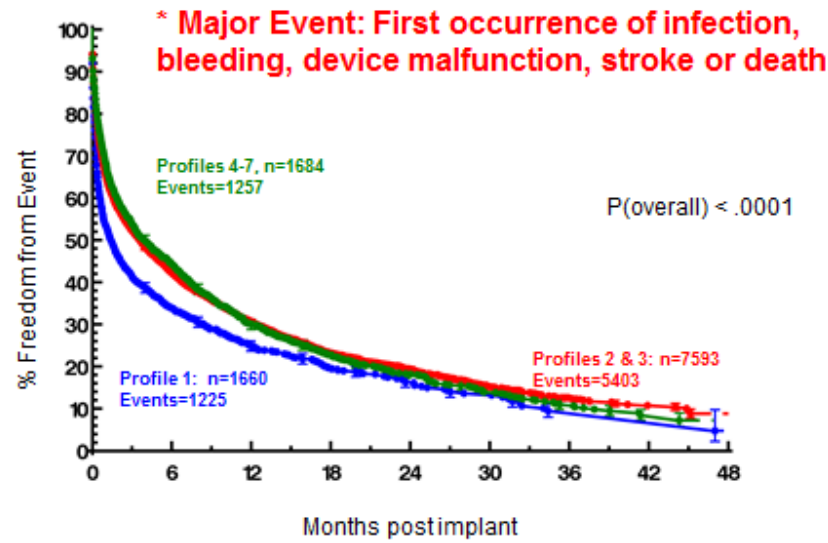


Figure 15

13

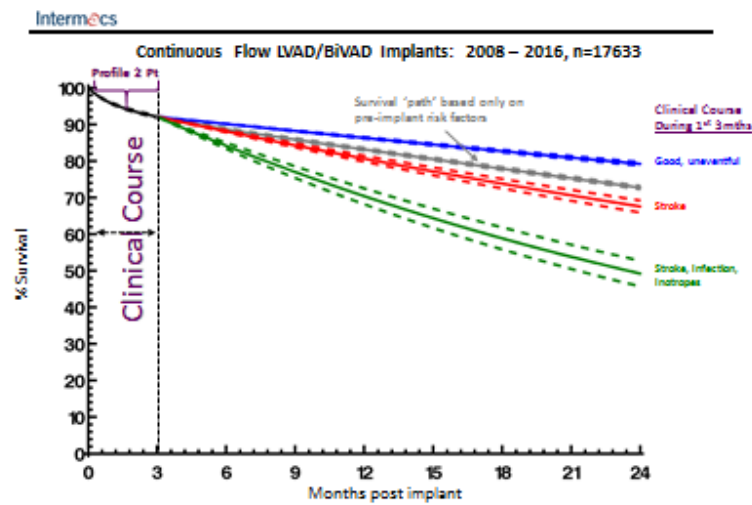


Figure 16

16

Intermacs

CF-LVAD/BiVAD Implants: April 2008 – December 2016, n= 17632

Device Strategy at time of implant	Implant Date Era						TOTAL	
	2008-2011		2012-2014		2015-2016			
	N	%	N	%	N	%	N	%
BTT Listed	1525	52.5%	1805	24.1%	1427	26.4%	4757	27.0%
BTT Likely	1164	24.7%	1390	18.5%	717	13.5%	3271	18.6%
BTT Moderate	476	10.1%	714	9.5%	415	7.7%	1605	9.1%
BTT Unlikely	165	3.5%	194	2.6%	125	2.3%	484	2.7%
Destination Therapy	1547	25.5%	3355	44.7%	2687	49.8%	7589	41.9%
BTR	29	0.6%	25	0.3%	5	0.2%	59	0.3%
Rescue Therapy	14	0.3%	24	0.3%	15	0.3%	53	0.3%
Other	4	0.1%	2	0.03%	5	0.2%	11	0.1%
TOTAL	4722	100%	7510	100%	5400	100%	17632	100%

Table 1

1

## Continuous Flow Devices

Intermacs

CF-LVAD/BiVAD Implants: April 2008 – December 2016, n=17632

Patient Profile at time of implant	Implant Date Era						TOTAL	
	2008-2011		2012-2014		2015-2016			
	N	%	N	%	N	%	N	%
1 Critical Cardiogenic Shock	741	15.7%	1073	14.3%	857	15.9%	2671	15.1%
2 Progressive Decline	1924	40.8%	2691	35.8%	1817	33.7%	6432	36.5%
3 Stable but Inotrope Dependent	1192	25.2%	2373	31.6%	2027	37.5%	5592	31.7%
4 Resting Symptoms	609	12.9%	1075	14.3%	607	11.2%	2291	13.0%
5 Exertion Intolerant	141	3.0%	197	2.6%	64	1.2%	402	2.3%
6 Exertion Limited	80	1.7%	58	0.8%	18	0.3%	156	0.9%
7 Advanced NYHA Class 3	35	0.7%	40	0.5%	5	0.1%	80	0.5%
Not Specified*	0	0.0%	3	0.04%	5	0.1%	8	0.05%
Totals	4722	100%	7510	100%	5400	100%	17632	100%

CF, continuous flow.

Table 2

\* Due to change in web-based data entry capture in protocol v3.0 (May 2012)

2

Interm@cs

Continuous Flow LVAD/BIVAD Implants: 2008 – 2016, n=17833

Pre-Implant Risk Factors for Death	Early hazard		Late hazard	
	Hazard Ratio	p-value	Hazard Ratio	p-value
<b>Demographics</b>				
Age <sup>2</sup> (older)	1.21	< .0001	1.16	< .0001
Female	1.27	< .0001		
BMI (higher)	1.02	< .0001		
Blood Type Non-O			0.66	.002
White race			1.20	.0003
<b>Clinical Status</b>				
ICD	1.34	.001	1.28	< .0001
INTERMACS Profile 1	1.66	< .0001		
INTERMACS Profile 2	1.29	< .0001		
Intervention within 48 hours LBP			1.19	.0004
Destination Therapy			1.22	< .0001
<b>Non-Cardiac Systems</b>				
Peripheral Vascular Disease			1.28	.004
Pre-COPD			1.27	.001
Albumin (lower)	0.90	< .0001		
Creatinine (higher)			1.12	< .0001
Dialysis	0.28	< .0001		
BUN (higher) (10 unit increase)	1.07	< .0001	1.05	< .0001
<b>Right Heart Dysfunction</b>				
RVAD in same operation	0.76	< .0001		
Bilirubin (higher) (5 unit increase)	1.24	< .0001		
<b>Surgical Complexity</b>				
History of cardiac surgery	1.21	.004		
History of CABG	1.24	.001		
Concomitant Cardiac Surgery	1.29	< .0001		
<b>Quality of Life – Pre Implant</b>				
Too Sick to complete EQDQ	1.65	< .0001		
Worse Self Care Score (pre-implant)			1.22	< .0001

Table 3

3

Adult Primary Continuous Flow LVADs and BiVADs Implants: Apr 2008 – Dec 2016, n=17632

Interm@cs

Adverse Event Rates (events/100 patient months)

Adverse Event	1st 3 months post		3–12 months post		Comparison of	
	events	rate	events	rate	1st 3 mths vs 3–12 months	p-value
Bleeding	7810	16.24	4205	4.08	4.00	< 0.0001
<b>Cardiac/Vascular</b>						
Myocardial Infarction	54	0.11	31	0.03	3.74	< 0.0001
Cardiac Arrhythmia	5026	10.45	1359	1.32	7.94	< 0.0001
Pericardial Drainage	858	1.79	17	0.02	108.30	< 0.0001
Arterial non-CNS Thrombosis	162	0.34	52	0.05	6.69	< 0.0001
Venous thrombotic event	663	1.38	80	0.08	17.78	< 0.0001
Infection	6552	13.63	4692	4.53	3.00	< 0.0001
Stroke	1162	2.42	1154	1.12	2.16	< 0.0001
Neurological: Non-Stroke	640	1.33	332	0.32	4.14	< 0.0001
Renal Dysfunction	1687	3.51	495	0.48	7.31	< 0.0001
Hepatic Dysfunction	453	0.94	167	0.16	5.92	< 0.0001
Respiratory Failure	3212	6.68	567	0.55	12.16	< 0.0001
Wound Dehiscence	194	0.40	58	0.06	7.18	< 0.0001
Psychiatric Episode	751	1.56	279	0.27	5.78	< 0.0001
Other SAE	3540	7.31	2170	2.10	3.48	< 0.0001
Total burden	34564	71.89	15658	15.19	201.28	< 0.0001

CNS, Central nervous System; LVAD, left ventricular assist device; BiVAD, biventricular assist device.

Table 4

4

Intermacs

Continuous Flow LVAD/BIVAD Implants: 2005 – 2016, n=17833

Risk Factors for Death in Patients who were alive at 3 months post-implant (n=14,337)

Event: Death after 3 months post-implant and before 24 months (Deaths=2372)

Risk Factors: Pre-implant, during the first 3 months after implant and at the 3 month follow-up evaluation

Risk Factors	Constant Phase of Hazard	
	Hazard ratio	P-value
<b>Pre-implant</b>		
Age (older) <sup>1</sup>	1.09	<.0001
Race: white	1.32	<.0001
Device strategy: Destination Therapy	1.18	.0003
ICD prior to implant	1.22	.0005
<b>Clinical Events during 3 months</b>		
Number of strokes	1.47	<.0001
Number of respiratory failures	1.16	.0003
Number of infections	1.16	<.0001
Number of device malfunctions	1.30	<.0001
Days in acute care	1.01	<.0001
<b>Clinical Condition at 3 months</b>		
BUN (higher)	1.01	<.0001
Creatinine (higher)	1.12	<.0001
Albumin (lower)	0.97	<.0001
LDH (higher)	1.00	<.0001
Asotia	1.73	.003
Pericardial effusion	1.50	.0008
Inotropes	1.70	<.0001
Warfarin (non-use)	0.74	<.0001
<b>Quality of Life/Neurocognitive</b>		
Visual Analog Scale (lower) <sup>2</sup>	0.93	<.0001
Mobility problems	1.31	<.0001
Trail making test (higher) <sup>3</sup>	1.07	<.0001

<sup>1</sup> Comparing age 60 to 50

<sup>2</sup> HR is for 10 unit decrease

<sup>3</sup> HR is for a 60 second increase

Table 5

5