

SPECIAL FEATURE

Fifth INTERMACS annual report: Risk factor analysis from more than 6,000 mechanical circulatory support patients

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mechanical support;
ventricular assist
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INTERMACS;
advanced heart failure;
destination therapy

The 5th annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) summarizes and analyzes the first 6 years of patient and data collection. The current analysis includes more than 6000 patients and updated risk factors for continuous flow pumps. Among continuous flow pumps, actuarial survival is 80% at 1 year and 70% at 2 years. Quality of life indicators are generally favorable and adverse event burden will likely influence patient selections of advanced heart failure therapies. *J Heart Lung Transplant* 2013;32:141–156

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The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),¹ a National Heart, Lung and Blood Institute (NHLBI)–sponsored database and partnership between NHLBI, the U.S. Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (CMS), received contract renewal on December 1, 2010, to fund an additional 5 years of data collection and analysis. A business plan has been initiated to provide long-term sustainability of this database through a public and private partnership involving industrial partners and participating hospitals in addition to the federal agencies and academic institutions. This report analyzes patient enrollment and outcomes from June 23, 2006, to June 30, 2012.

Site and patient enrollment

Between June 23, 2006, and June 30, 2012, 6,885 patients who received an FDA-approved durable mechanical

circulatory support (MCS) device were entered in the database (Figure 1). Of the 145 participating hospitals, 131 of these have actively contributed data, including the 114 centers approved for destination therapy (DT) by CMS.

Of the 6,885 patients who received a durable MCS device, 72 were pediatric patients, 243 had a previous durable MCS device, and 9 received an isolated right ventricular assist device (VAD); (Figure 2). The remaining 6,561 patients are the focus of this analysis.

Approved devices

Table 1 lists the current FDA-approved durable MCS devices. The Berlin Heart Excor Pediatric VAD (Berlin Heart GmbH, Berlin, Germany) received FDA approval on December 16, 2011, and the Heartware HVAD (HeartWare International, Inc. Framingham, MA) was approved on November 20, 2012.

Evolution of device type

The dominance of continuous-flow technology² has continued since the approval of the HeartMate II device (Thoratec, Pleasanton, CA) in 2008 for bridge-to-transplant

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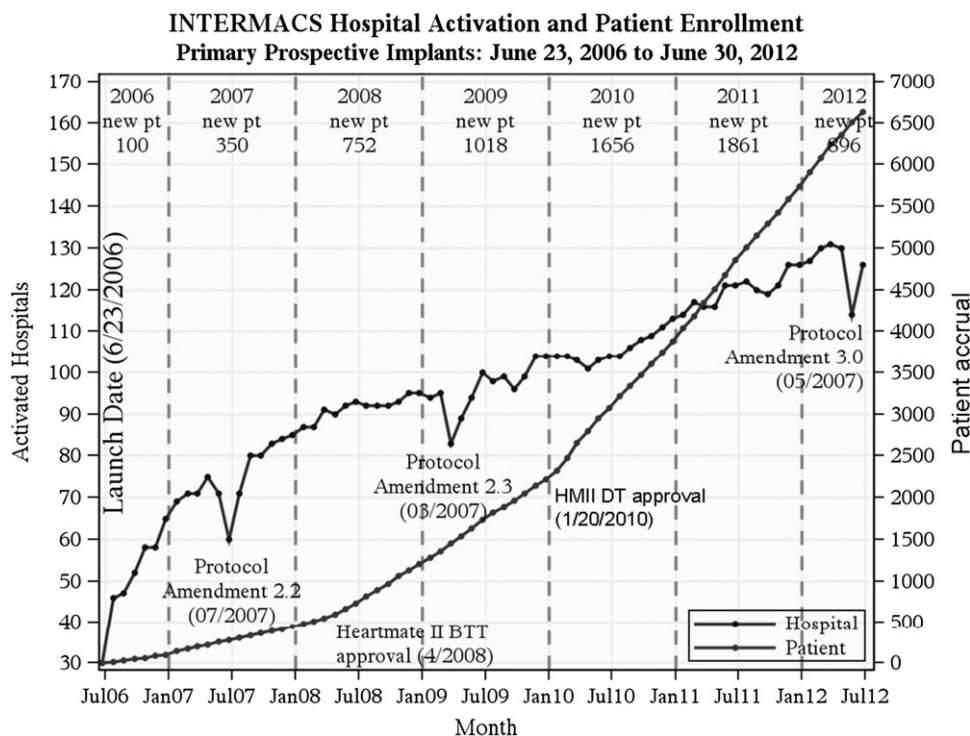


Figure 1 Time of cumulative hospital participation and patients entered into the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database. Between June 23, 2006 and June 30, 2012, 145 hospitals participated in INTERMACS, and 131 of these hospitals actively contributed information on 6,633 patients. Cumulative patient accrual and the number of participating hospitals over this time period are displayed. BTT, bridge to transplant; DT, destination therapy. HMII, HeartMate II.

(BTT) therapy and for DT in 2010 (Figure 3). Since 2010, among patients stratified to a DT designation, essentially 100% received a continuous-flow pump (Figure 4).

continuous-flow pump for DT in 2010 (Table 2). During 2012, more than 40% of implants have been designated as DT.

Device strategy

The application of MCS as long-term therapy (DT)³ has dramatically increased since the approval of a

Survival

The overall survival curves, stratified by pulsatile-flow vs continuous-flow technology, are depicted in Figure 5.

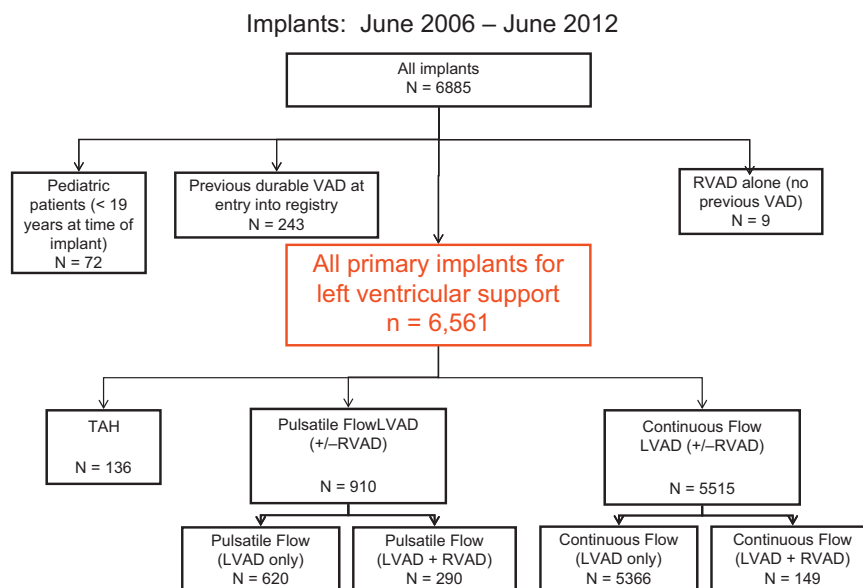


Figure 2 Categories of patients who received durable mechanical circulatory support devices in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database between June 2006, and June 2012 are shown. LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart.

Table 1 Food and Drug Administration-Approved Devices

Type	Device
Durable devices	
Continuous flow	Thoratec HeartMate II Heartware HVAD MicroMed DeBakey Child VAD
Pulsatile extracorporeal	Thoratec PVAD Heart Excor
Pulsatile intracorporeal	HeartMate IP Heart Mate VE HeartMate XVE Thoratec IVAD NovaCor PC NovaCor PCq
Total artificial heart	SynCardia CardioWest AbioCor TAH
Temporary devices	
Short-term devices	Abiomed AB5000 Abiomed BVS 5000 Levitronix Centrimag Biomedicus Tandem Heart

Among all continuous-flow pumps (Figure 6), actuarial survival was 80% at 1 year and 70% at 2 years.

Risk factors for mortality

An updated risk factor analysis for patients receiving continuous-flow left VADs (LVADs) is reported in Table 3.

Older age

Older age is a risk factor for early mortality, but the actuarial survival of patients aged older than 70 years is only

modestly inferior to that of patients older than approximately age 50 (Figure 7). However, as seen below, older age is a marker for increased fragility in patient tolerance for other important risk factors.

Clinical status

The evolution of clinical practice is partly reflected by the proportion of patients in the various INTERMACS Profile Levels who receive implants (Table 4). The proportion of patients in progressive cardiac decompensation (Level 2) or cardiogenic shock (Level 1) at the time of implant has decreased from approximately 64% before 2011 to just less than 54% in 2012. During the first half of 2012, 13% of patients had heart failure symptoms at rest and only about 5% of patients were in less ill profiles.

Patients with ongoing cardiac decompensation or shock (INTERMACS Profile Levels 1 and 2) continue to show inferior survival compared to more stable patients, with decrease of approximately 5–8% in 1-year survival (Figure 8). The interaction between age and INTERMACS Level⁴ demonstrates the reduced tolerance of the elderly when LVAD implantation occurs during acute cardiac decompensation (Figure 9).

Destination therapy

DT continues to carry a slightly higher risk than BTT therapy (Figure 10). The small survival difference likely relates to the availability of transplantation for some BTT patients in the event of device-related complications. When adjusted for risk factor prevalence in each group, the difference in predicted 1-year survival is approximately 5% (Figure 11).

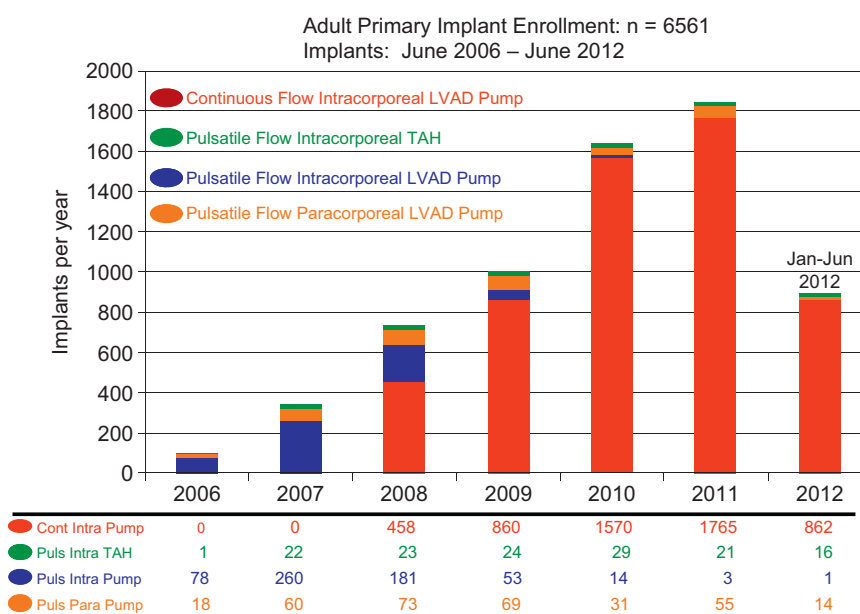


Figure 3 Primary adult implants in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database are shown by year of implant. LVAD, left ventricular assist device; TAH, total artificial heart.

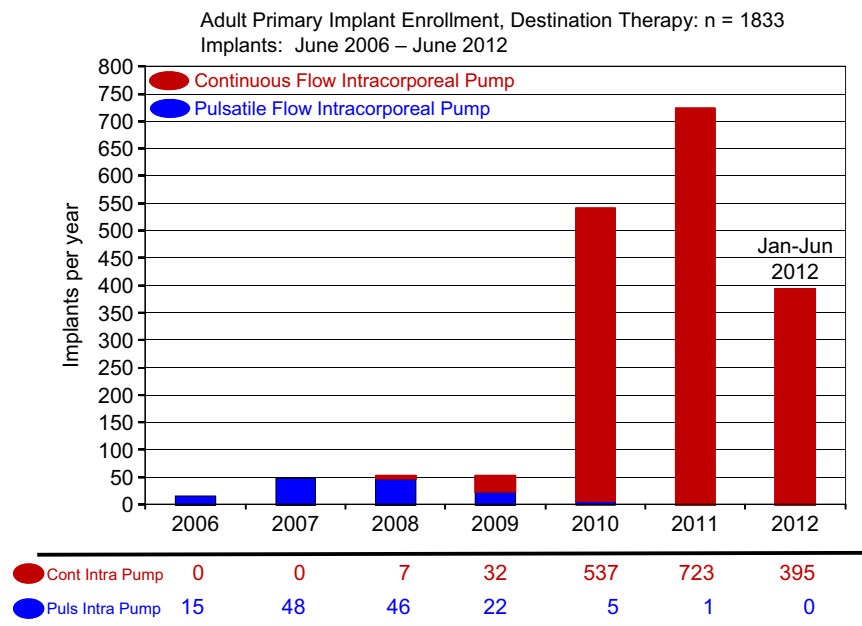


Figure 4 Primary adult implants as destination therapy are shown by year of implant.

Table 2 Implants: June 2006–June 2012

Device Strategy at Time of Implant	Implant Date Period						Total	
	Pre 2001		2001		2012 (Jan-Jun)			
	n	%	n	%	n	%	n	%
BTT Listed	1245	39.8%	421	22.6%	189	21.0%	2155	32.4%
BTT Likely	994	25.6%	417	22.4%	196	21.8%	1607	24.2%
BTT Moderate	392	10.1%	186	9.9%	79	8.8%	657	9.9%
BTT Unlikely	127	3.2%	75	4.0%	23	2.5%	225	3.3%
Destination Therapy	714	18.4%	725	38.9%	395	44.0%	1834	27.6%
BTR	57	1.4%	16	0.8%	9	1.0%	82	1.2%
Rescue Therapy	33	0.8%	9	0.4%	4	0.1%	46	0.6%
Other	14	0.3%	12	0.6%	1	0.4%	27	0.4%
Total	3876	100.0%	1861	100.0%	896	100.0%	6633	100.0%

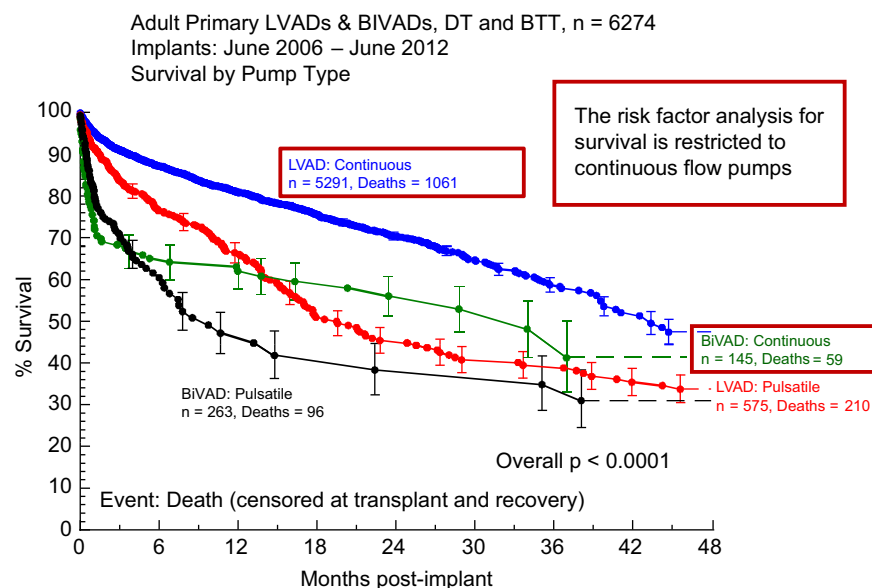


Figure 5 Primary adult left ventricular assist devices (LVADs) and biventricular assist devices BIVADs) are shown stratified by continuous-flow vs pulsatile pumps. Patients were censored at time of transplant or device explant. The error bars indicate ± 1 standard error. BTT, bridge to transplant; DT, destination therapy.

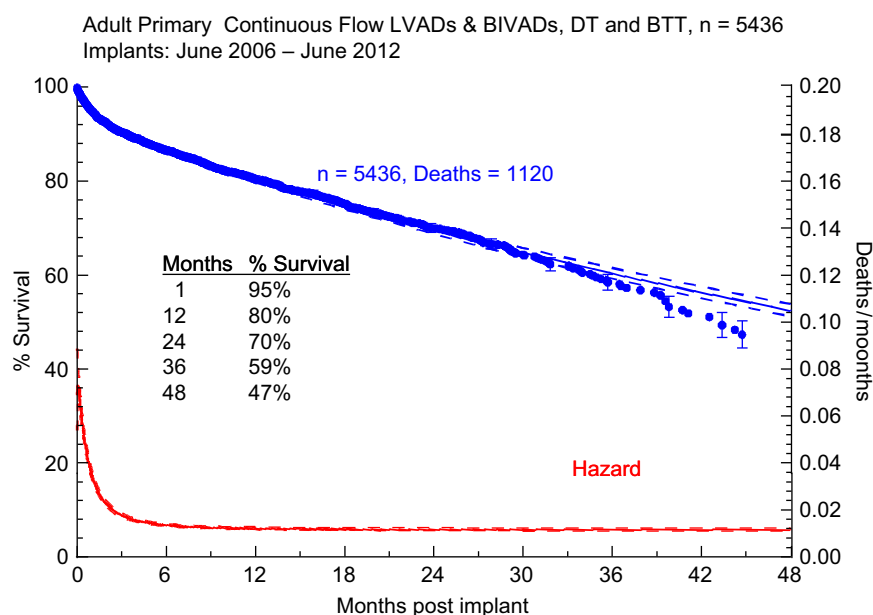


Figure 6 Actuarial and parametric survival is shown after implantation of primary continuous-flow left ventricular assist devices (LVAD) and biventricular assist devices (BIVAD). The lower curve indicates the hazard function, or instantaneous risk, over time. The dashed lines indicate the 70% confidence limits. BTT, bridge to transplant; DT, destination therapy.

Renal dysfunction

The incremental effect of worsening renal dysfunction was examined by assigning moderate renal dysfunction for patients with the creatinine level >2 mg% or blood

urea nitrogen >60 mg%, and severe renal dysfunction for patients requiring dialysis near the time of implant (Figure 12; Table 3). Severe renal dysfunction was associated with a major reduction in early survival.

Table 3 Implants: June 2006–June 2012, Adult Primary Continuous-Flow LVADs and BiVADS, DT and BTT ($n = 5,436$)

Risk factors for death	Early hazard		Constant hazard	
	Hazard ratio	p-value	Hazard ratio	p-value
Demographics				
Age (older)	1.69	<0.0001		
Body mass index (higher)	1.47	<0.0001		
Clinical status				
Ventilator	1.65	0.009		
History of stroke	1.69	0.009		
INTERMACS Level 1	2.45	<0.0001		
INTERMACS Level 2	1.89	0.0004	1.30	0.003
Destination therapy			1.25	0.01
Non-cardiac systems				
Diabetes			1.22	0.02
Creatinine (higher)			1.10	0.008
Dialysis	2.22	0.002		
Blood urea nitrogen (higher)	1.10	<0.0001		
Right heart dysfunction				
RVAD in same operation	3.73	<0.0001		
Right atrial pressure (higher)	1.36	0.002		
Bilirubin (higher)	1.08	<0.0001		
Ascites			1.32	0.05
Surgical complexities				
History of cardiac surgery			1.50	<0.0001
Concomitant cardiac surgery	1.34	0.02		

BiVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support LVAD, left ventricular assist device; RVAD, right ventricular assist device.

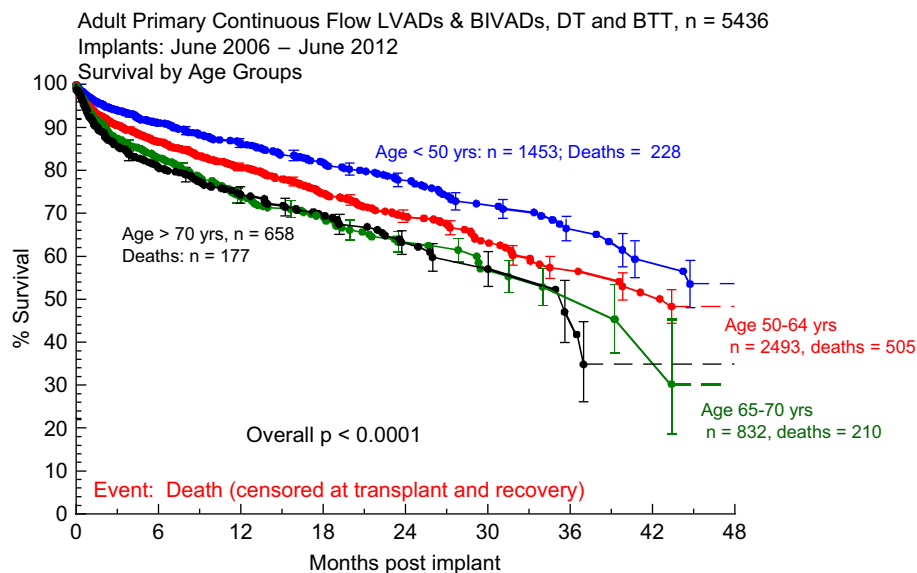


Figure 7 Actuarial survival is shown stratified by age at implant. The error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

Table 4 Implants: June 2006–June 2012

Patient Profile at Time of Implant	Implant Date Period						Total	
	Pre 2001		2001		2012 (Jan-Jun)			
	n	%	n	%	n	%	n	%
Unspecified	1	0.0%	.	.	6	0.6%	7	0.1%
1 Critical Cardiogenic Shock	860	22.1%	298	16.0%	148	16.6%	1307	19.7%
2 Progressive Decline	1627	41.9%	708	38.0%	329	36.7%	2664	40.1%
3 Stable but Inotrope dependent	750	19.3%	519	27.8%	246	27.4%	1515	22.8%
4 Resting Symptoms	441	11.3%	233	12.5%	117	13.0%	791	11.9%
5 Exertion intolerant	91	2.3%	66	3.5%	27	3.0%	184	2.7%
6 Exertion limited	59	1.5%	31	1.6%	14	1.5%	104	1.5%
7 Advanced NYHA Class 3	47	1.2%	6	0.3%	8	0.8%	61	0.9%
Total	3876	100.0%	1861	100.0%	896	100.0%	6633	100.0%

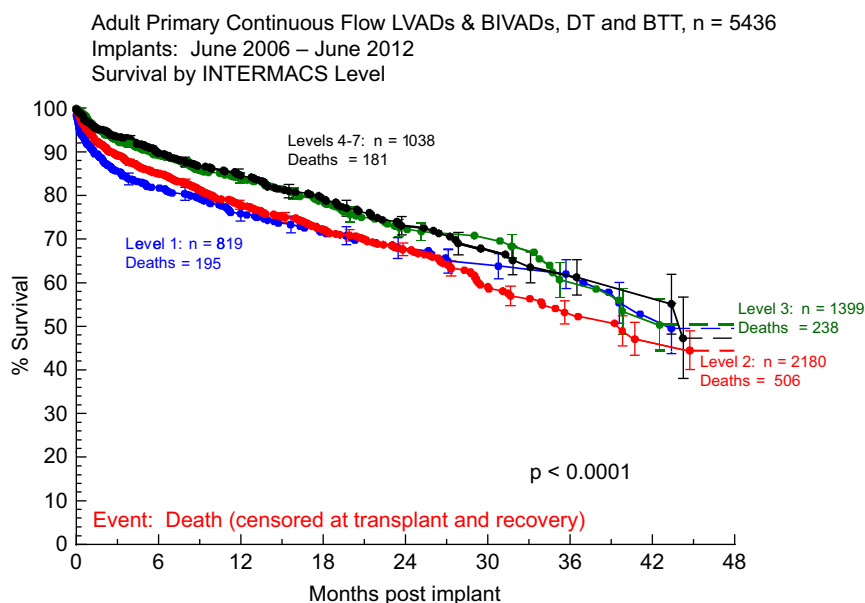


Figure 8 Actuarial survival is shown stratified by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Profile Level. The error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n = 5436
Implants: June 2006 – June 2012

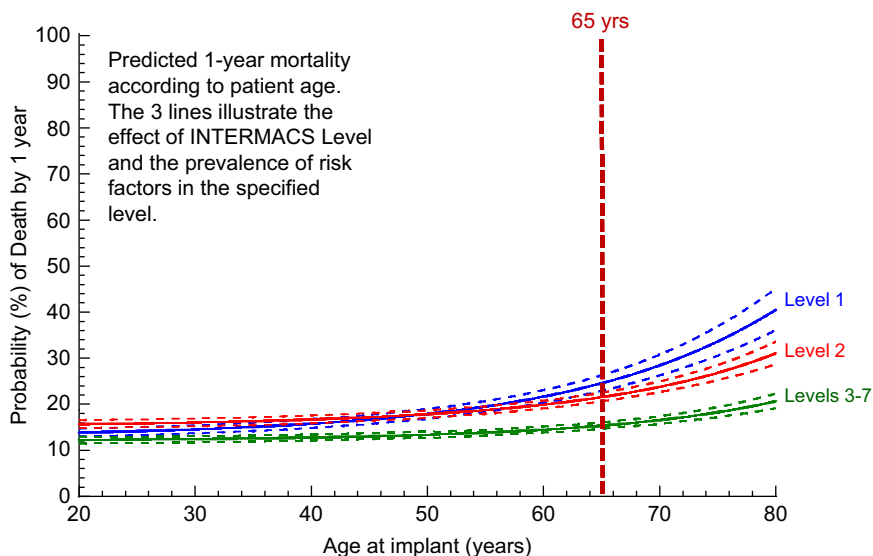


Figure 9 Nomogram depicts a solution of the multivariate risk factor equation, showing the interaction between age and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Levels. The average risk profile for each of the INTERMACS levels is illustrated. The dashed lines indicate the 70% confidence limits. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

Right ventricular dysfunction

Right ventricular function was categorized as moderate if right atrial pressure pre-implant was 18 mm Hg or higher, bilirubin exceeded 2.0 mg%, or ascites was documented. The requirement for a right VAD indicated severe right ventricular failure (Table 3). The major detrimental impact of progressive right ventricular dysfunction was in early

mortality (within 1 to 2 months) in the group receiving biventricular support (Figure 13).

Surgical complexity

Additional surgical complexities during device implantation are known to complicate the operation itself, and are also

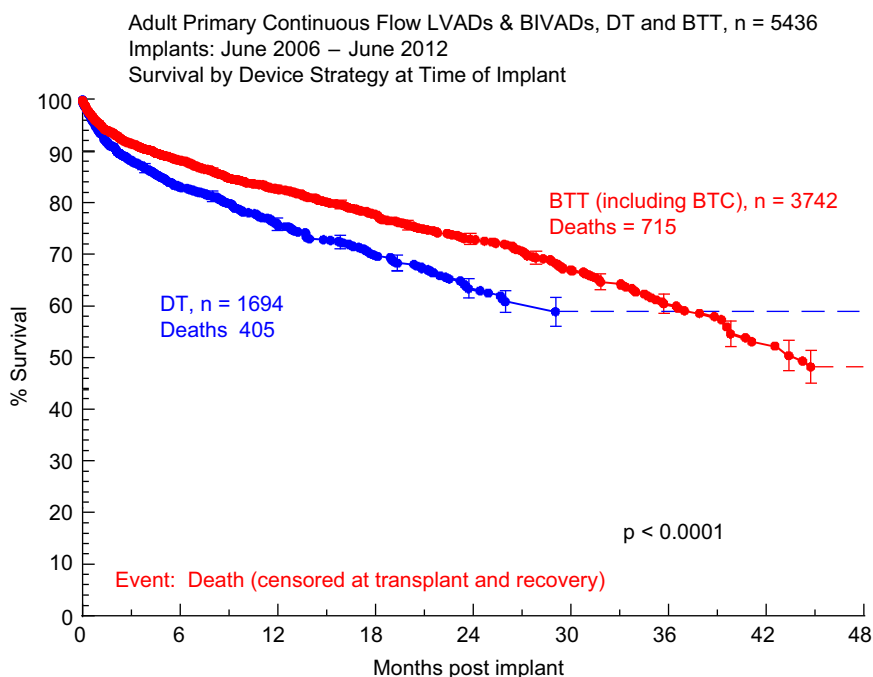


Figure 10 Actuarial survival is depicted stratified by implant strategy of destination therapy (DT), bridge to transplant (BTT), or bridge to candidacy (BTC). The error bars indicate ± 1 standard error. BIVAD, biventricular assist device; LVAD, left ventricular assist device.

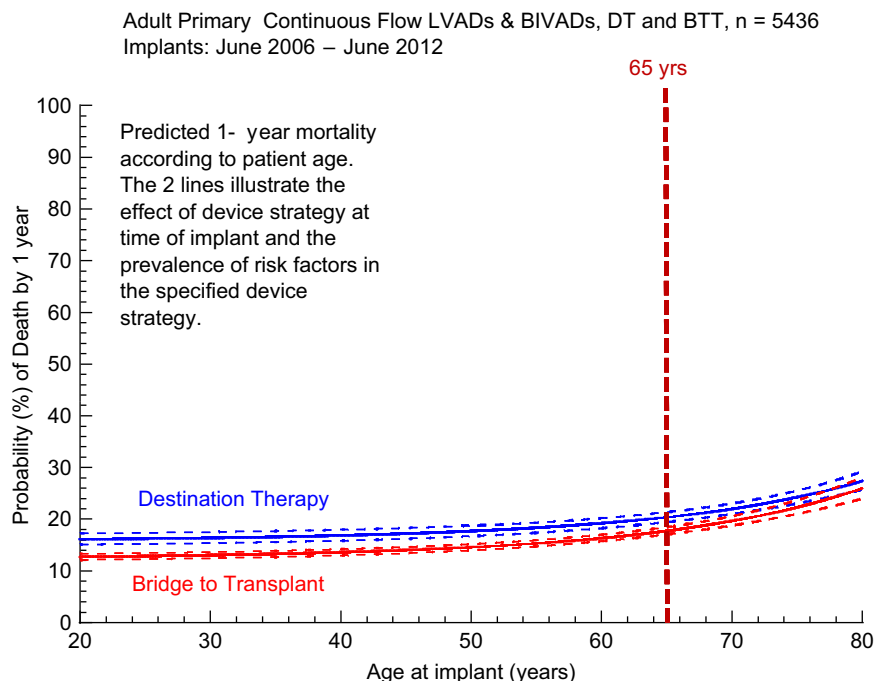


Figure 11 Nomogram depicts solution of the risk factor equations for destination therapy (DT) and bridge-to-transplant (BTT) plotted against age at implant. Dashed lines indicate the 70% confidence limits. BIVAD, biventricular assist device; LVAD, left ventricular assist device.

identified as risk factors for mortality by multivariable analysis (Table 3). Precise reasons for “prior cardiac surgery” exerting risk in the constant phase (throughout the period of follow-up) and “concomitant cardiac surgical procedures” increasing risk only early after implant remain to be clarified. The incremental mortality risk of 1 or both of these factors appears to be about 6% to 8% at 1 year (Figure 14).

Adverse events

Individual adverse events

Actuarial freedom from a major neurologic event was approximately 89% at 1 year and 83% at 2 years among all devices (Figure 15). Freedom from device malfunction

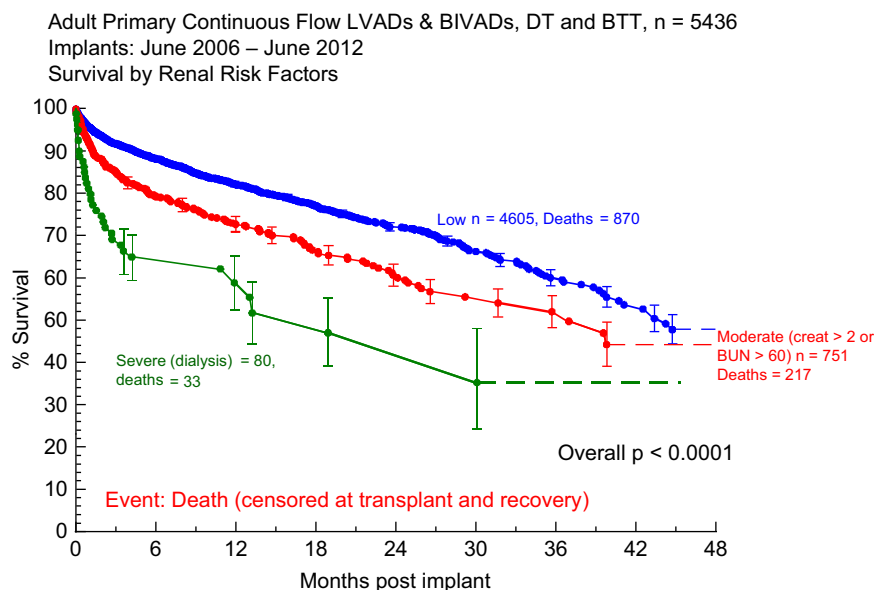


Figure 12 Actuarial survival after device implant, stratified by severity of renal dysfunction. Error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; BUN, blood urea nitrogen; DT, destination therapy; LVAD, left ventricular assist device.

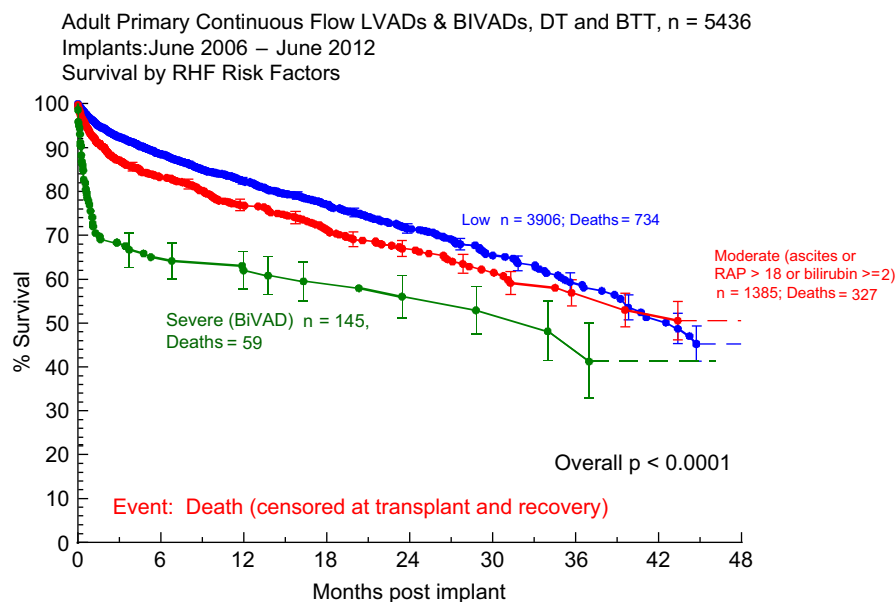


Figure 13 Actuarial survival after device implant, stratified by severity of right ventricular dysfunction. Error bars indicate ± 1 standard error. BiVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device; RAP, right atrial pressure; RHF, right heart failure.

leading to device exchange or death was dramatically different between continuous-flow and pulsatile intracorporeal devices (Figure 16). Pump interior infections and pocket infections were uncommon events (Figure 17). The risk of initial driveline infection continued as long as patients were monitored. Freedom from subsequent pump-related infections was similar for all INTERMACS Profile Levels (Figure 18). Table 5 compares the adverse event rates between pulsatile and continuous-flow technology. Note the reduction

in event rates for most adverse events with continuous-flow pumps

Adverse event burden

When comparing overall patient life-satisfaction with MCS vs transplantation or medical therapy, potential complications that affect patient satisfaction differ

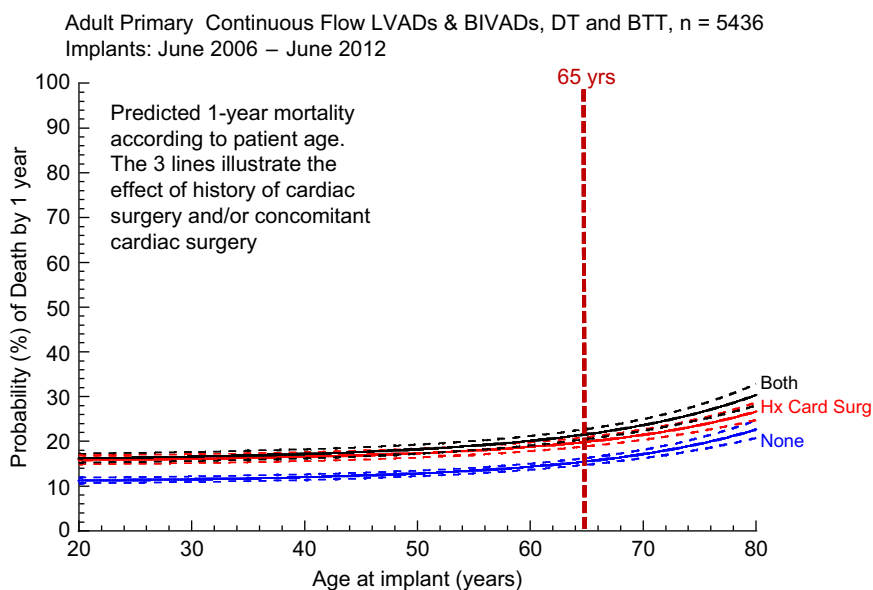


Figure 14 Nomogram depicts the solution of the risk factor equation for surgical complexities. Dashed lines indicate the 70% confidence limits. Hx Card Surg, history of cardiac surgery; Both, prior cardiac surgery and concomitant procedure(s) at time of implant. BiVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device. Depiction is as in Figure 11.

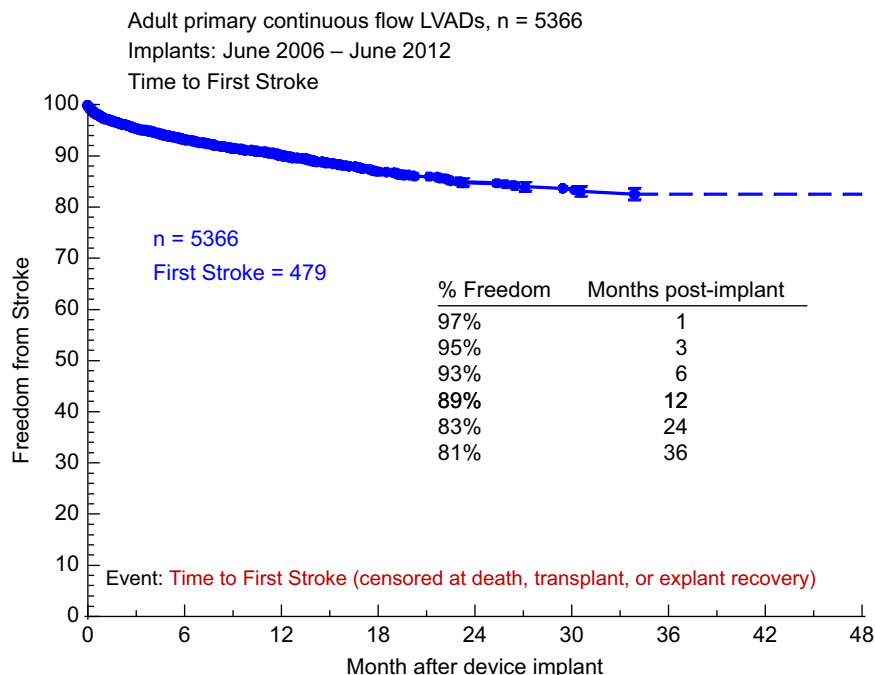


Figure 15 Actuarial freedom from stroke. The error bars indicate ± 1 standard error. LVAD, left ventricular assist device.

considerably between therapies. Thoughtful and possibly unconventional analyses will drive the process of comparing the effect of MCS complications (driveline infection, device malfunction, stroke, and bleeding) with transplantation (rejection, opportunistic infection, malignancy, and allograft vasculopathy) or medical therapy for advanced heart failure (recurrent hospital admissions for heart failure, symptoms of severe congestion and pulmonary venous

hypertension, and progressive lack of energy). The adverse event burden for MCS (Figure 19) indicates that approximately 30% of patients are free from any major adverse event at 1 year. Patients with biventricular support appear severely prone to adverse events (Figure 20), but only small differences are seen with respect to INTERMACS Profile Level at implant (Figure 21) or patient age (Figure 22).

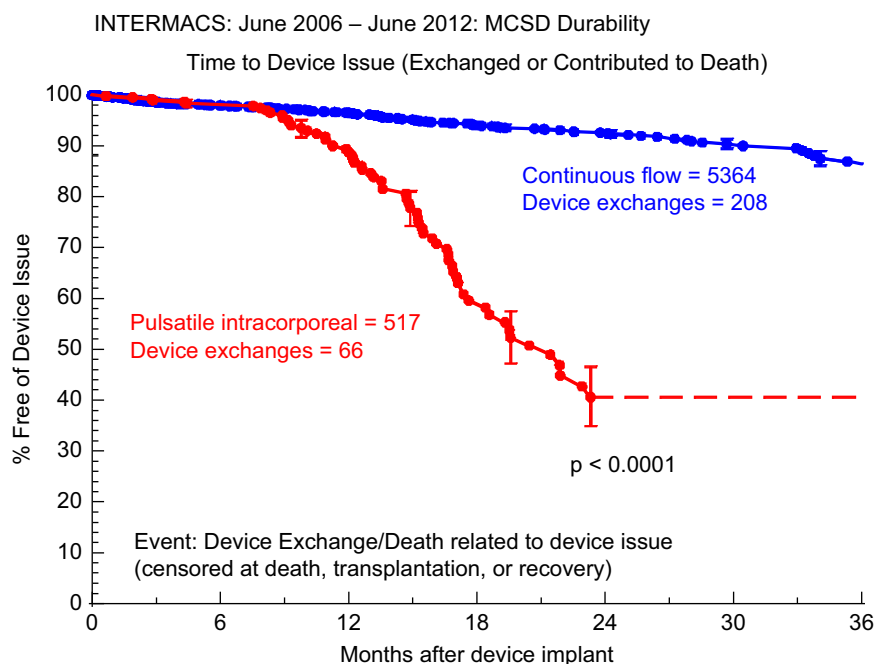


Figure 16 Actuarial freedom from device exchange or death related to device malfunction, stratified by device type. MCS, mechanical circulatory support device. The error bars indicate ± 1 standard error.

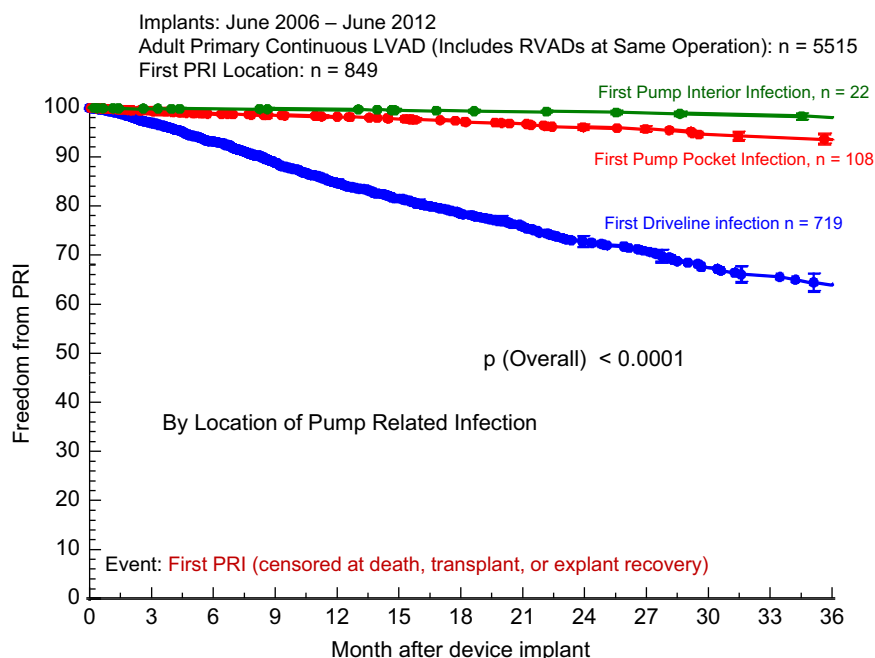


Figure 17 Actuarial freedom from pump-related infections (PRI). Note: a patient can have multiple locations for a single infection episode, therefore the total number of infection locations will not add up to the total number of patients. The error bars indicate ± 1 standard error. LVAD, left ventricular assist device; RVAD, right ventricular assist device.

Quality of life

Although quality of life data are somewhat limited in MCS patients, available data suggest an important and sustained improvement in general well-being (Figure 23), self-care (Figure 24), and usual activities (Figure 25) out to at least 1 year.

Knowledge gaps

Pediatric MCS

The Pediatric Mechanically Assisted Circulatory Support (PEDIMACS) registry is a newly developed focused version of the registry that contains data elements and definitions

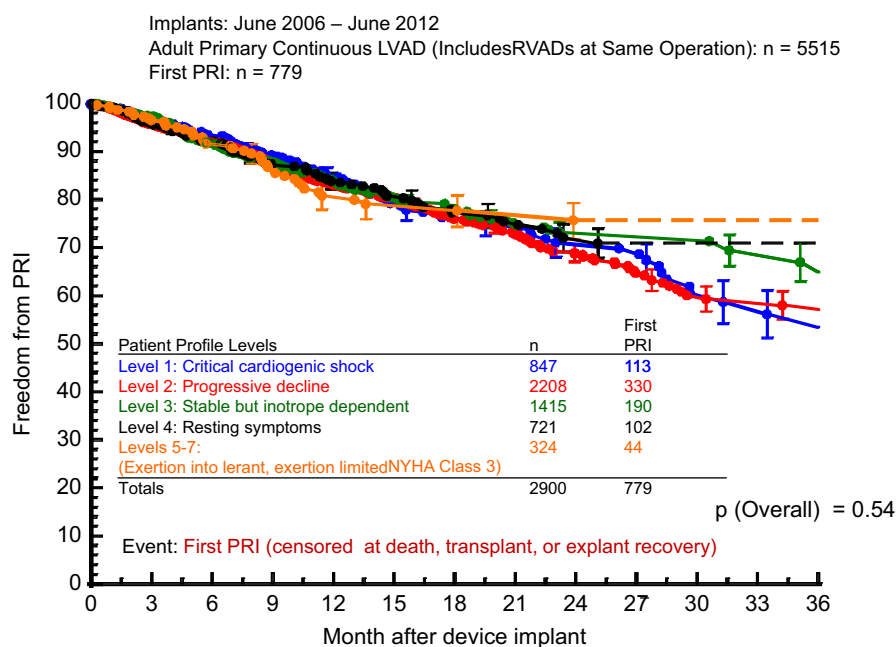


Figure 18 Actuarial freedom from pump-related infections (PRI), stratified by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile level. Error bars indicate ± 1 standard error. LVAD, left ventricular assist device; NYHA, New York Heart Association; RVAD, right ventricular assist device.

Table 5 Implants: June 2006–June 2012^a

Adverse event	Pulsatile (<i>n</i> = 594)		Continuous (<i>n</i> = 5,358)		Pulsatile/Continuous	
	Events	Rate	Events	Rate	Ratio	<i>p</i> -value
Device malfunction	119	3.26	660	1.60	2.04	<0.0001
Bleeding	630	17.28	3895	9.45	1.83	<0.0001
Cardiac/vascular						
Right heart failure	90	2.47	737	1.79	1.38	0.001
Myocardial infarction	2	0.05	30	0.07	0.75	0.47
Cardiac arrhythmia	254	6.96	1919	4.66	1.50	<0.0001
Pericardial drainage	64	1.75	251	0.61	2.88	<0.0001
Hypertension ^b	118	3.24	351	0.85	3.80	<0.0001
Arterial non-CNS thrombosis	14	0.38	74	0.18	2.14	0.001
Venous thrombotic event	59	1.62	289	0.70	2.31	<0.0001
Hemolysis	23	0.63	299	0.73	0.87	0.69
Infection	832	22.81	3302	8.01	2.85	<0.0001
Neurological dysfunction	139	3.81	754	1.83	2.08	<0.0001
Renal dysfunction	108	2.96	582	1.41	2.10	<0.0001
Hepatic dysfunction	48	1.32	247	0.60	2.20	<0.0001
Respiratory failure	206	5.65	1038	2.52	2.24	<0.0001
Wound dehiscence	18	0.49	74	0.18	2.75	<0.0001
Psychiatric episode	87	2.39	425	1.03	2.31	<0.0001
Total burden	2811	77.07	14927	36.22	2.13	<0.0001

CNS, central nervous system.

^aAdverse event rates (events/100 patient months) in the first 12 months after implant for primary left ventricular assist device with implant device strategy bridge to transplant, bridge to candidacy, and destination therapy.^bWith current reporting, identification of hypertension with continuous-flow pumps is unreliable.

tailored to pediatric patients who receive an MCS. PEDIMACS was formally launched on September 20, 2012. In addition to FDA-approved durable devices, the

PEDIMACS registry will also include FDA-approved temporary devices. The Pediatric Committee is actively recruiting all hospitals that implant pediatric devices.

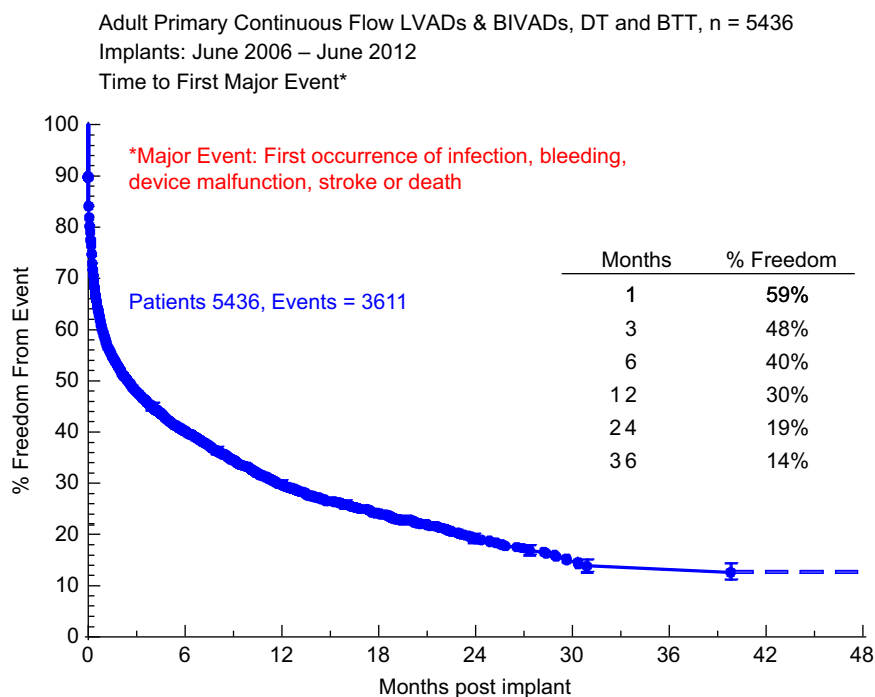


Figure 19 Actuarial freedom from any of the following adverse events: infection, bleeding, device malfunction, stroke, or death. Error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

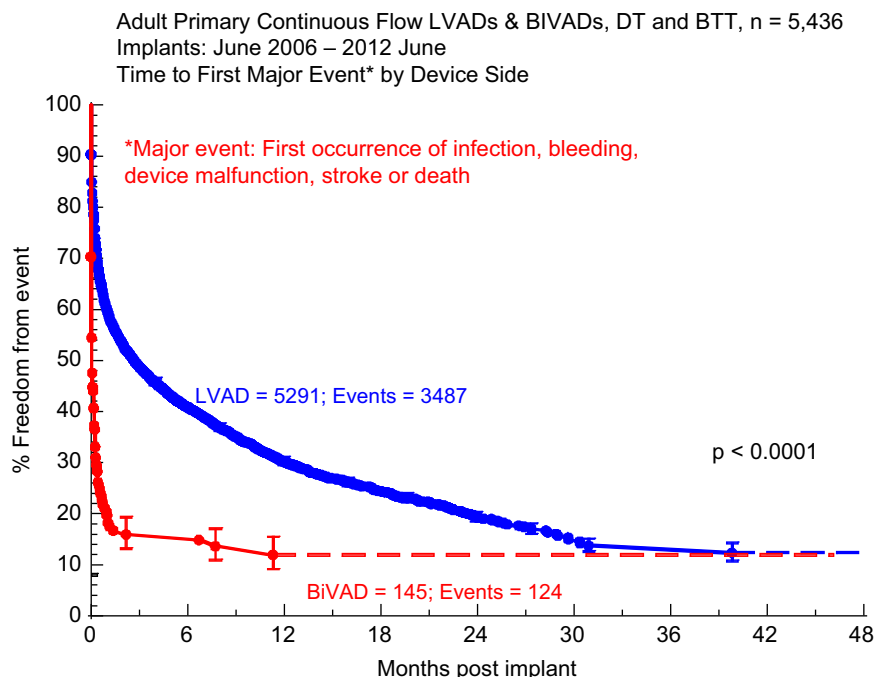


Figure 20 Freedom from adverse events listed in Figure 19, stratified by left (LVAD) or biventricular (BIVAD) support. Error bars indicate ± 1 standard error. BTT, bridge to transplant; DT, destination therapy.

Medical Therapy for INTERMACS Levels 4 to 6

During the past year, the Medical Arm of INTERMACS (MEDAMACS) has been developed to assess medically treated patients who might become candidates for MCS

devices. The intent is to investigate outcomes in these patients to better understand the “gray” area between medical treatment and VAD therapy, particularly in INTERMACS Levels 4 to 6. This registry will be launched in January 2013, with 12 hospitals identified for the initial pilot study.

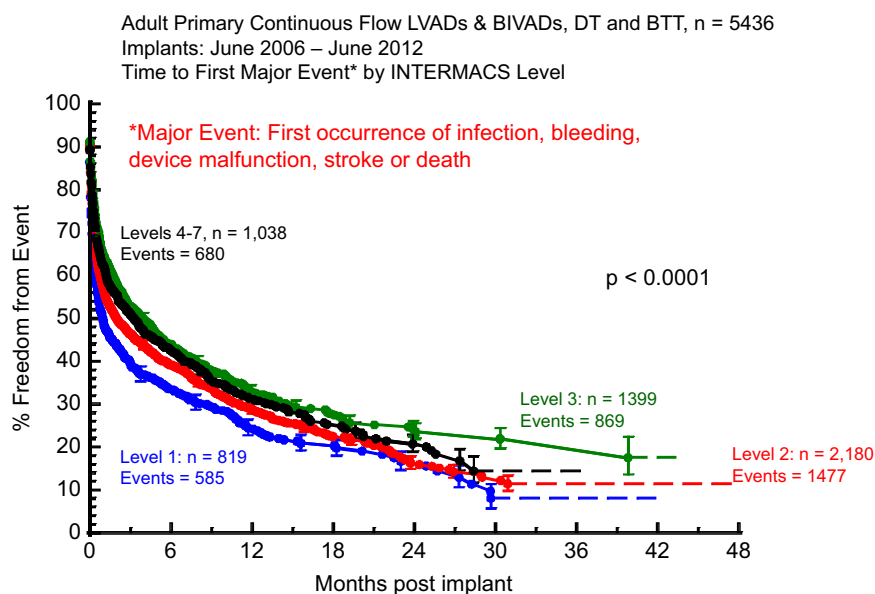


Figure 21 Freedom from adverse events listed in Figure 19, stratified by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level. Error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

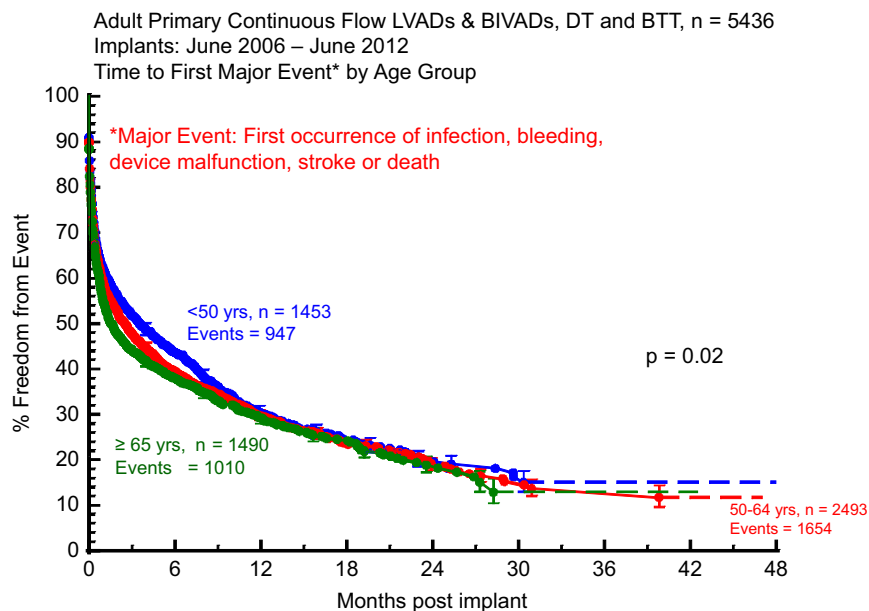


Figure 22 Freedom from adverse events listed in Figure 19, stratified by age. Error bars indicate ± 1 standard error. BIVAD, biventricular assist device; BTT, bridge to transplant; DT, destination therapy; LVAD, left ventricular assist device.

Summary

1. The INTERMACS database now includes more than 6,800 patients and 145 participating hospitals.
2. The Heartware HVAD and Berlin Heart Excor Pediatric VAD have recently received FDA approval.
3. Greater than 95% of implants are currently continuous-flow devices.
4. Current survival is approximately 80% at 1 year and 70% at 2 years.
5. Elderly patients have generally favorable outcomes but have less tolerance for additional risk factors.
6. Patients in INTERMACS Levels 1 and 2 have about a 5–8% decrease in 1-year survival compared with other INTERMACS levels.
7. Worsening degrees of right ventricular failure and renal dysfunction are associated with an incremental likelihood of early mortality.
8. Adverse event burden will play an important role in driving therapeutic choices for INTERMACS Levels 4 to 7.

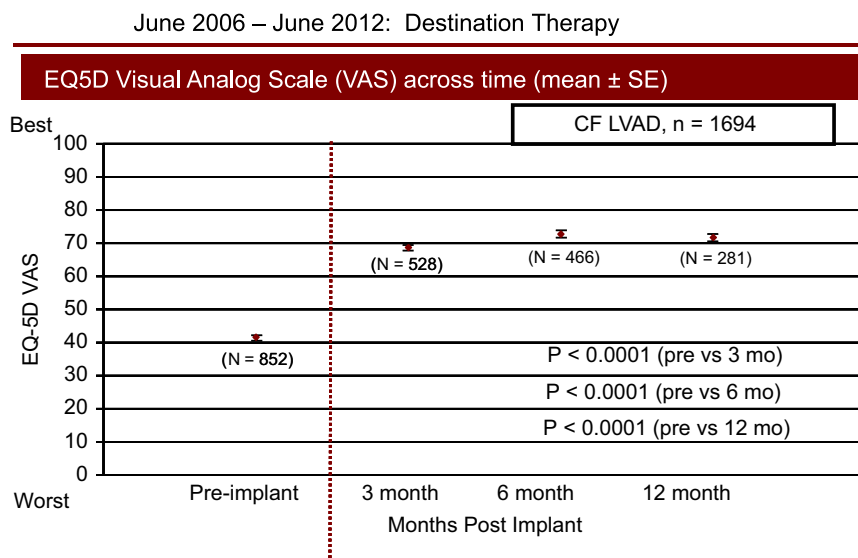


Figure 23 Visual analog scale (VAS) of general well-being before and after device implant. The numbers in parenthesis indicate number of responses received by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). CF LVAD, continuous-flow left ventricular assist device.

June 2006 – June 2012: Destination Therapy

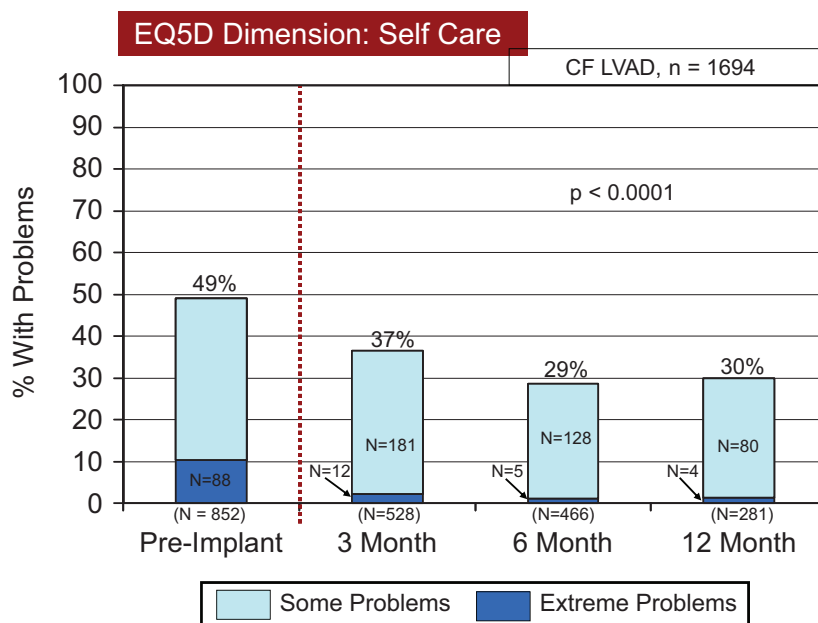


Figure 24 Self-care component of the study before and after device implant. CF LVAD, continuous-flow left ventricular assist device.

9. Quality of life indicators are generally positive after device implant for at least the first year.
10. Major knowledge gaps will be addressed by the addition of dedicated pediatric (PEDIMACS) and medical (MEDAMACS) components within INTERMACS.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

June 2006–June 2012: Destination Therapy

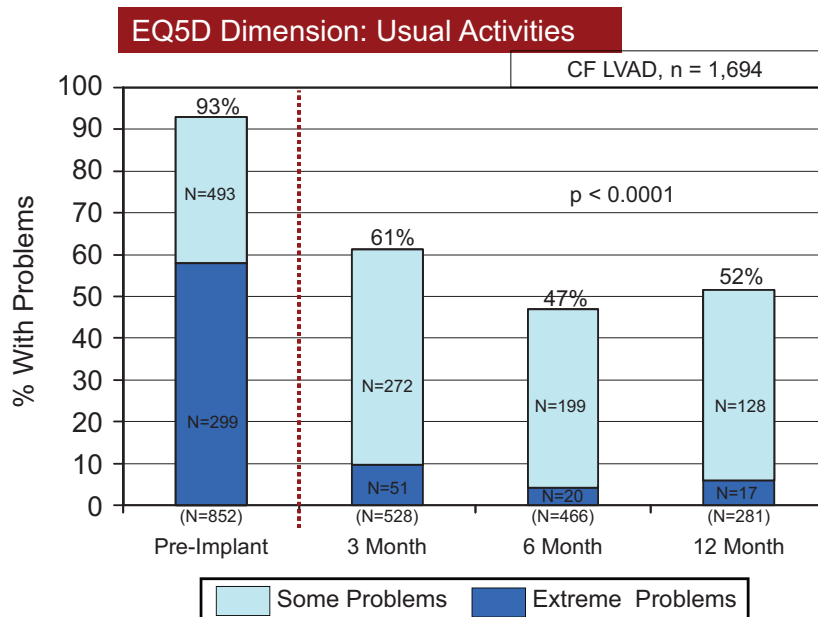


Figure 25 Usual activities component of study before and after device implant. CF LVAD, continuous flow left ventricular assist device.

Disclosure statement

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