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SPECIAL FEATURE

Third INTERMACS Annual Report: The evolution of destination therapy in the United States

James K. Kirklin, MD,[a] David C. Naftel, PhD,[a] Robert L. Kormos, MD,[b] Lynne W. Stevenson, MD,[c] Francis D. Pagani, MD,[d] Marissa A. Miller, DVM, MPH,[e] Karen L. Ulisney, MSN, CRNP,[f] J. Timothy Baldwin, PhD,[g] and James B. Young, MD[h]

From the [a]University of Alabama at Birmingham, Birmingham, Alabama; [b]University of Pittsburgh Medical Center, Presbyterian University Hospital, Pittsburgh Pennsylvania; [c]Cardiovascular Division, Brigham & Women's Hospital, Boston, Massachusetts; [d]University of Michigan, Ann Arbor, Michigan; [e]National Heart Lung and Blood Institute (NHLBI), Bethesda, Maryland; [f]National Institutes of Health/NHLBI, Division of Cardiovascular Diseases, Advanced Technologies and Surgery Branch, and [g]NHLBI at Two Rockledge Center, Bethesda, Maryland; and [h]Cleveland Clinic Foundation, Lerner College of Medicine, Cleveland, Ohio

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The third annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) provides documentation of the current landscape of durable mechanical circulatory support in the United States. With nearly 3,000 patients entered into the database, the transition to continuous-flow pump technology is evident and dramatic. This report focuses on the rapidly expanding experience with mechanical circulatory support as destination therapy. The current 1-year survival of 75% with continuous-flow destination therapy provides a benchmark for the evolving application of this therapy.
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The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS),[1,2] a National Heart Lung and Blood Institute (NHLBI)–sponsored collaborative database, collects information on durable mechanical circulatory support (MCS) device implants in the United States. Prospective patient enrollment and data collection began on June 23, 2006, and through September 2010, more than 2,800 patients have been enrolled in the database. United States MCS centers designated by the Centers for Medicare and Medicaid Services (CMS) as destination therapy (DT) centers are required to enter all implants of durable devices into the INTERMACS database.

During the 5 years of data collection in INTERMACS, a dramatic change has occurred in the landscape of MCS support in the United States. After nearly a decade of various clinical trials, the first continuous-flow axial pump (HeartMate II, Thoratec, Pleasanton, CA), was approved as bridge-to-transplant therapy in the United States in April 2008. In January 2010, 20 months later, the same device was approved for permanent DT for patients with terminal heart failure who were not eligible for cardiac transplantation. The *Second Annual INTERMACS Report*[2] focused on the emergence of continuous-flow pump technology in the United States MCS arena. This report will analyze the evolution of destination MCS therapy in the United States.

Evolution of the MCS landscape

Overall, the INTERMACS database shows that 2,868 patients have received implantation of one or more durable MCS devices between June 23, 2006, and September 30, 2010. A total of 79 centers in the United States have entered patient data, of which 69 have been designated as DT centers by CMS. The transition from pulsatile-flow pump

Reprint request: Dr. James K. Kirklin, MD, University of Alabama at Birmingham, Cardiovascular Division, 1900 University Blvd. Birmingham, AL 35294. Telephone: 205-934-5486. Fax: 205 975 2553.
E-mail address: jkirklin@uab.edu

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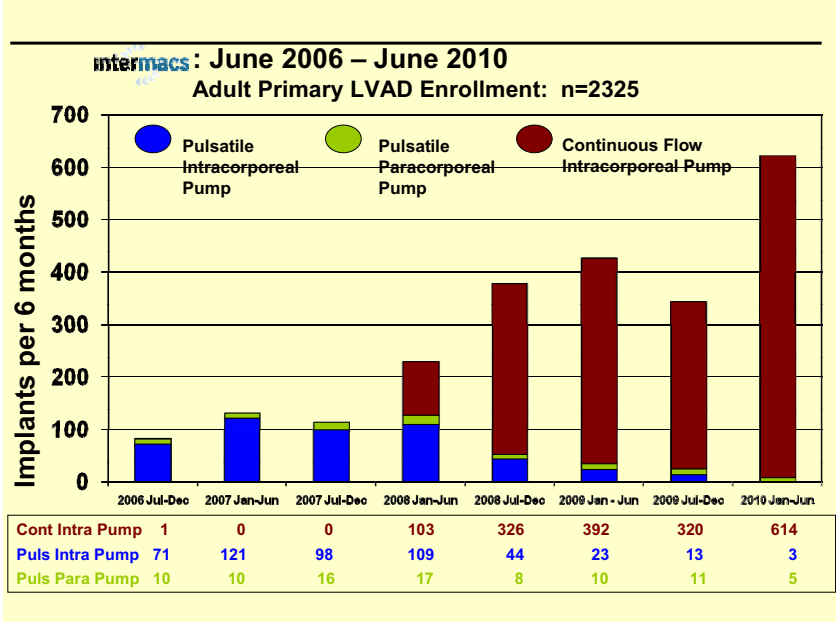

Figure 1 Bar chart shows pump types implanted between July 2006 and June 2010 in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database. Cont, continuous; INTRA, intracorporeal; PULS, pulsatile; PARA, paracorporeal.

Table 1 Device Type—Adult Primary Implants: INTERMACS, June 2006–June 2010

Device	Jun–Dec 2006 No. (%) (*N* = 100)	Jan–Dec 2007 No. (%) (*N* = 335)	Jan–Dec 2008 No. (%) (*N* = 703)	Jan–Dec 2009 No. (%) (*N* = 874)	Jan–Jun 2010 No. (%) (*N* = 668)	Total No. (%) (*N* = 2,680)
LVAD	82 (82)	245 (73)	607 (86	769 (88)	622 (93)	2,325 (87)
Bi-VAD	17 (17)	68 (20)	74 (11)	83 (9)	35 (5)	277 (10)
TAH	1 (1)	22 (7)	22 (3)	22 (3)	11 (2)	78 (3)
Total	100 (100)	335 (100)	703 (100)	874 (100)	668 (100)	2,680 (100)

Bi-VAD, biventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; TAH, total artificial heart.

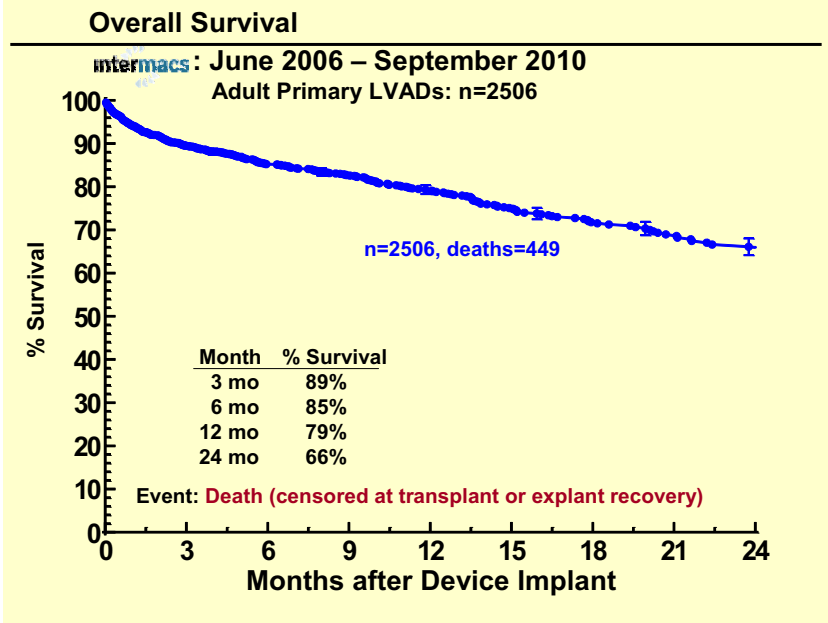

Figure 2 Actuarial survival of primary adult left ventricular assist device (LVAD) patients is shown with censoring at time of transplant or device explant for recovery. The error bars indicate ± 1 standard deviation. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

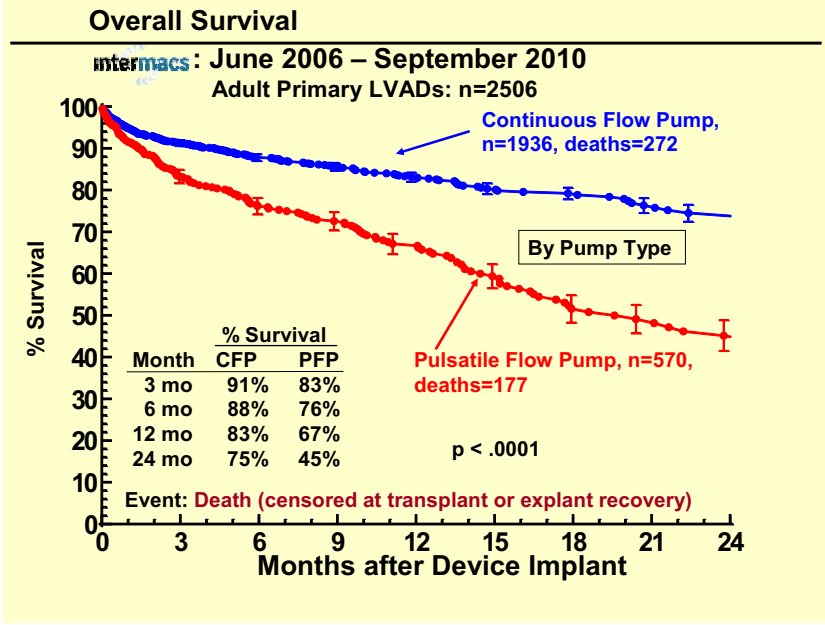

Figure 3 Actuarial survival after implantation of left ventricular assist devices (LVADs) has been stratified by continuous-flow (CFP) or pulsatile-flow (PFP) pump type in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database. The depiction is as in Fig 2.

support to continuous-flow pump technology has been dramatic, beginning in 2008 (Figure 1). For the most recent 6-month period (January through June 2010), continuous-flow pumps accounted for greater than 98% of adult primary left ventricular assist device (LVAD) implants. The distribution of implants by the type of support (Table 1) shows a preponderance of isolated LV support. Among patients receiving primary LVAD support, the overall actuarial survival, with censoring at transplant or explant, was 79% at 1 year and 66% at 2 years (Figure 2). To date, continuous-flow pump technology has provided a significant survival advantage compared with pulsatile-flow pump support (Figure 3).

The overall device strategy at the time of MCS implant (Table 2) reflects the large proportion of patients that receive a device before a final decision about transplantation has been rendered. A gradual change in the distribution of strategies has occurred during the past 5 years, with a trend toward a greater number of DT patients (Table 3). Similarly, a gradual change in the severity of illness of patients at

Table 2 Strategy for Device Implant—Adult Primary Implants: INTERMACS, June 2006–June 2010

Strategy	Jun 2006–Jun 2010 No. (%) (*N* = 2,680)
Bridge to transplant, listed	1,161 (43.3)
Bridge to candidacy	1,131 (42.2)
Likely	759 (28.3)
Moderate	280 (0.4)
Unlikely	92 (3.4)
Destination therapy	309 (11.5)
Bridge to recovery	48 (1.8)
Rescue therapy	22 (0.8)
Other	9 (0.3)
Total	2,680 (100)

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Table 3 Strategy for Device Implant—Adult Primary Implants: INTERMACS, June 2006–June 2010

Device strategy	June 2006–Dec 2008 No. (%) (*N* = 1,138)	Jan 2009–June 2010 No. (%) (*N* = 1,542)
Bridge to transplant, listed	529 (46.5)	632 (41.0)
Bridge to candidacy	468 (41.1)	663 (43.0)
Likely	312 (27.4)	447 (29.0)
Moderate	102 (9.0)	178 (11.5)
Unlikely	54 (4.7)	38 (2.5)
Destination therapy	96 (8.4)	213 (13.8)
Bridge to recovery	32 (2.8)	16 (1.0)
Rescue therapy	13 (1.1)	9 (0.5)
Other	0 (0)	9 (0.5)
Total	1,138 (100)	1,542 (100)

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.
$P < 0.0001$.

Table 4 Patient Profile Level—Adult Primary Implants: INTERMACS, June 2006–June 2010

Level	June 2006–Dec 2008 No. (%) (N = 1,138)	Jan 2009–June 2010 No. (%) (N = 1,542)
1. Critical cardiogenic shock	395 (34.7)	267 (17.3)
2. Progressive decline	457 (40.2)	697 (45.2)
3. Stable but inotrope-dependent	148 (13.0)	300 (19.5)
4. Recurrent advanced HF	96 (8.4)	178 (11.5)
5. Exertion intolerant	15 (1.3)	51 (3.3)
6. Exertion limited	11 (1.0)	32 (2.1)
7. Advanced NYHA class III	16 (1.4)	17 (1.1)
Total	1,138 (100)	1,542 (100)

HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.
$P < 0.0001$.

Table 5 Demographics—Adult Primary Implants: INTERMACS, June 2006–June 2010

Variable	DT patients (N = 385)	All other LVADs (N = 2134)	p-value
Gender, No. (%)			0.01
Male	322 (84)	1,663 (78)	
Female	63 (16)	471 (22)	
Race, No. (%)			0.01
White	291 (76)	1,452 (68)	
African American	69 (18)	506 (24)	
Other	25 (6)	176 (8)	
Age at implant			
Mean years	61.7	52.7	<0.0001
Range	23–82	19–88	

DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device.

implant has occurred during the course of the INTERMACS study (Table 4). The proportion of patients in critical cardiogenic shock (level 1) has decreased from 35% to 17% in the most recent INTERMACS era.

Patient population for DT

Among the 2,506 primary adult LVADs implanted between June 23, 2006, and September 30, 2010, 385 (15%) were implanted with an initial strategy of permanent, DT. The marked increase in the number of DT patients since January of 2010 is depicted in Figure 4. A comparison of basic demographics for DT patients vs all other primary LVAD recipients is detailed in Table 5. Of note, DT patients were significantly older than other LVAD patients in INTERMACS. At the time of LVAD implant, the INTERMACS level was 2, 3, or 4 in more than 80% of DT patients (Table 6).

Indications for DT therapy

The most common contraindication to cardiac transplantation was advanced age, followed by renal dysfunction and a high body mass index (Table 7). It is noteworthy that more

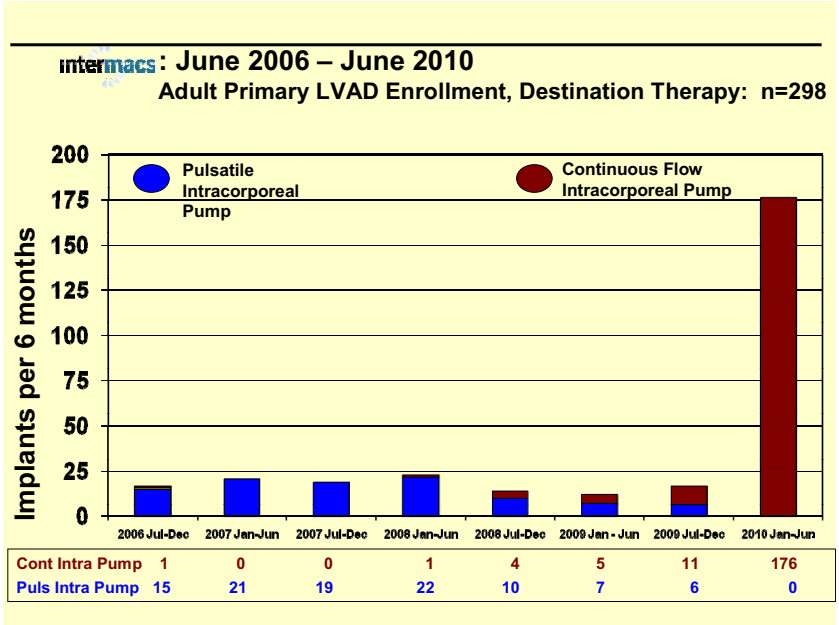

Figure 4 Bar graph shows destination therapy patients entered into the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database during 6-month intervals between July 2006 and June 2010. The general depiction is as in Fig 1.

Table 6 Patient Profile Levels—Adult Primary Implants: INTERMACS, June 2006–June 2010

Level	DT patients No. (%) (N = 385)	All other LVADs No. (%) (N = 2134)
1. Critical cardiogenic shock	36 (9)	467 (22)
2. Progressive decline	159 (41)	947 (44)
3. Stable but inotrope-dependent	101 (26)	374 (18)
4. Recurrent advanced HF	57 (15)	233 (11)
5. Exertion intolerant	19 (5)	51 (2)
6. Exertion limited	7 (2)	34 (2)
7. Advanced NYHA class III	6 (2)	28 (1)
Total	385 (100)	2,134 (100)

DT, destination therapy; HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; NYHA, New York Heart Association.

$P < 0.0001$.

Table 7 Transplant Contraindications—Adult Primary Implants: INTERMACS, June 2006–June 2010

Contraindications	No. (%) (N = 385)
Modifiable	
Renal dysfunction	86 (22)
High body mass index	62 (16)
Pulmonary hypertension	45 (12)
Still smoking	27 (7)
Limited social support	20 (5)
Severe diabetes	20 (5)
Repeated non-compliance	16 (4)
Illicit drug use	14 (4)
Alcohol abuse	13 (3)
Patient refuses transplant	11 (3)
Limited cognition/understanding	8 (2)
Contraindication to immunotherapy	7 (2)
Risk of recurrent infection	5 (1)
Severe depression	4 (1)
Current infection	3 (1)
Malnutrition/cachexia	3 (1)
Musculoskeletal limitations	3 (1)
Non-modifiable	
Advanced age	128 (33)
Other comorbidity	35 (9)
Peripheral vascular disease	31 (8)
Pulmonary disease	30 (8)
Frailty	20 (5)
Fixed pulmonary hypertension	18 (5)
History of solid-organ cancer	18 (5)
History of lymphoma, leukemia	12 (3)
Multiple sternotomies	12 (3)
Other major psychiatric diagnosis	6 (2)
Heparin-induced thrombocytopenia	5 (1)
Major stroke	5 (1)
Allosensitization	1 (<1)
Recent pulmonary embolus	1 (<1)

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

than half of the contraindications were considered "modifiable," leaving the possibility open for eventual cardiac transplantation. The frequency with which patients originally selected for DT are later considered for cardiac transplantation and actually receive an allograft is depicted in the competing outcomes analyses, indicating that nearly 10% of patients undergo cardiac transplantation by 12 months after LVAD implant (Figure 5).

Survival after MCS support as destination therapy

The overall survival among all patients undergoing MCS DT was 67% at 1 year and a disappointing 46% at 24 months (Figure 6). However, a very important and highly significant trend has emerged with the conversion from pulsatile technology to continuous-flow pumps (Figure 7). Although the follow-up remains relatively short, the survival curves have already demonstrated significant divergence, with a 1-year survival that has improved from 61% with pulsatile-flow pumps to 74% with continuous-flow technology. Multivariable analysis was used to identify risk factors in the early and constant phases of hazard (Table 8). The finding of pulmonary hypertension (as a contraindication to heart transplantation) as a risk factor in the constant phase will require further study to understand its implications. The effect of older age as a risk factor is depicted in Figure 8.

Biventricular support during DT therapy

Of the 385 primary DT patients, 13 received a temporary right ventricular assist device (RVAD) for unexpected RV failure at the time of LVAD implant, and 9 patients received an RVAD at a mean of 9 days after the LVAD implant (range, 1–26 days). Among DT patients who required an RVAD for unexpected RV failure during the LVAD implant operation, survival was poor, with 3-month mortality exceeding 50% (Figure 9). By multivariate analysis, only higher right atrial pressure was identified as a possible ($p = 0.1$) risk factor for the need for RVAD support.

Causes of death

The overall causes of death are listed in Table 9 according to those occurring during and after the first month. The

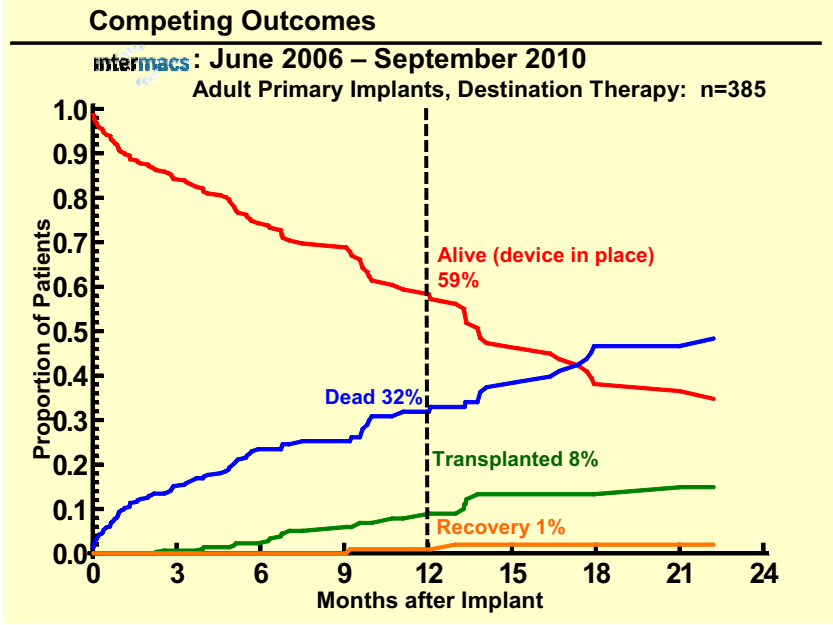

Figure 5 Competing outcomes are depicted for patients receiving a destination therapy left ventricular assist device in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database.

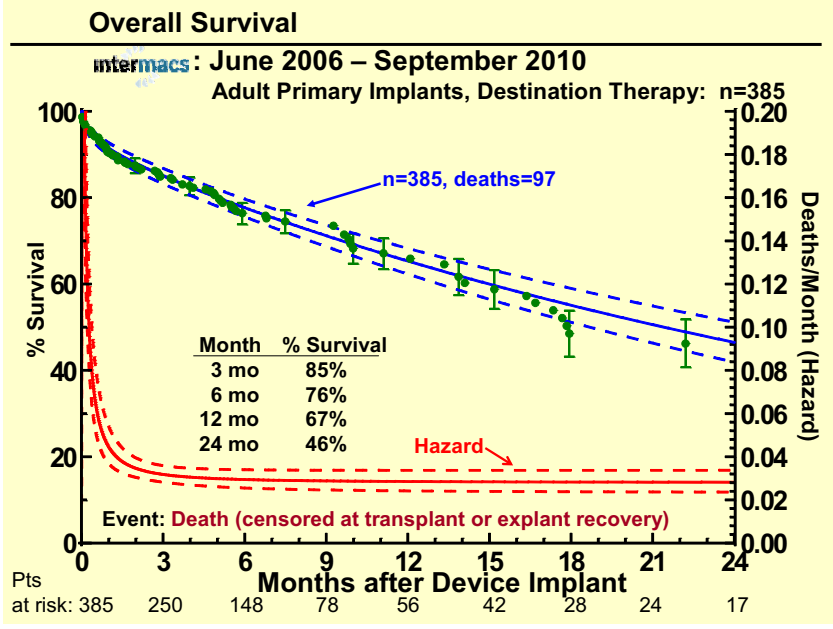

Figure 6 Actuarial survival and hazard curve is shown for patients after left ventricular assist device implant for destination therapy. The error bars show the SD, and the dashed lines enclose the 70% confidence limits. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

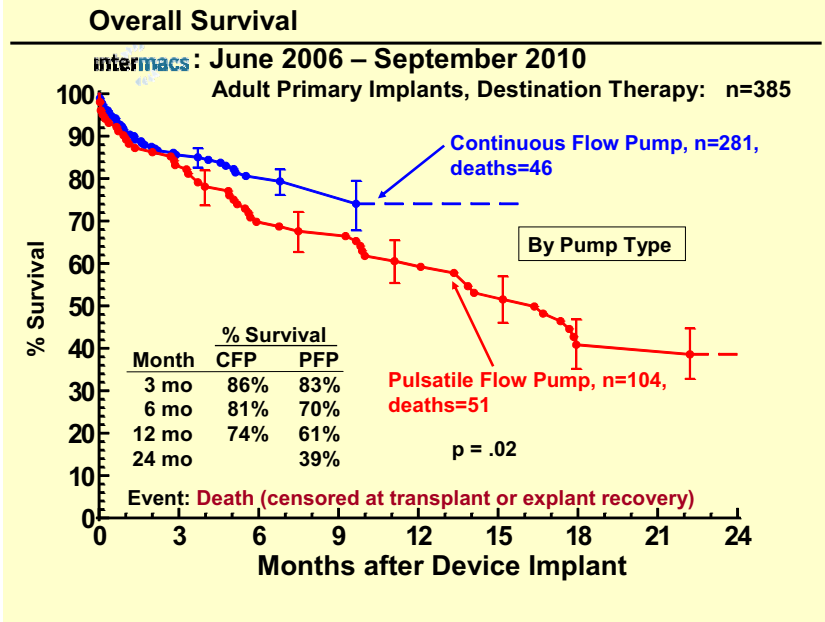

Figure 7 Actuarial survival after left ventricular assist device implant for destination therapy, stratified by continuous-flow (CFP) and pulsatile-flow (PFP) pumps. Depiction is as in Fig 3. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

multitude of causes of death, particularly early after implant, likely reflect the important associated comorbidities and generally limited reserves of these patients, who are ineligible for cardiac transplantation.

Table 8 Risk Factors for Death in Destination Therapy Patients—Adult Primary Implants: INTERMACS, June 2006–June 2010

	Early hazard		Constant hazard	
Risk factors	HR	*p*-value	HR	*p*-value
Age (older)			1.78[a]	<0.0001
Critical cardiogenic shock	3.52	0.0078		
Diabetes			1.98	0.01
Pulmonary hypertension			3.56	0.0001
BUN (higher)	1.27[b]	0.001		
Sodium (lower)			2.14[c]	0.005
Concomitant surgery	3.02	0.02		
Bi-VAD	8.42	0.0002		
Pulsatile flow LVAD			2.75	0.002

BUN, blood urea nitrogen; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; HR, hazard ratio.

[a]The hazard ratio denotes the increased risk from age 60 to 70 years.

[b]The hazard ratio denotes the increased risk of a 10-unit increase in BUN.

[c]The hazard ratio denotes the increased risk of a 10-unit decrease in sodium.

Summary

INTERMACS continues to accrue vital information regarding the evolution of durable MCS in the United States, with nearly 3,000 patient implants during the past 4.5 years. The clinical technology has transitioned almost completely toward continuous flow pumps. Including all indications, the actuarial survival (with censoring at transplant or explant) for patients receiving continuous-flow pumps has improved to nearly 80% at 2 years. The patient profile of heart failure severity level has evolved during the past 4 years, with the percentage of patients implanted in critical cardiogenic shock (level 1) decreasing from 35% to 17%. DT has accounted for 15% of the overall MCS implants, with a dramatic increase in the number of DT patients since January 2010. At the time of DT, the INTERMACS level was 2, 3, or 4 in more than 80% of DT patients.

The major contraindications to cardiac transplantation that drive the decision for DT are older age, renal dysfunction, and a high body mass index. Potentially modifiable contraindications of cardiac transplantation are present in more than 50% of DT patients, and approximately 10% of DT patients undergo cardiac transplantation or the device can be explanted due to recovery within the first year. RV failure severe enough to require RV MCS during DT therapy is uncommon, but highly lethal, with a mortality exceeding 50% by 3 months. Improvement in medium-term survival of DT patients has been dramatic since the availability of continuous-flow pumps, with 1-year survival of 74%. Risk factors for death during DT therapy reflect the multiple comorbidities and generally reduced reserves of these patients with terminal heart failure.

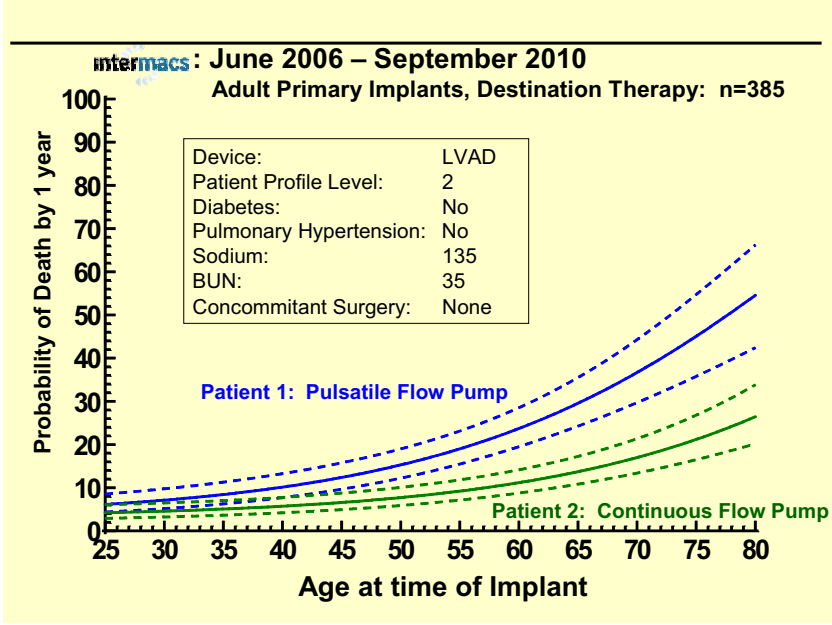

Figure 8 Solution to the multivariable equation for death after left ventricular assist device implant (LVAD) as destination therapy in the constant phase. The setting of other significant variables in the model is indicated in the box. Dashed lines enclose the 70% confidence limits. BUN, blood urea nitrogen; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

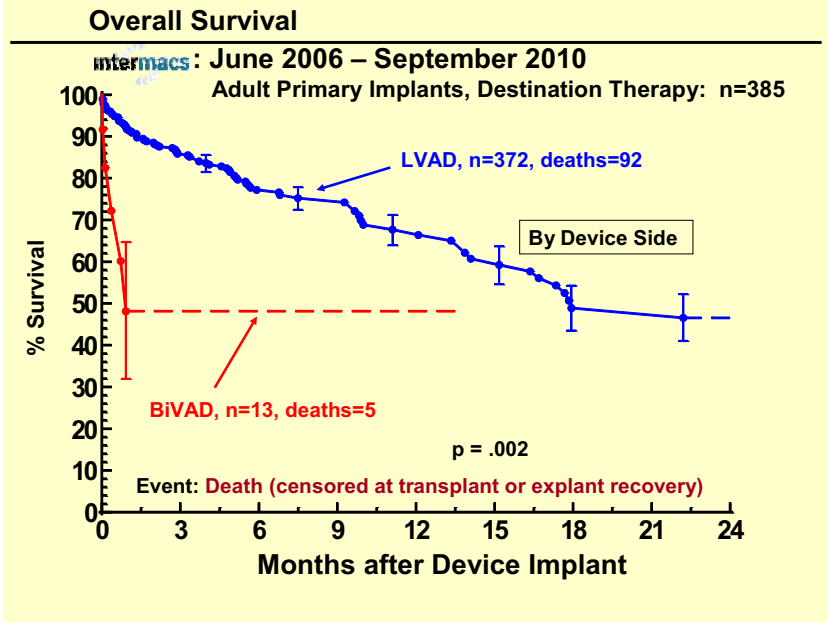

Figure 9 Actuarial survival after left ventricular assist device (LVAD) implant for destination therapy has been stratified by the presence or absence of biventricular assist device (BiVAD) support during the same procedure as LVAD implant. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Table 9 Destination Therapy: n = 385 Adult Primary Implants: INTERMACS, June 2006–June 2010

	Early (<1 mo)		Later (≥1 mo)		Total	
Primary cause of death	n	% of 35	n	% of 62	n	% of 97
Cancer	0	0%	1	2%	1	1%
Cardiac Failure	2	5%	7	11%	9	9%
Cardiovascular: Other	4	11%	4	6%	8	8%
Device Malfunction	0	0%	3	5%	3	3%
Hematologic Other	0	0%	1	2%	1	1%
Hemorrhage: Disseminated Intravas Coagulation	2	5%	0	0%	2	2%
Hemorrhage: Post-Operative surgery related	4	11%	0	0%	4	4%
Hemorrhage: Pulmonary	2	5%	0	0%	2	2%
Hemorrhage: Other	0	0%	3	5%	3	3%
Infection	1	2%	5	8%	6	6%
Other chronic illness	1	2%	0	0%	1	1%
Pulmonary: Respiratory Failure	2	5%	2	3%	4	4%
Renal Failure	1	3%	2	3%	3	3%
Other	4	11%	10	16%	14	14%
Unknown	3	11%	11	21%	14	18%
CNS cause of death	4	11%	5	8%	9	9%
MOF	5	14%	8	13%	13	13%
Total	35		62		97	100%

CNS, central nervous system; LVAD, left ventricular assist device.
Cardiac Failure includes RV Failure and VT/VF.

Disclosure statement

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