

MEDCAC Meeting

November 14, 2012

Management of Heart Failure with the Use of Ventricular Assist Devices

Evidence from INTERMACS

James K. Kirklin, MD: Principal Investigator

David C. Naftel, PhD: Co-Principal Investigator

On behalf of the INTERMACS Investigators

Disclosures:

James K. Kirklin:

David C. Naftel:

- I. INTERMACS Description
- II. Evolving Devices
- III. Survival
- IV. Adverse Events
- V. Quality of Life
- VI. Functional Capacity
- VII. Knowledge Gaps
- VIII. Panel Questions

I. INTERMACS Description

“Implantation of an MCSS is not a simple, time-limited treatment episode. Because of the patient’s total dependence on the device and because problems can occur at any time, clinical trial subjects should be followed closely during the trials: they and other MCSS patients should be followed, through a registry, for the remainder of their lives...Maintaining a registry of MCSS recipients should be considered a routine aspect of this care...The committee recommends that NHLBI...support long term follow up studies of an adequate sample of MCSS patients.”

The Artificial Heart: Prototypes Policies and Patients; Institute of Medicine Report, 1991.

intermacs

**Interagency Registry for Mechanically
Assisted Circulatory Support
NHLBI Contract #HHSN268200548198C**



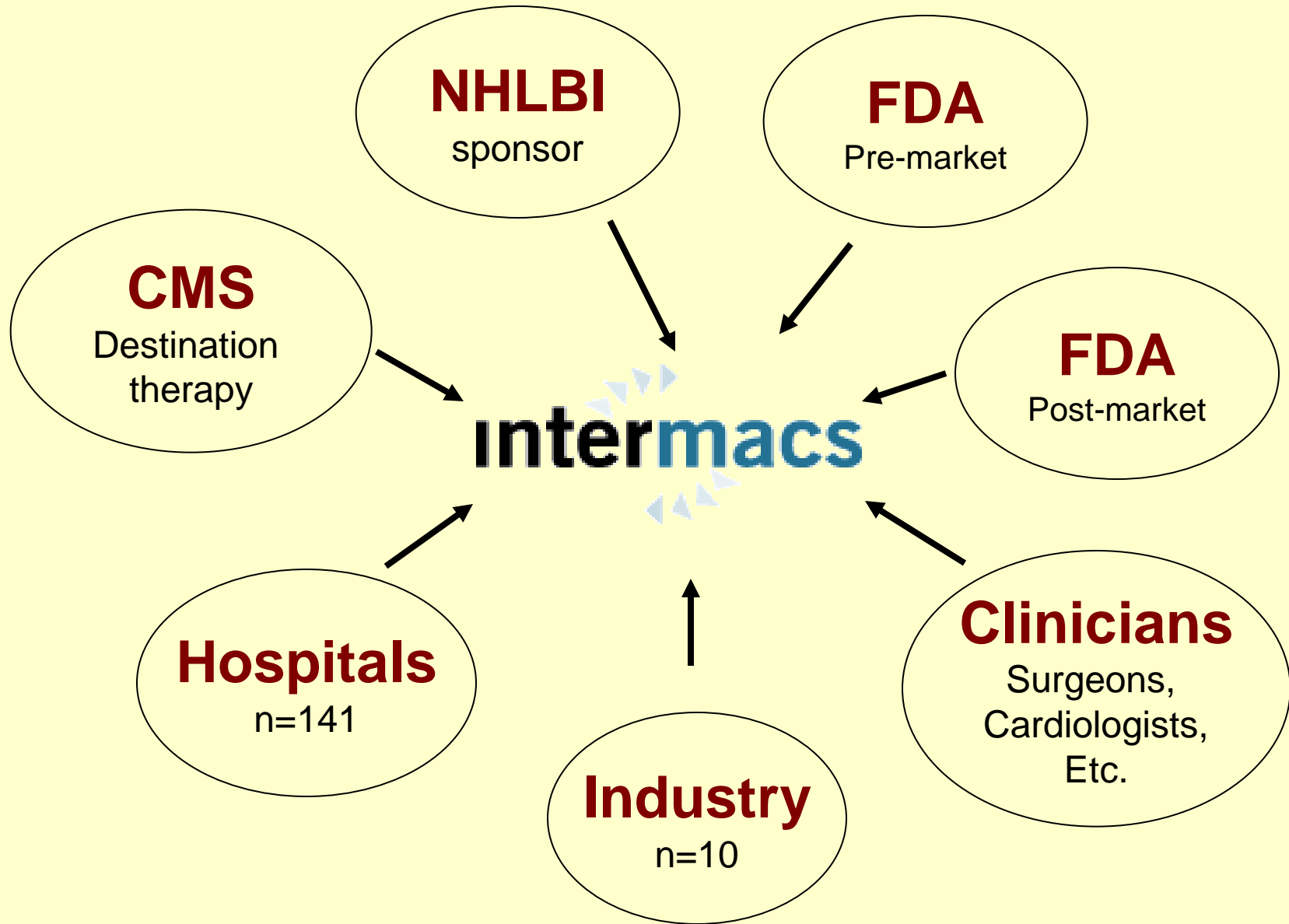
National Heart, Lung, and Blood Institute



**Centers for Medicare and Medicaid
Services**



Food and Drug Administration



What is INTERMACS ?

INTERMACS is the North American registry for patients who are receiving durable, FDA approved mechanical circulatory support device therapy to treat advanced heart failure. This registry was devised as a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives.

Goals of the Registry

- Facilitate the refinement of patient selection to *maximize outcomes* with current and new device options.
- Identify predictors of good outcomes as well as risk factors for adverse events after device implantation.
- Develop consensus “*best practice*” guidelines to improve clinical management by reducing short and long term complications of MCSD therapy.
- Guide clinical application and evolution of next generation devices.
- Utilize Registry information to guide improvements in technology, particularly as next generation devices evolve.

Original Contract

May 31, 2005 – 2010

Contract Extension

2010 – 2015

Long-term Business Plan

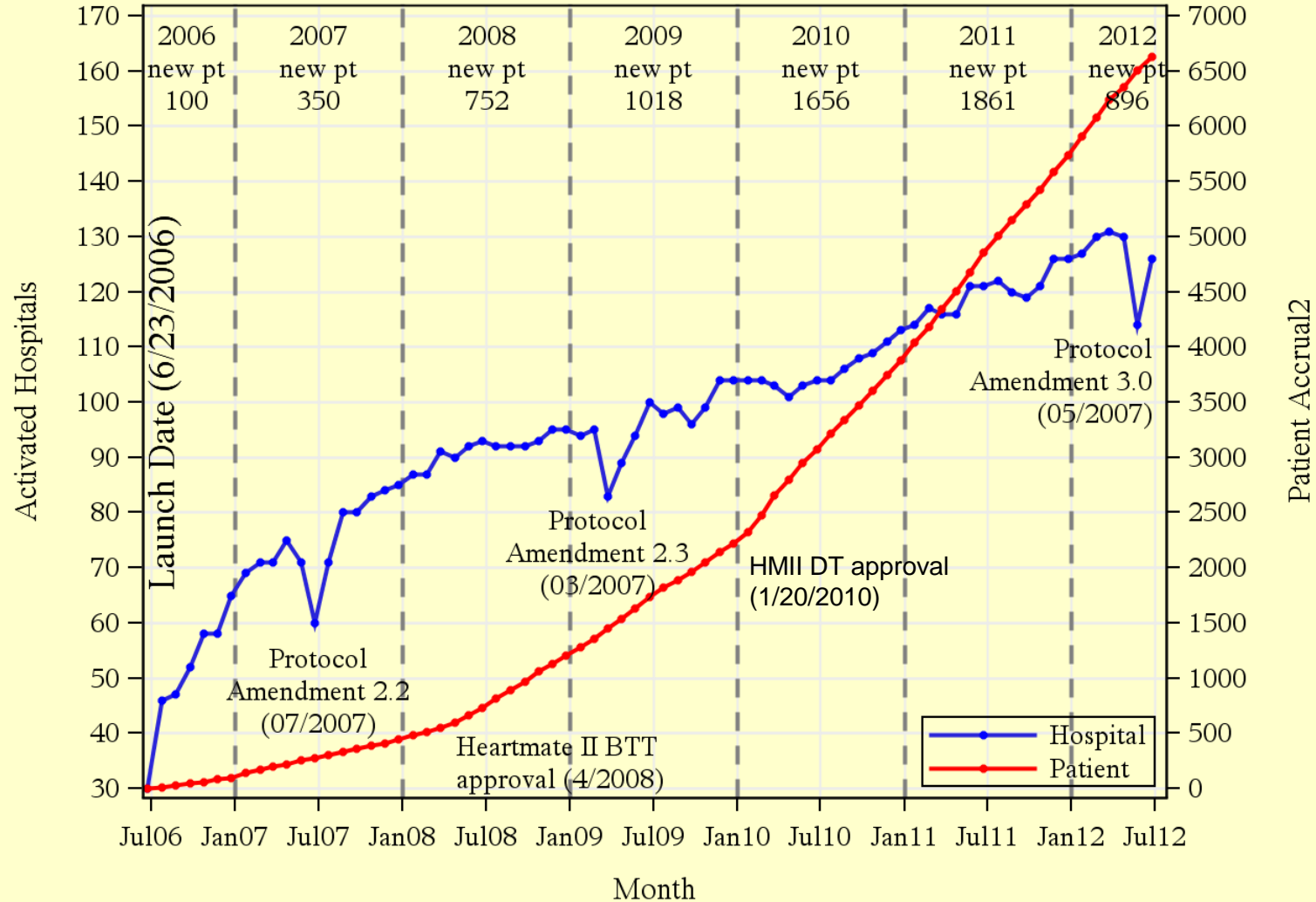
2015 ---

As of October 22, 2012

Activated Sites: 141

Enrolled Patients: 8028

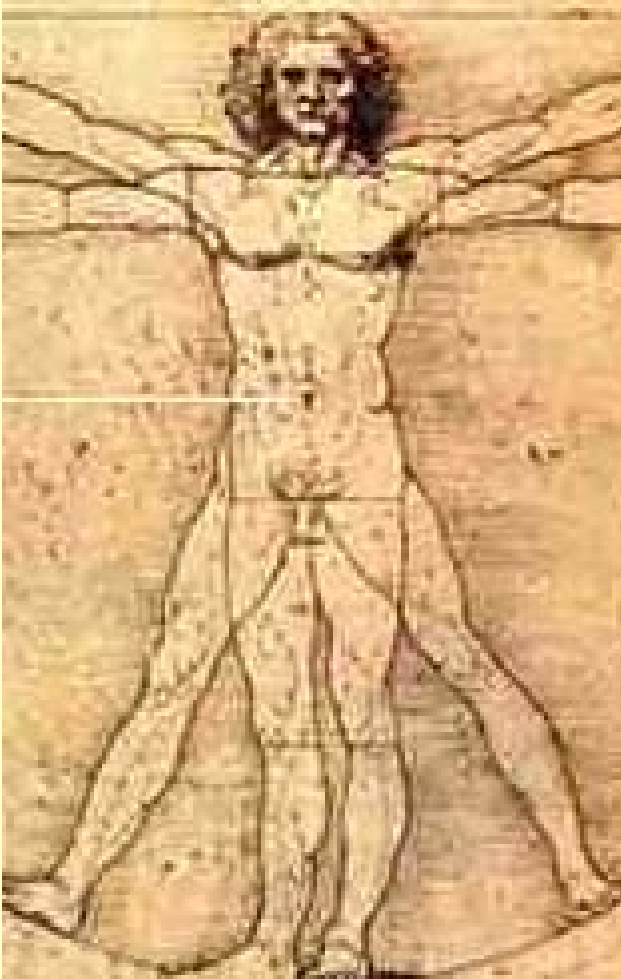
INTERMACS Hospital Activation and Patient Enrollment Primary Prospective Implants: June 23, 2006 to June 30, 2012



Between June 23, 2006 and June 30, 2012, 145 hospitals participated in INTERMACS and, of these, 131 hospitals actively contributed information on a total of 6633 patients. Cumulative patient accrual and the number of participating hospitals over this time period are displayed above.

Data Collected	Pre-Implant	Implant	1wk/1mth	3mth/q 6mth	Disch
Demographic	X				
Medical Support Status	X				
Co-morbidities	X				
Hemodynamics	X		X	X	X
Medications	X		X	X	X
Laboratory	X		X	X	X
Medical Condition	X		X	X	
Exercise Functions	X			X	
Patient Status	X			X	
Device Information		X			
Device Details		X			
Device Parameters				X	X
Quality of Life	X			X	
Trail Making Test	X			X	
Adverse Event Reminders			X	X	X
Chronology of Hospital Time					X

Adverse Events

<u>Right Heart Failure</u>	<u>Psychiatric Episode</u>	<u>Neurological Dysfunction</u>	<u>Major Infection</u>
<u>Myocardial Infarction</u>			<u>Device Malfunction</u>
<u>Renal Dysfunction</u>			<u>Respiratory Failure</u>
<u>Cardiac Arrhythmia</u>			<u>Arterial Non-CNS Thromboembolism</u>
<u>Pericardial Drainage</u>			<u>Venous Thrombosis</u>
<u>Hypertension</u>			<u>Wound Dehiscence</u>
<u>Hemolysis</u>			<u>Bleeding</u>
	<u>Hepatic Dysfunction</u>	<u>Other Major SAE</u>	

II. Evolving Devices

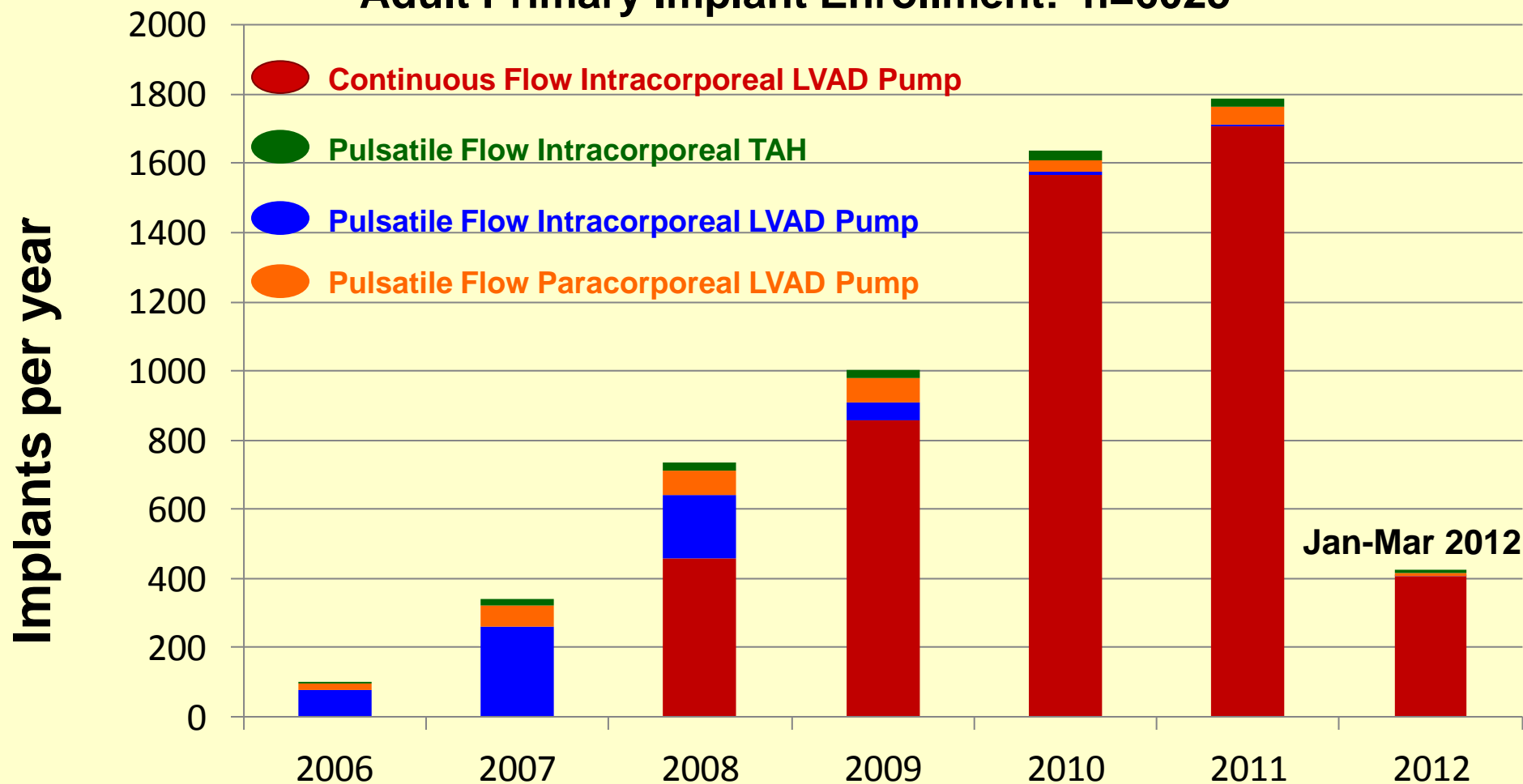
1. Approved Durable Devices (potential for patient discharge): These devices should be entered into INTERMACS except in rare circumstances where a patient with an approved device is in the control arm of an FDA approval study.

Company	Device	Position
Abiomed, Inc.	AbioCor TAH	TAH
Micromed Technology, Inc.	MicroMed DeBakey VAD – Child	L
SynCardia Systems, Inc.	SynCardia CardioWest	TAH
Thoratec Corporation	HeartMate II LVAS	L
	HeartMate IP	L
	HeartMate VE	L
	HeartMate XVE	L
	Thoratec IVAD	L/R
	Thoratec PVAD	L/R
	NovaCor PC	L
WorldHeart, Inc.	NovaCor PCq	L

2. Approved Temporary Devices: These devices SHOULD NOT be entered into INTERMACS (unless they are simultaneously implanted with a durable device or implanted after a durable device). They do not meet the INTERMACS definition for “potential patient discharge”.

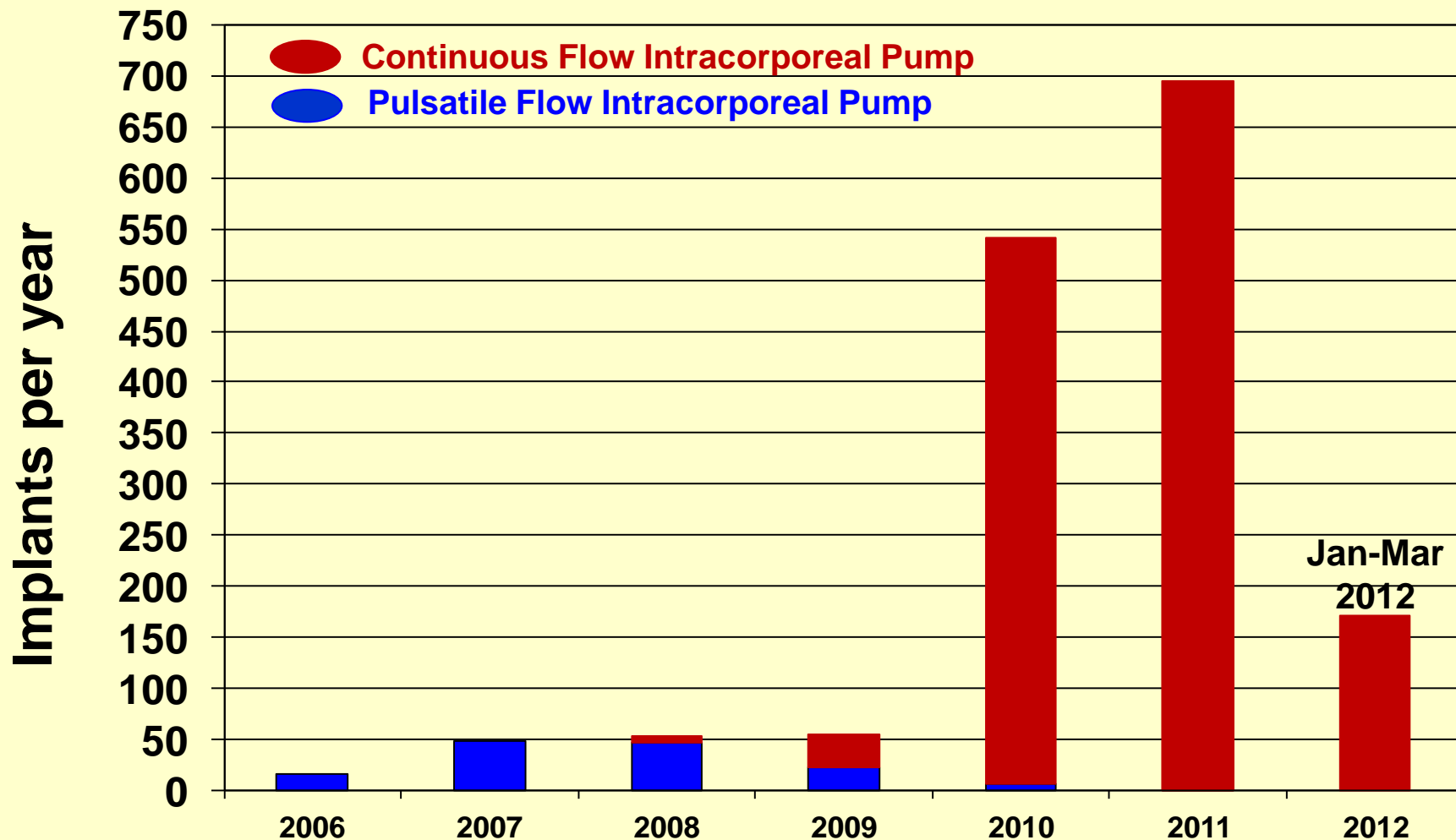
Company	Device	Position
Abiomed, Inc.	Abiomed AB5000	L/R
	Abiomed BVS 5000	L/R
CardiacAssist, Inc.	Tandem Heart	L/R
Levitronix Medical Division	Levitronix Centrimag	L/R
Medtronic Biomedicus, Inc.	Biomedicus	R

Adult Primary Implant Enrollment: n=6025



Cont Intra Pump	0	0	458	858	1564	1706	405
Puls Intra TAH	1	22	23	24	29	20	7
Puls Intra Pump	78	260	181	53	14	4	2
Puls Para Pump	18	60	73	69	31	55	10

Adult Primary Implant Enrollment, Destination Therapy: n=1577



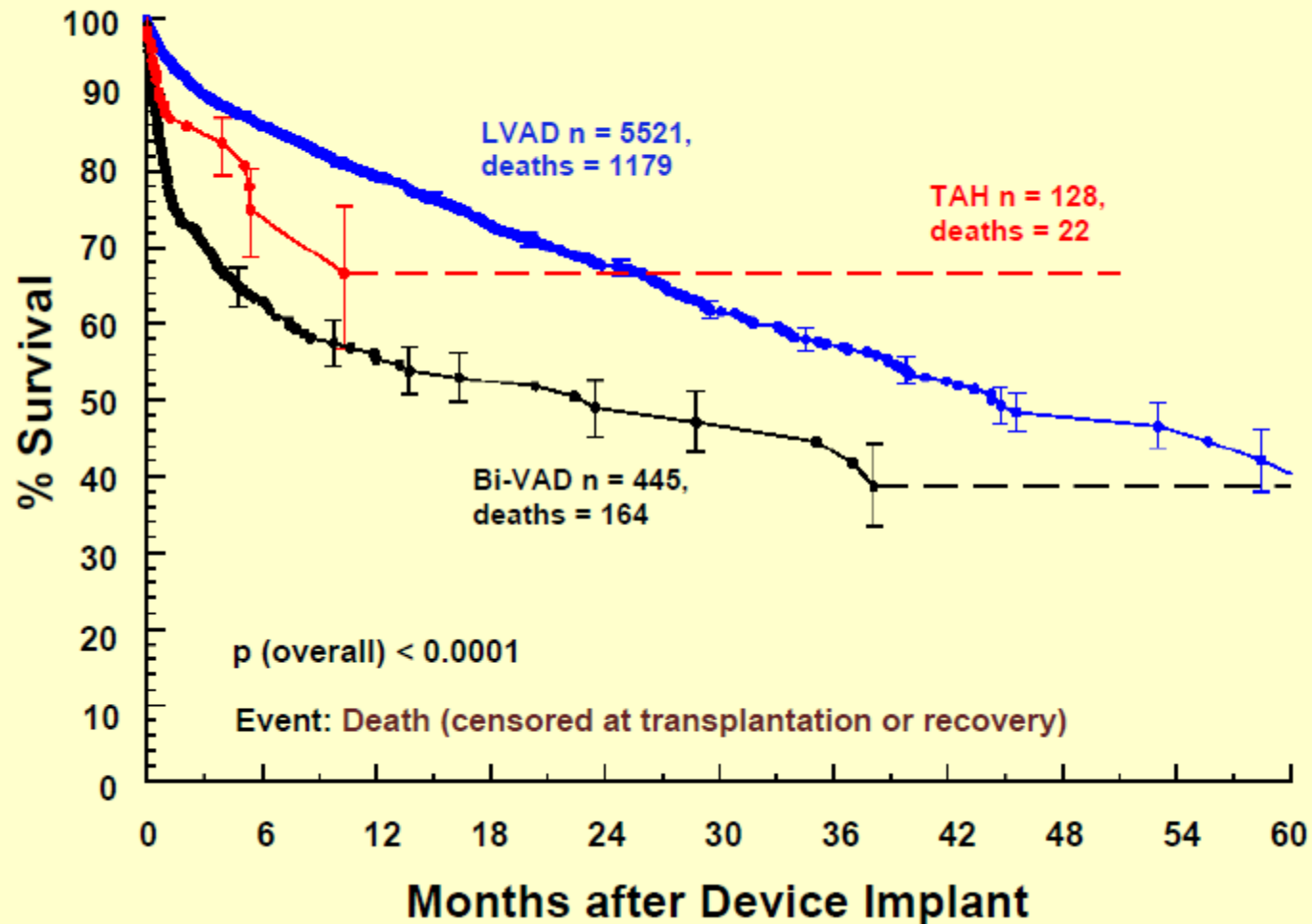
Cont Intra Pump	0	0	7	32	535	694	170
Puls Intra Pump	15	48	46	22	5	1	0

Implants: June 2006 – June 2012

DEVICE STRATEGY AT TIME OF IMPLANT	Implant Date Period						TOTAL	
	Pre 2011		2011		2012 (Jan-Jun)			
	n	%	n	%	n	%	n	%
BTT Listed	1545	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	0.4 %	46	0.6 %
Other	14	0.3 %	12	0.6 %	1	0.1 %	27	0.4 %
TOTAL	3876	100.0 %	1861	100.0 %	896	100.0 %	6633	100.0 %

III. Survival

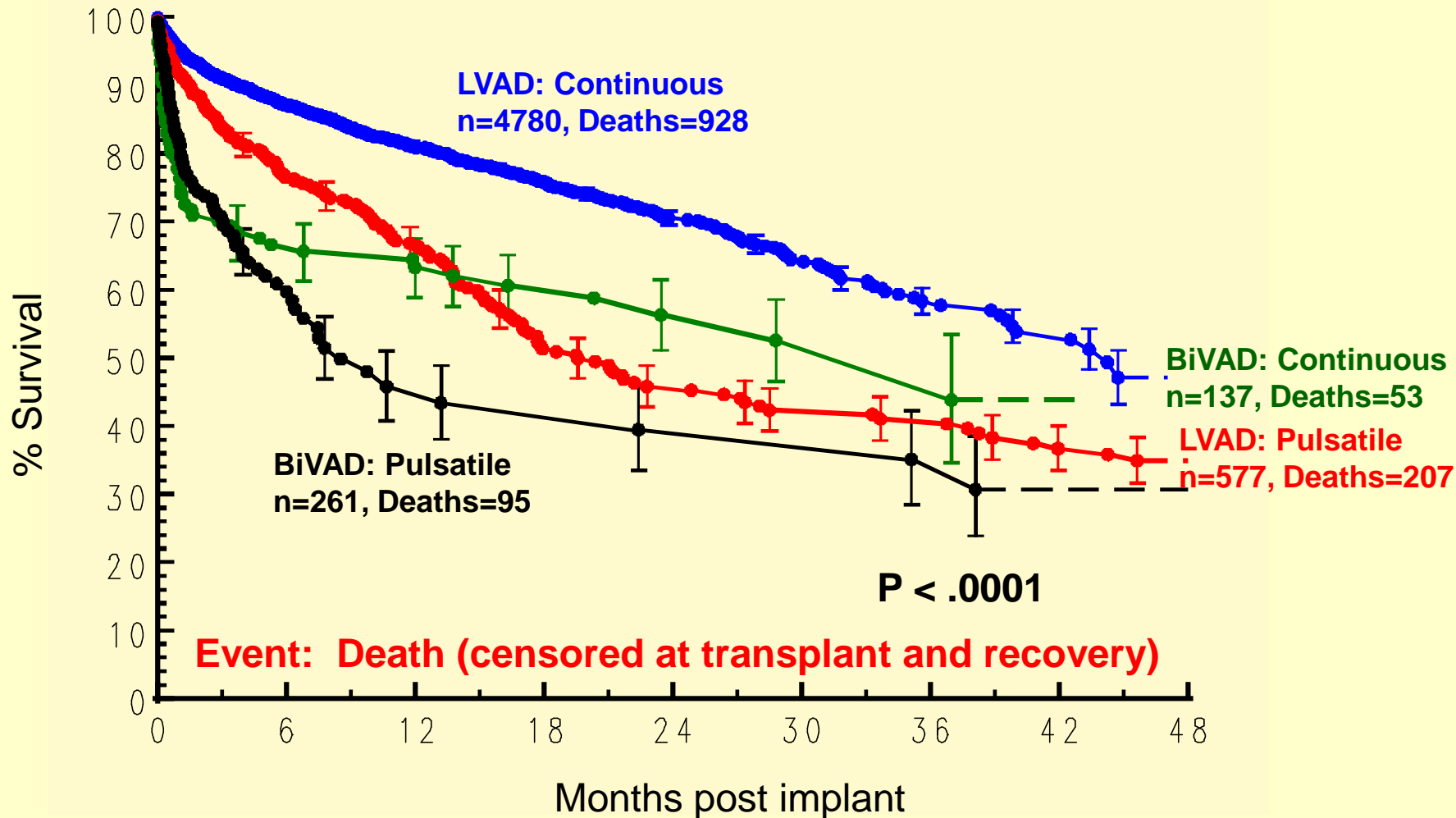
Implant Dates: June 23, 2006 – March 31, 2012



Adult Primary LVADs & BIVADs, DT and BTT , n=6025

Implants: June 2006 – March 2012

Survival by pump type

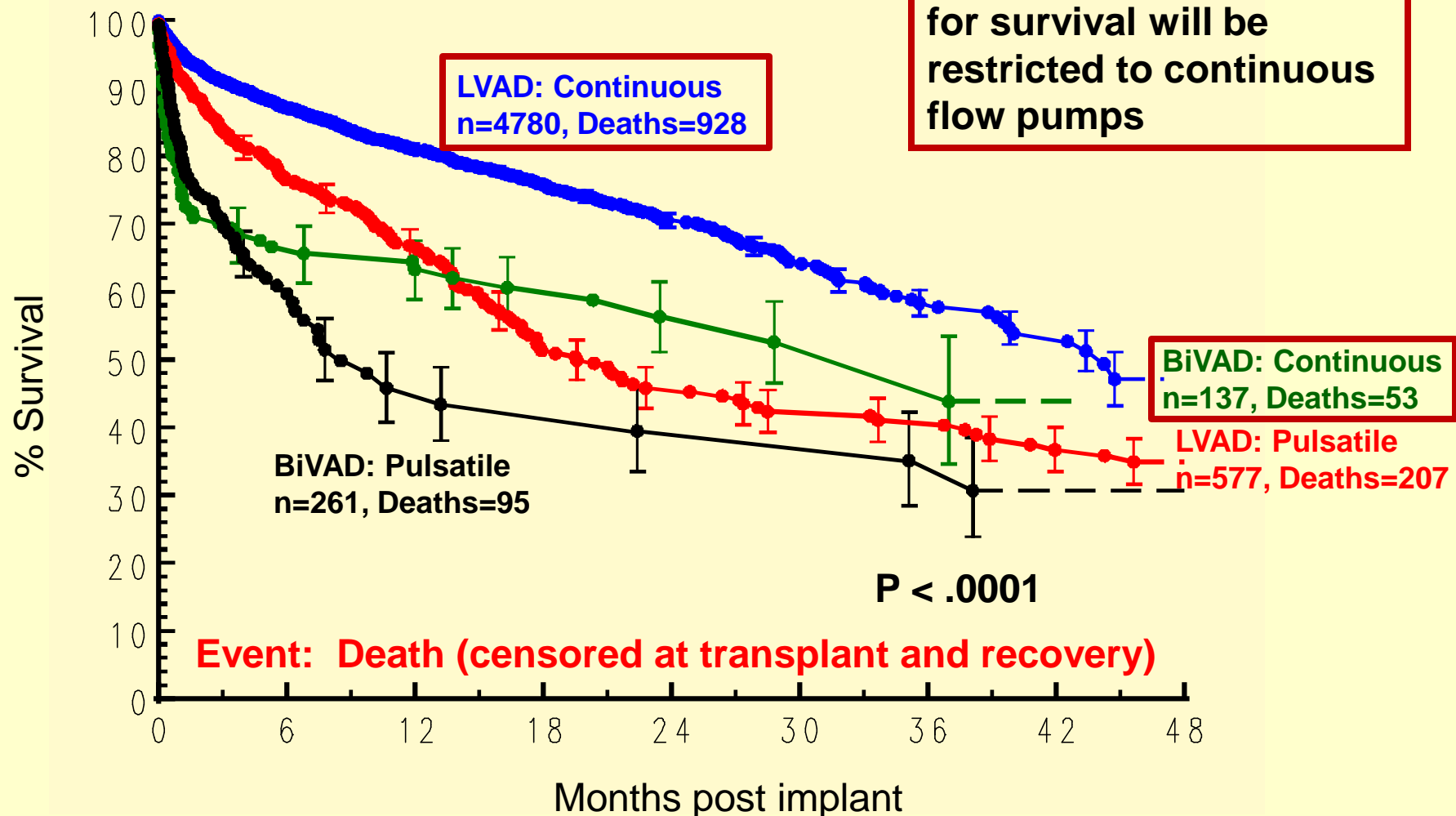


Adult Primary LVADs & BIVADs, DT and BTT , n=6025

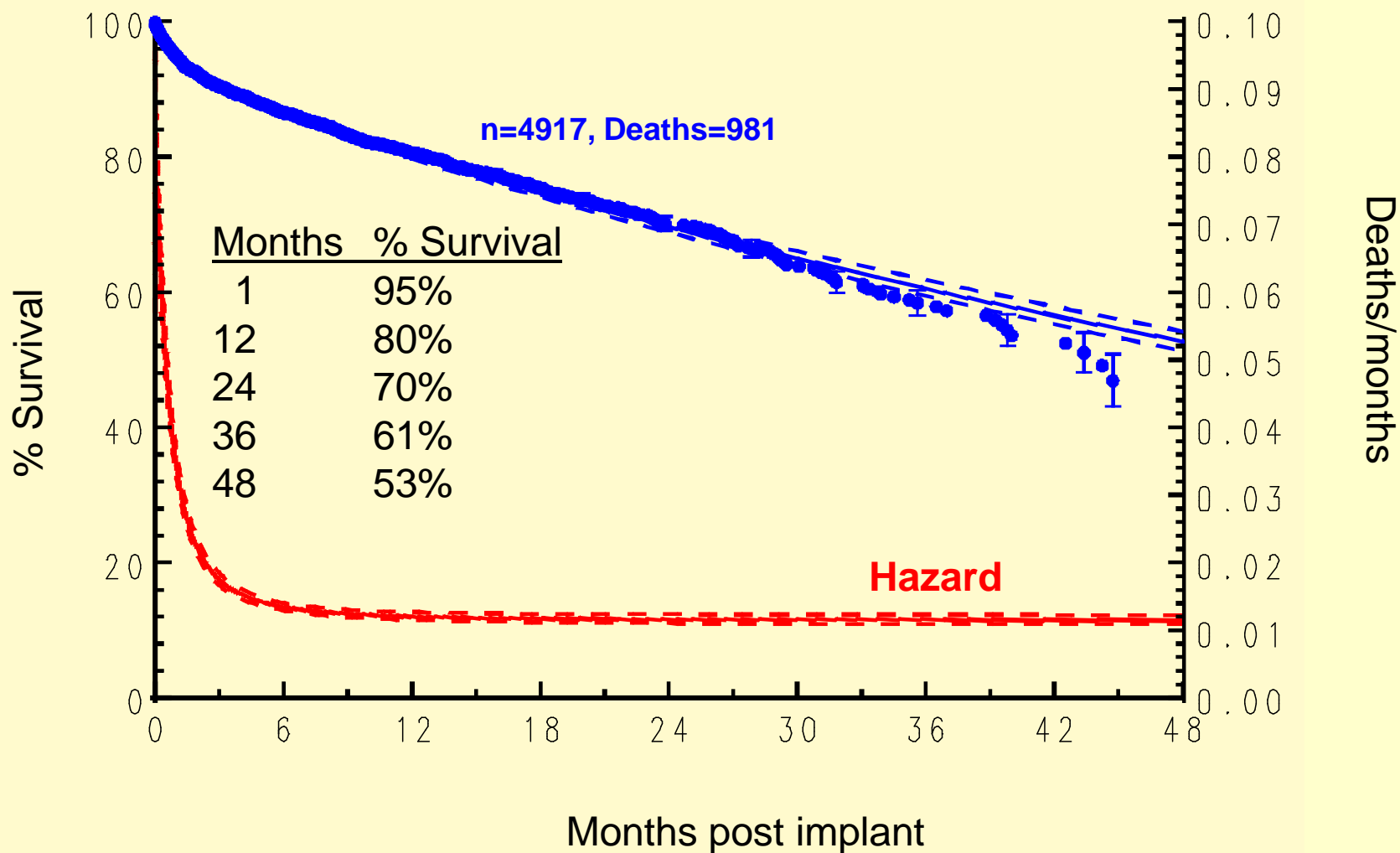
Implants: June 2006 – March 2012

Survival by pump type

The risk factor analysis for survival will be restricted to continuous flow pumps



Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012



Pre-Implant Variables examined in risk factor analysis

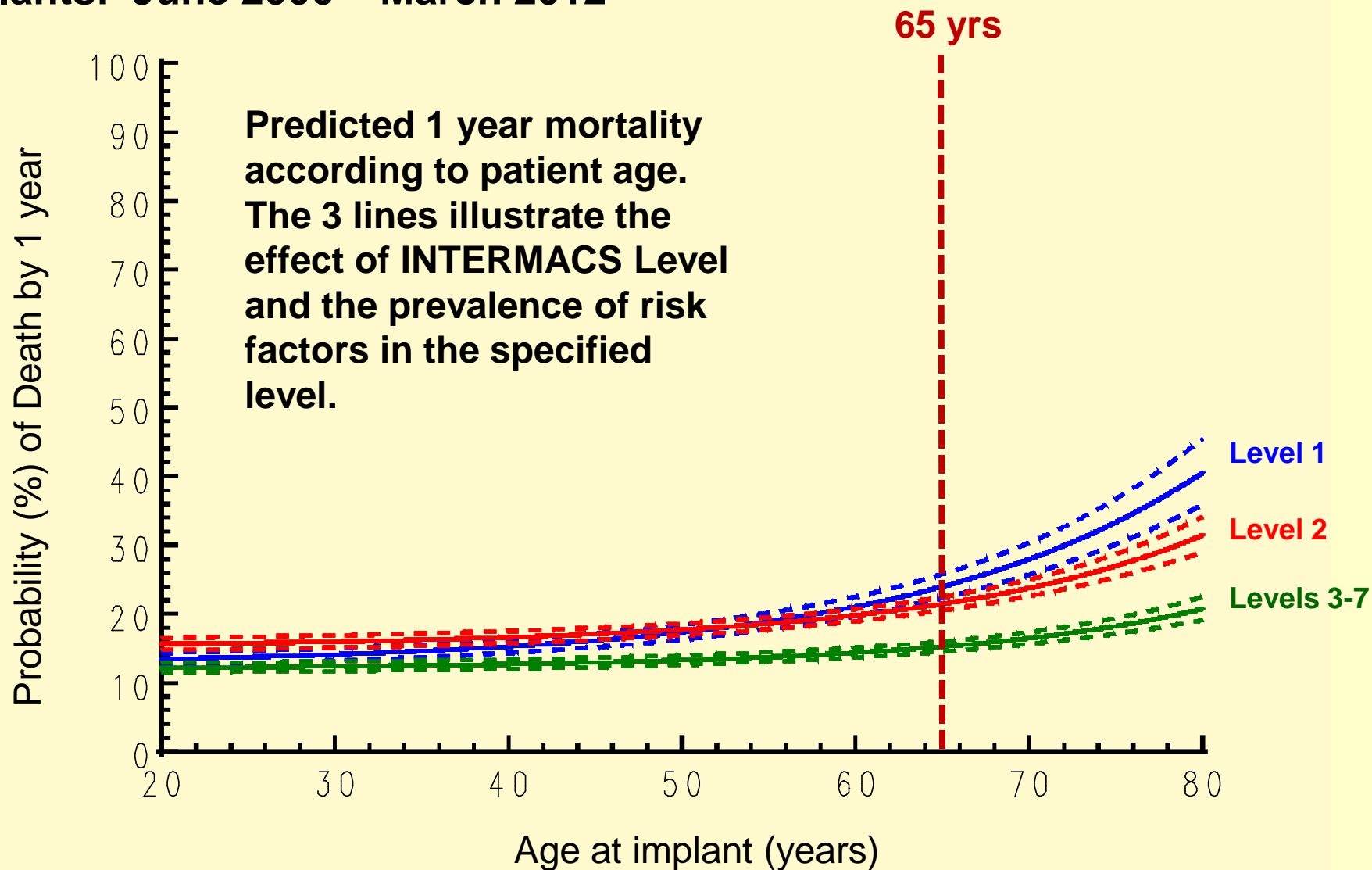
- **Demographics**
- **Clinical**
 - **Medical history**
 - **Current status**
- **Laboratory measurements**
- **Hemodynamics**
- **Pre-Implant interventions**
- **INTERMACS Levels**
- **Device Strategy**
- **Implant details**

(Note: Hospital and operator descriptors and characteristics are not included in the INTERMACS data collection)

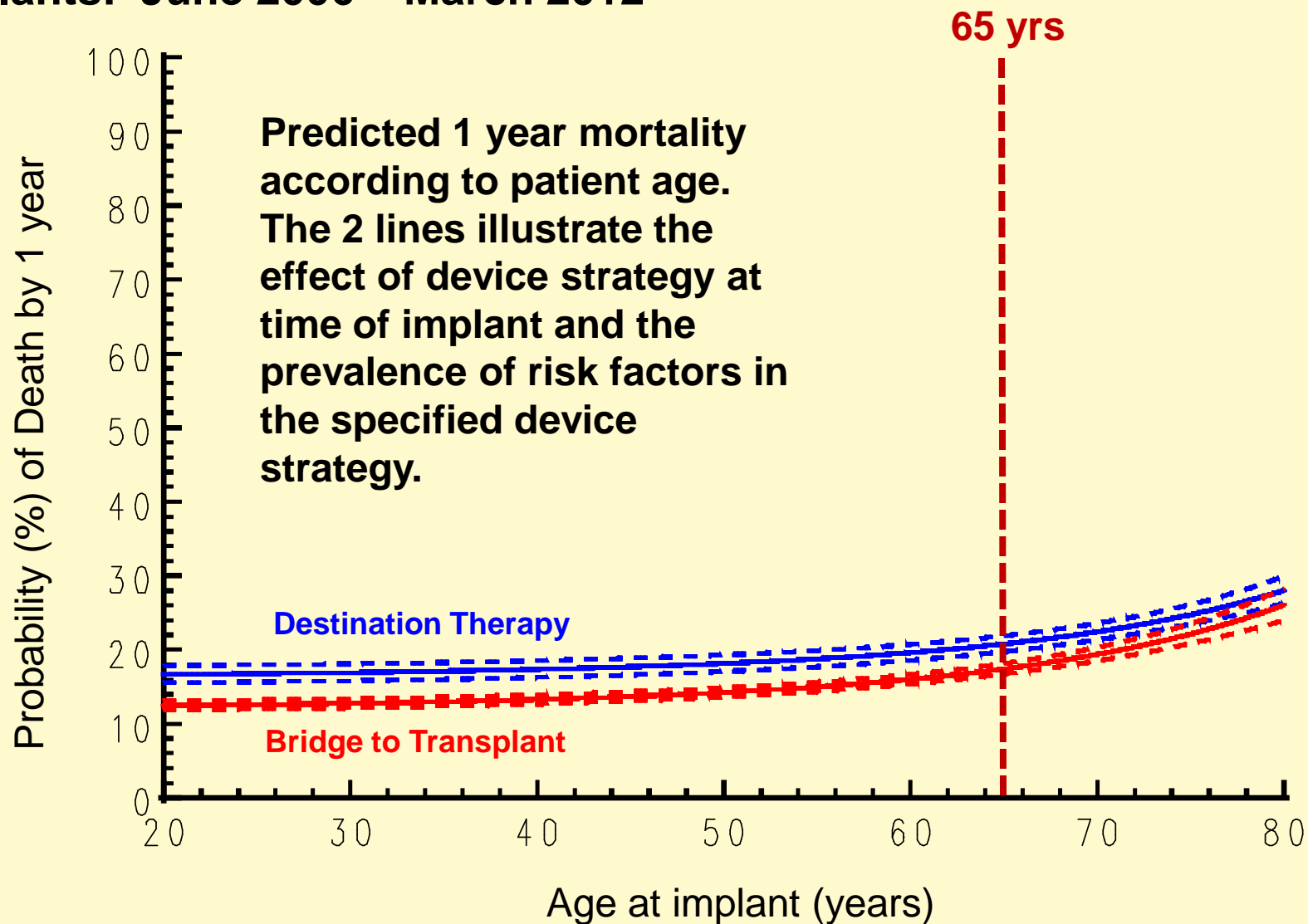
intermacs Implants: June 2006 – March 2012, Adult Primary Continuous Flow LVADs and BiVADS, DT and BTT, n=4917

	Early hazard		Constant hazard	
Risk Factors for Death	Hazard Ratio	p-value	Hazard Ratio	p-value
Demographics				
Age (older)	1.74	< .0001		
BMI (higher)	1.47	< .0001		
Clinical Status				
Ventilator	1.90	.0008		
History of cardiac surgery			1.54	< .0001
History of Stroke	1.68	.01		
INTERMACS Level 1	2.35	< .0001		
INTERMACS Level 2	1.91	.0007	1.32	.004
Destination Therapy			1.32	.004
Non-Cardiac Systems				
Diabetes			1.25	.01
Creatinine (higher)			1.09	.03
Dialysis	2.35	.0004		
BUN (higher)	1.09	.001		
Bilirubin (higher)	1.07	< .0001		
Right Heart Dysfunction				
Ascites			1.41	.03
RVAD in same operation	3.46	< .0001		
Right atrial pressure (higher)	1.38	.003		
At Time of Implant Operation				
Concomitant Cardiac Surgery	1.38	.02		

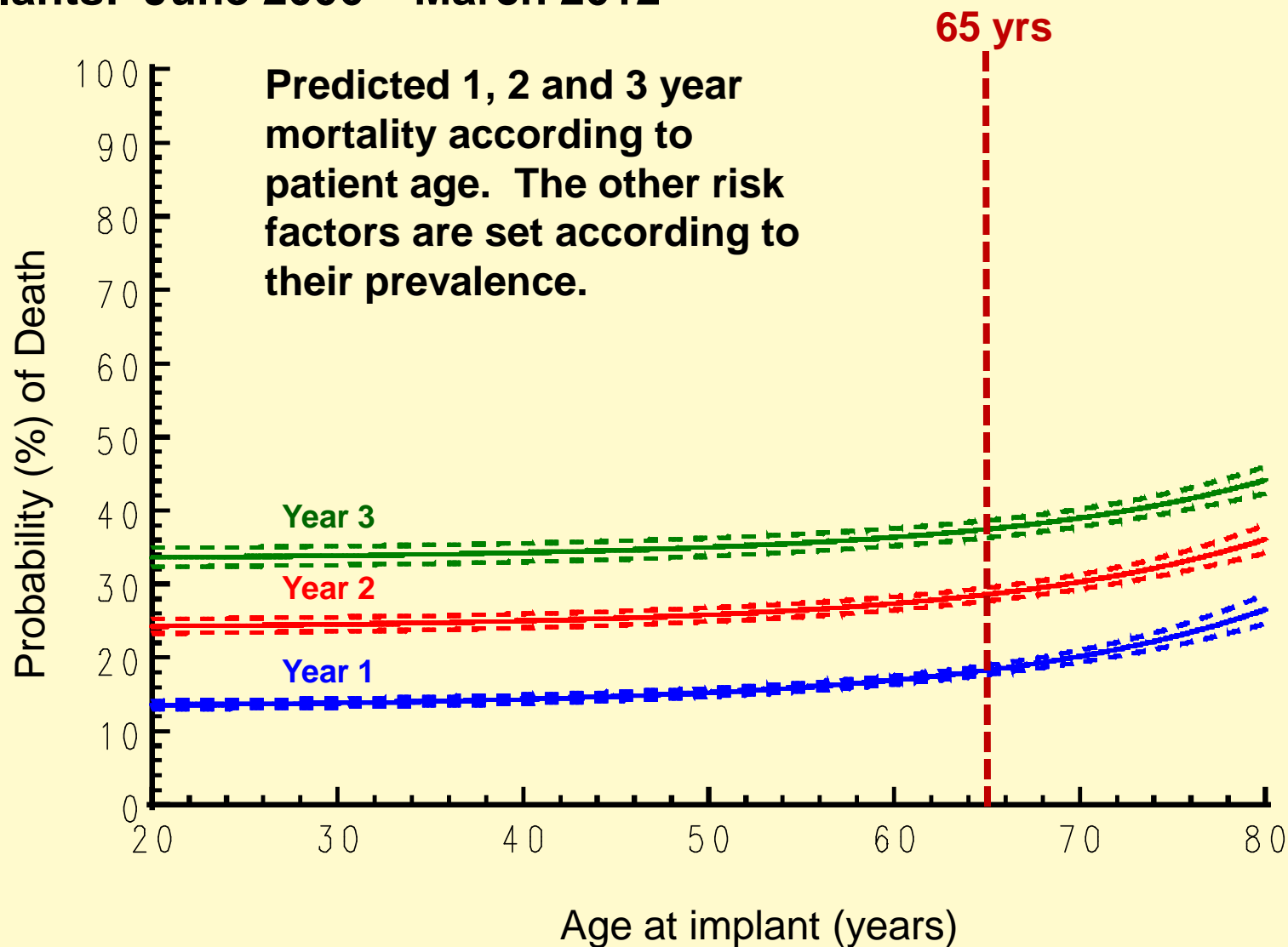
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012



Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012

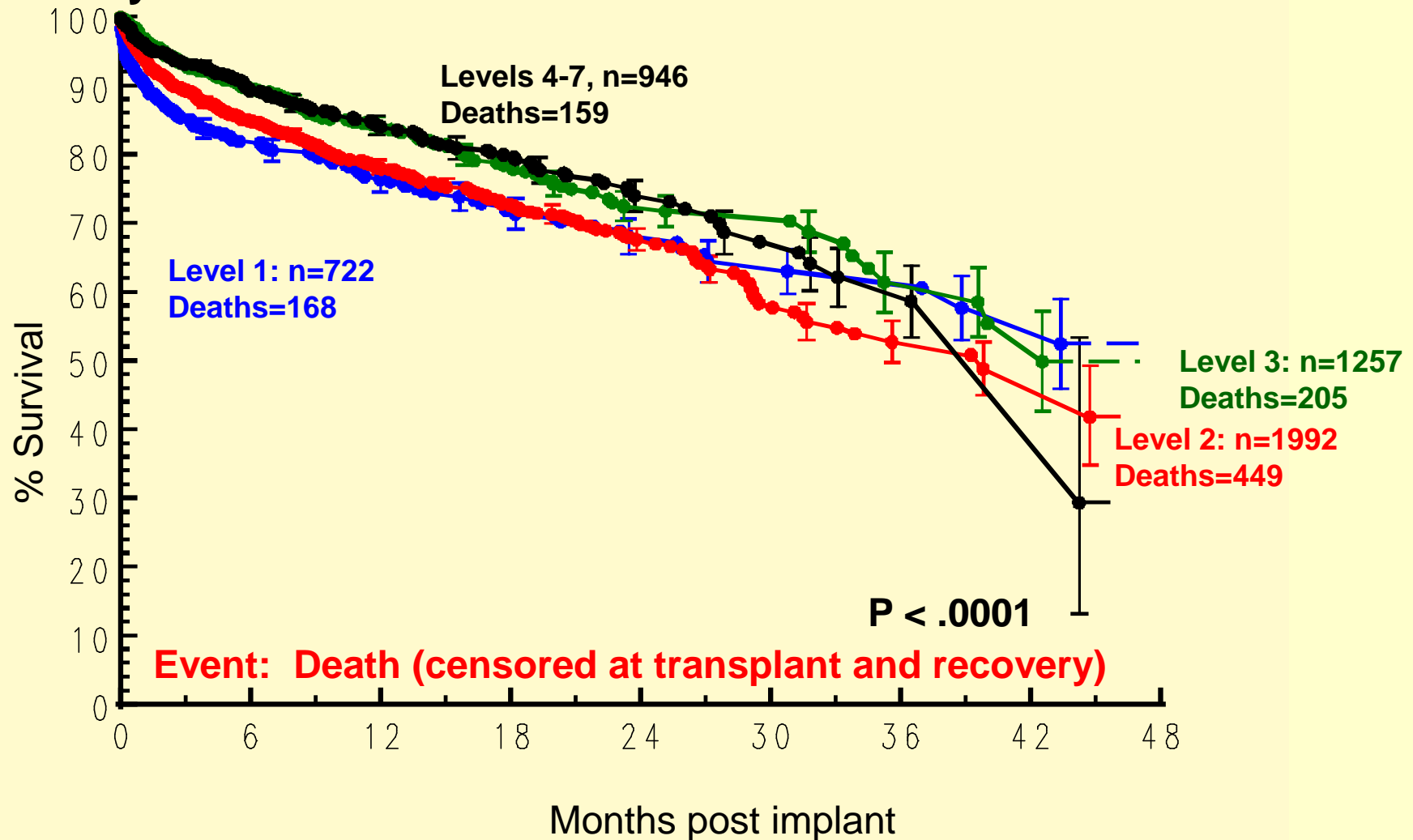


Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012



Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT , n=4917 Implants: June 2006 – March 2012

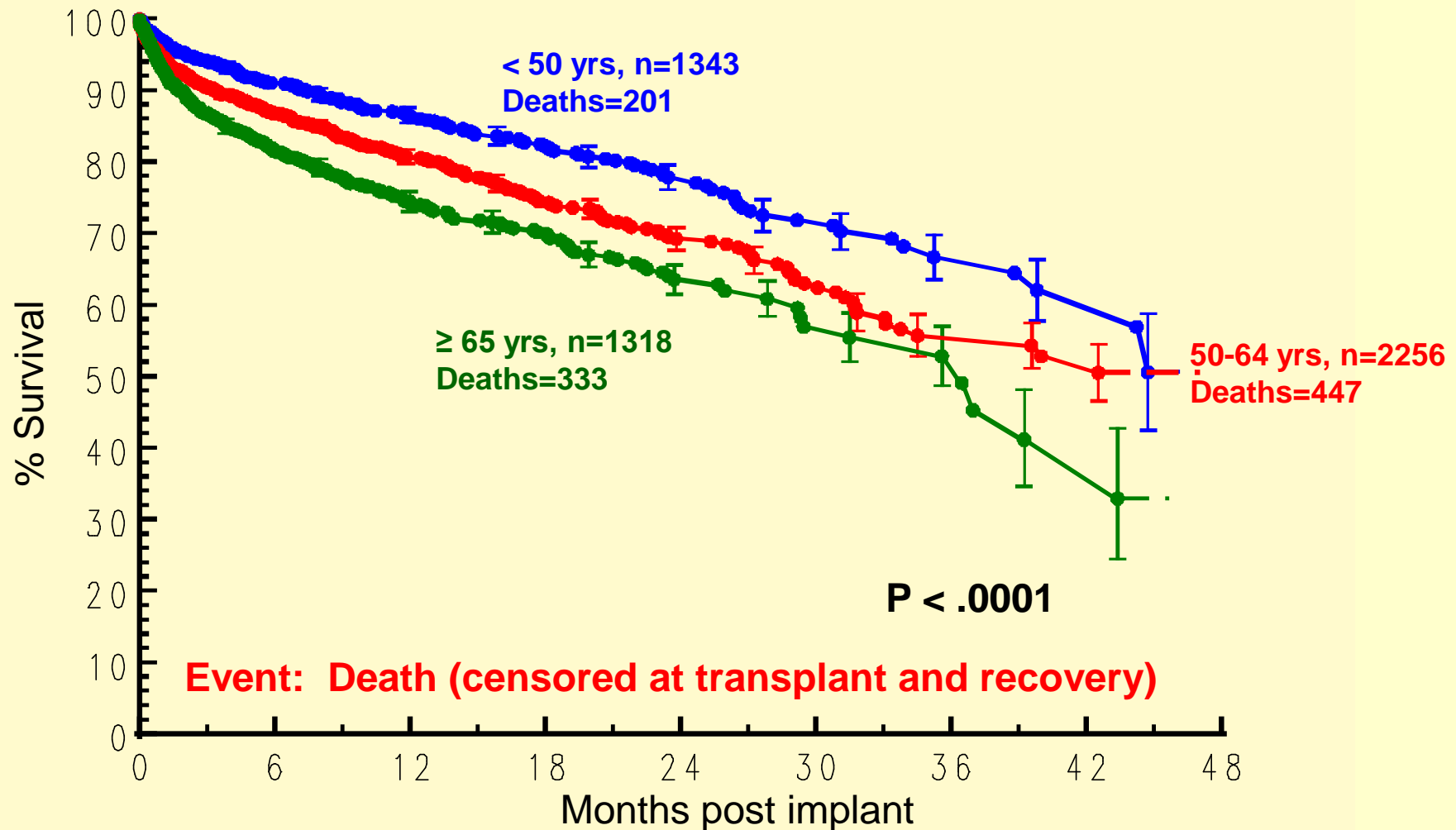
Survival by INTERMACS Level



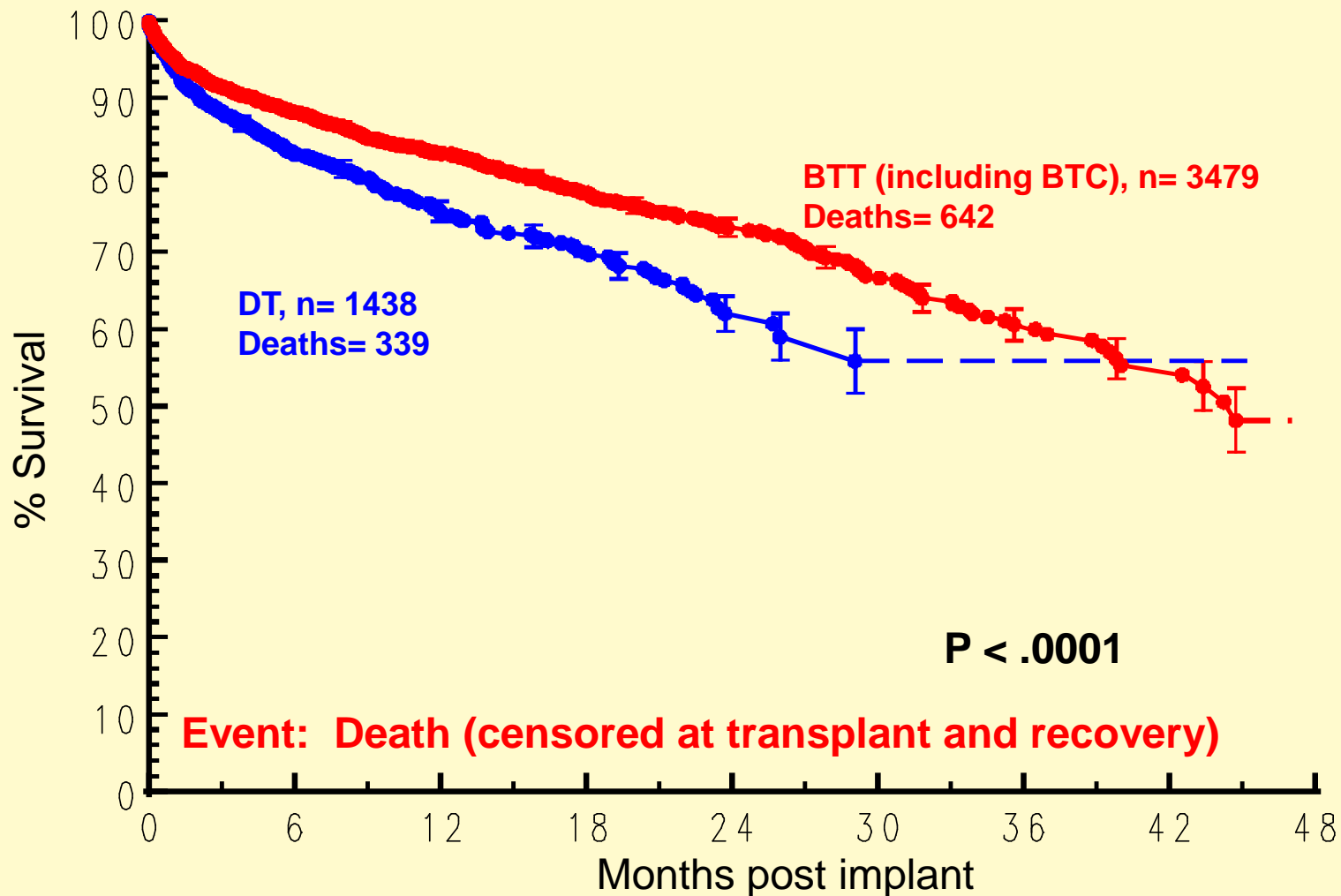
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012

PATIENT PROFILE AT TIME OF IMPLANT	Implant Date Period						TOTAL	
	Pre 2011		2011		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 %	149	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 %

Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012 Survival by Age groups



**Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917
Implants: June 2006 – March 2012
Survival by Device Strategy at time of implant**



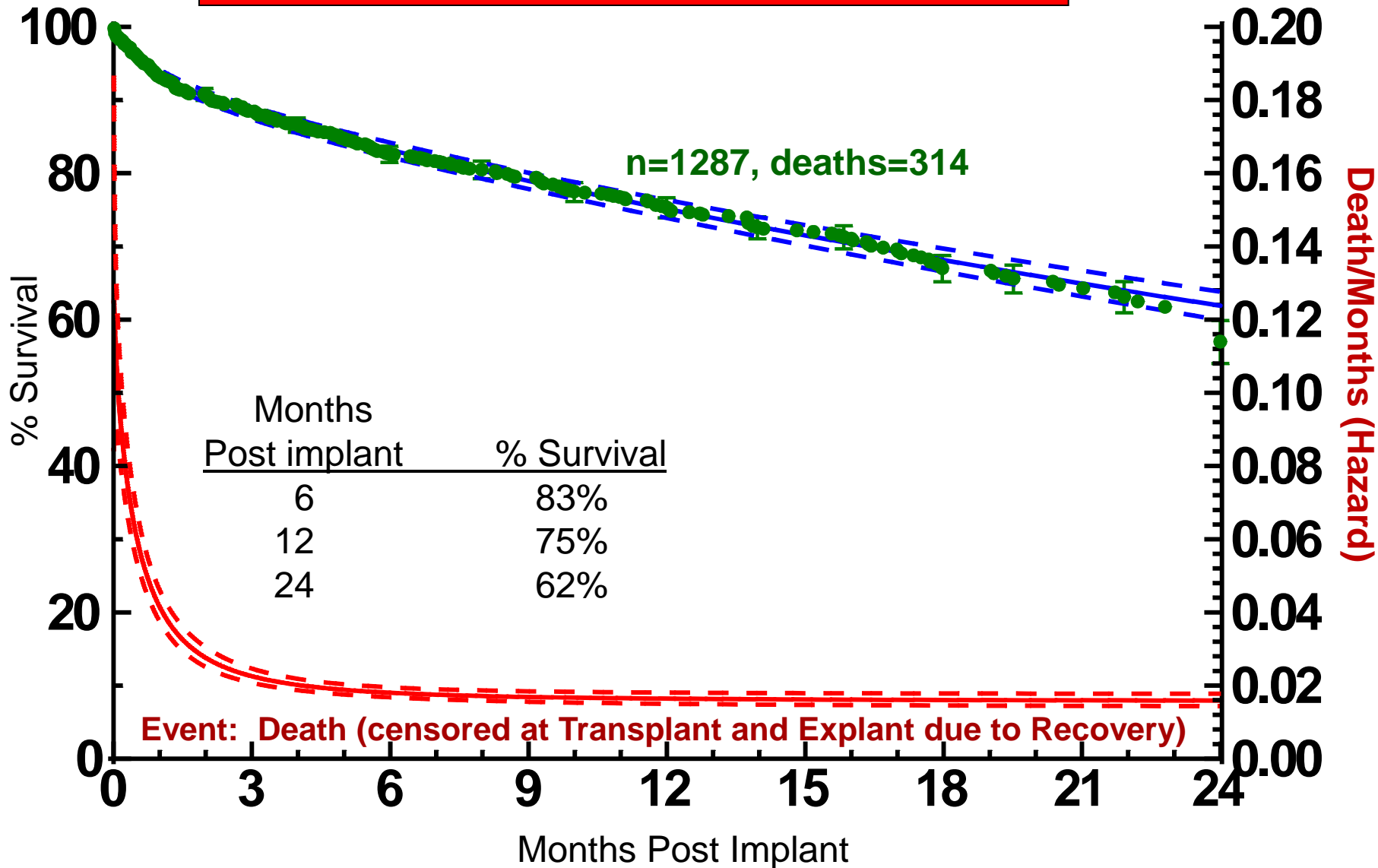
Sub analysis of Destination Therapy patients includes both:

- Pulsatile Flow Pumps (n=127)
- Continuous Flow Pumps (n=1160)

Long-Term Mechanical Circulatory Support (Destination Therapy): On Track to Compete with Heart Transplantation?

J Kirklin, D Naftel, F Pagani, R Kormos, L Stevenson, M Miller, J Young

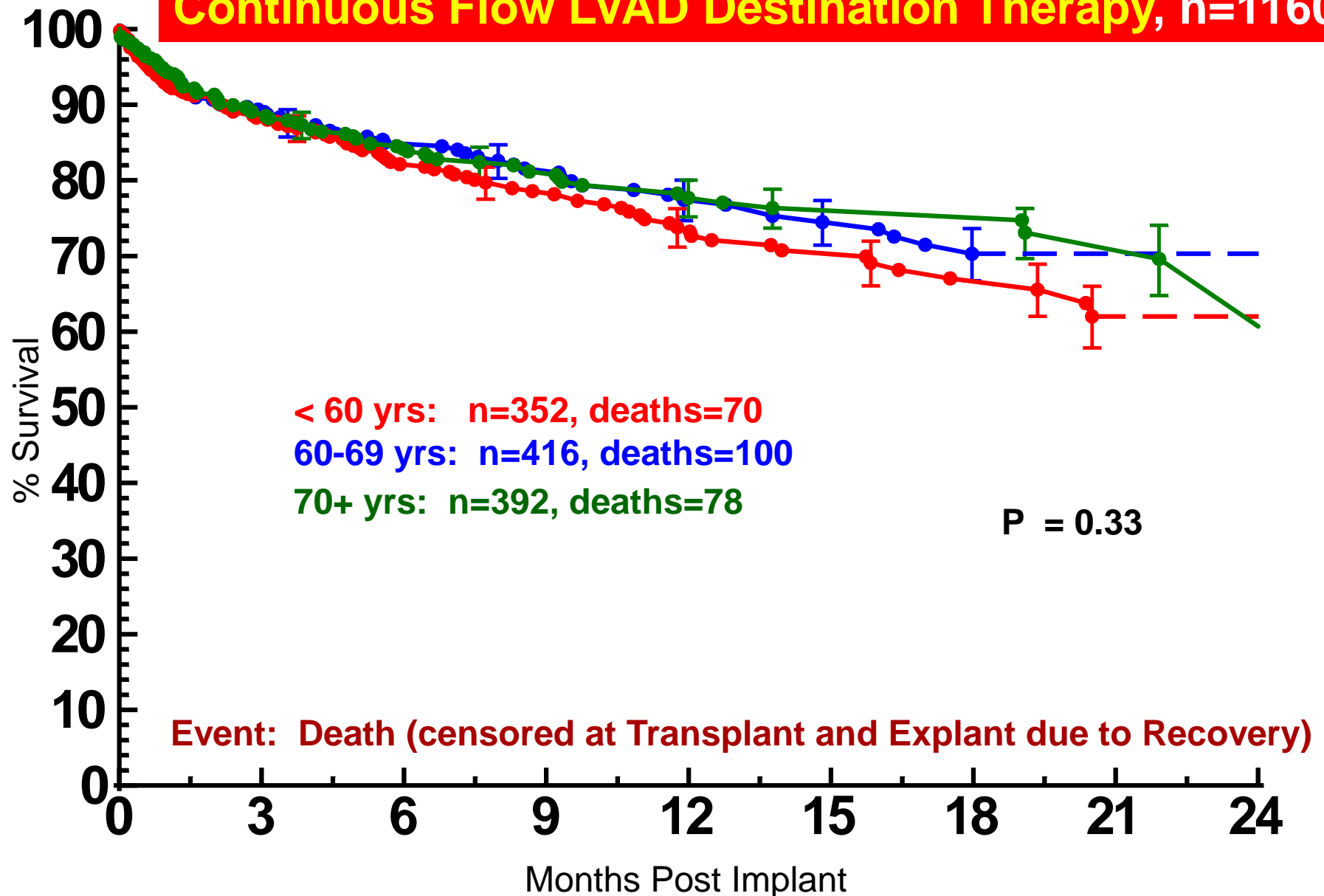
LVAD Destination Therapy, n=1287

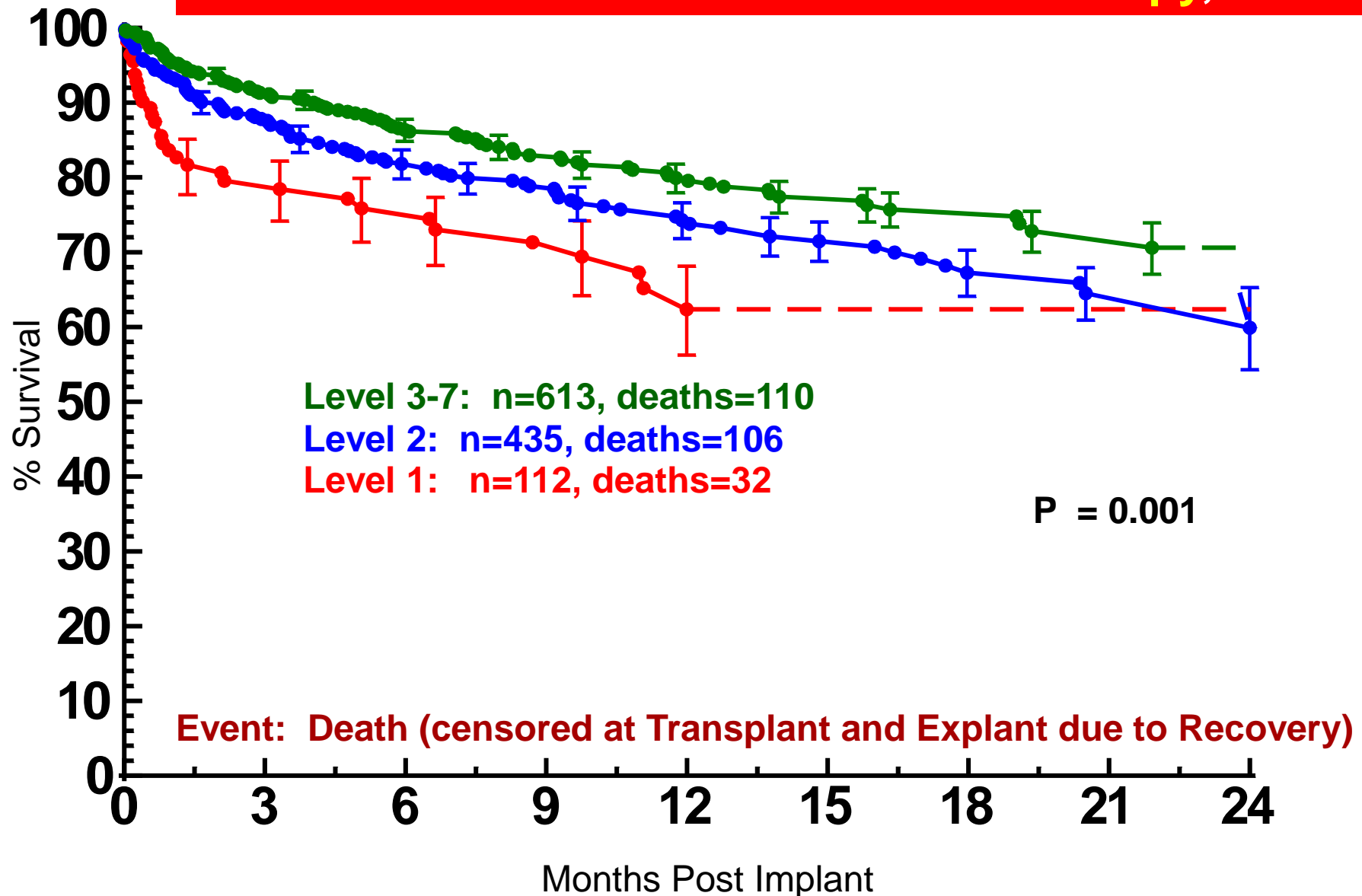


Risk Factors for Death in Destination Therapy Patients – Adult Primary Implants: INTERMACS, June 2006 - December 2011

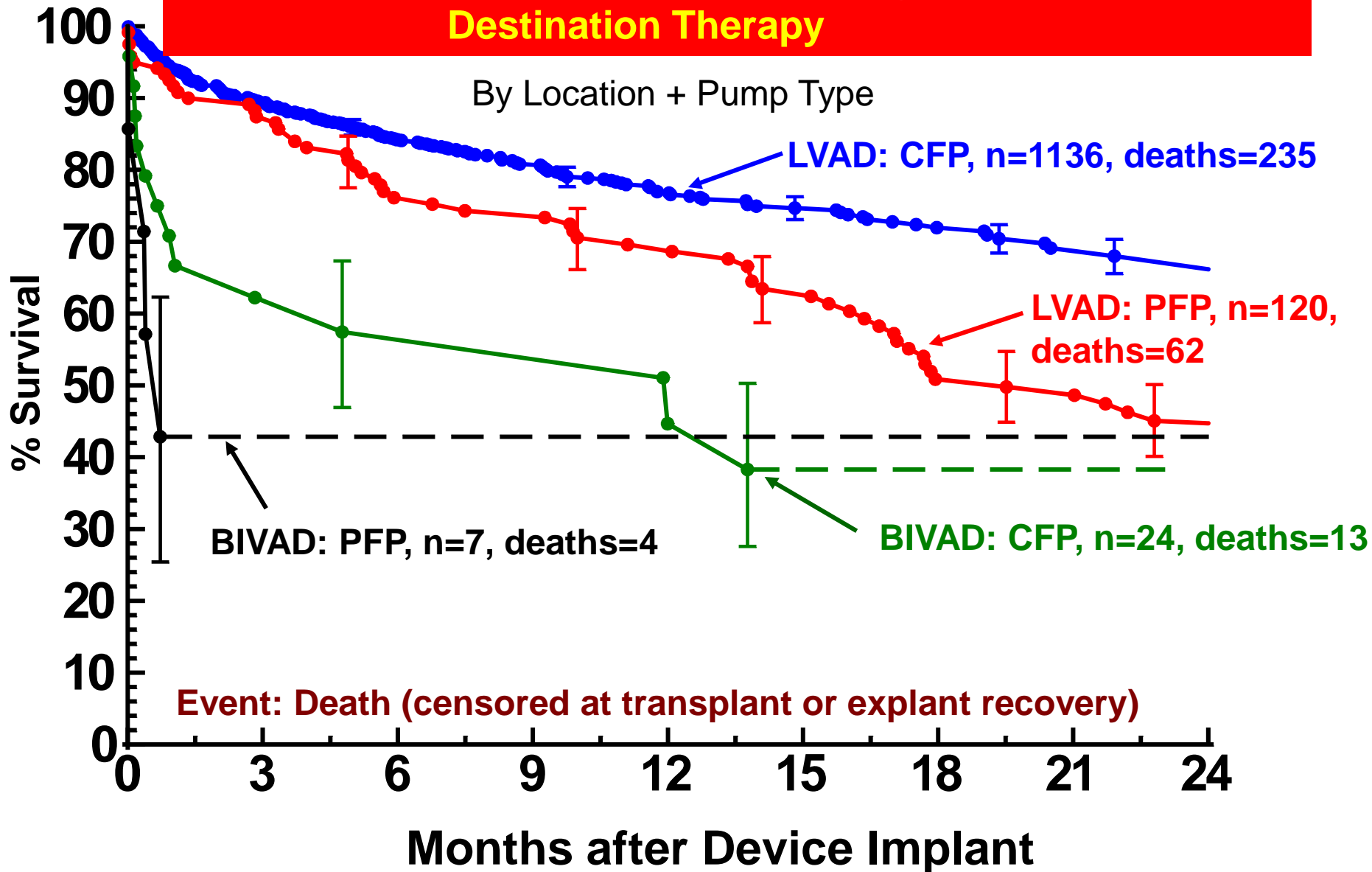
Risk Factors	<u>Early hazard</u>		<u>Constant hazard</u>	
	HR	<i>p</i> -value	HR	<i>p</i> -value
Age (older)			1.24	.01
BMI (higher)			1.04	.03
History of cancer	1.89	.04		
History of cardiac surgery	1.69	.001		
Dialysis	3.14	.004		
BUN			1.08	.009
INTERMACS Level 1	4.58	<.0001		
INTERMACS Level 2	2.35	.02		
Use of pulsatile LVAD			2.63	<.0001
RVAD in same operation			3.22	.002

Continuous Flow LVAD Destination Therapy, n=1160

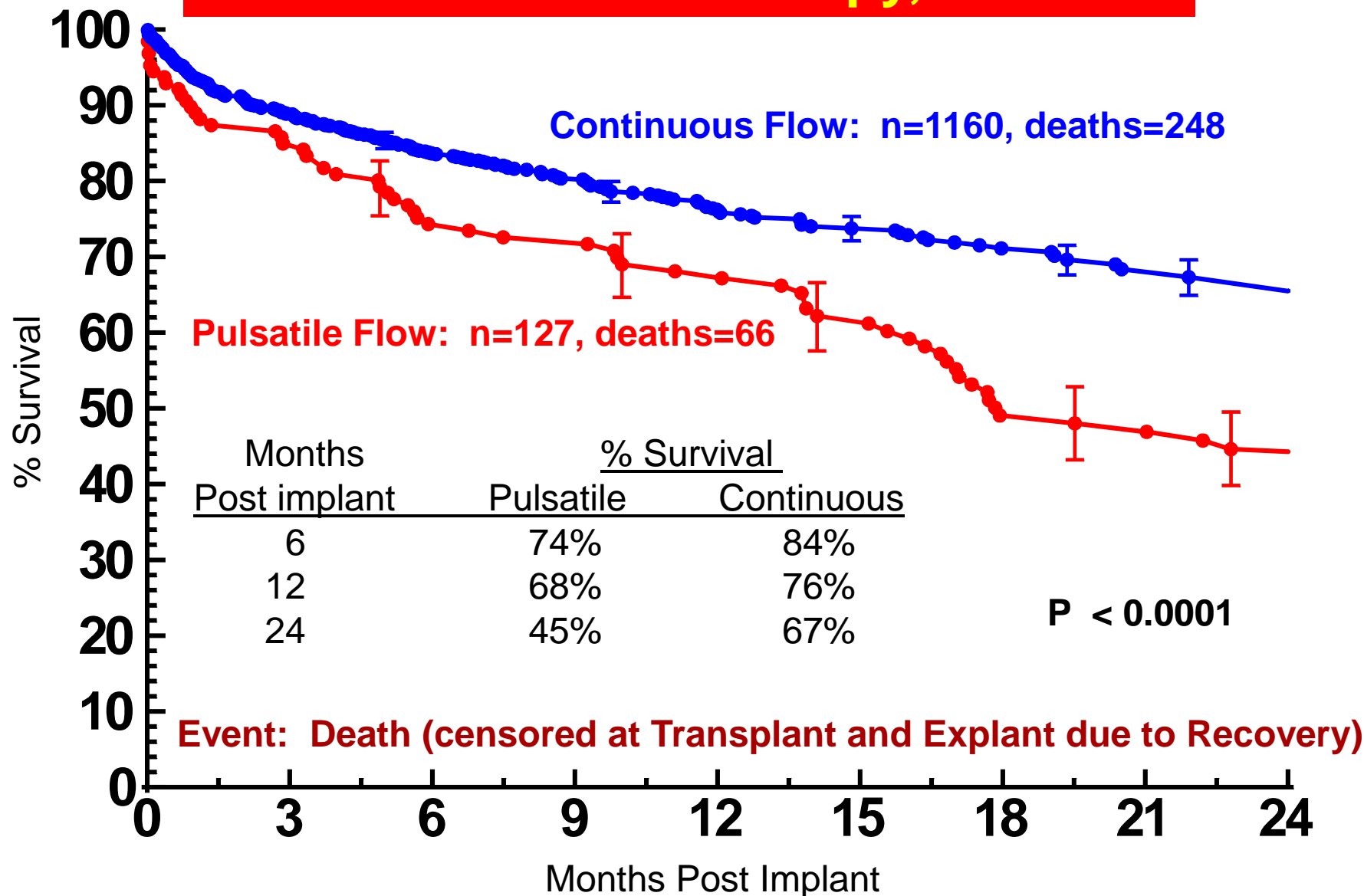


Continuous Flow LVAD Destination Therapy, n=1160

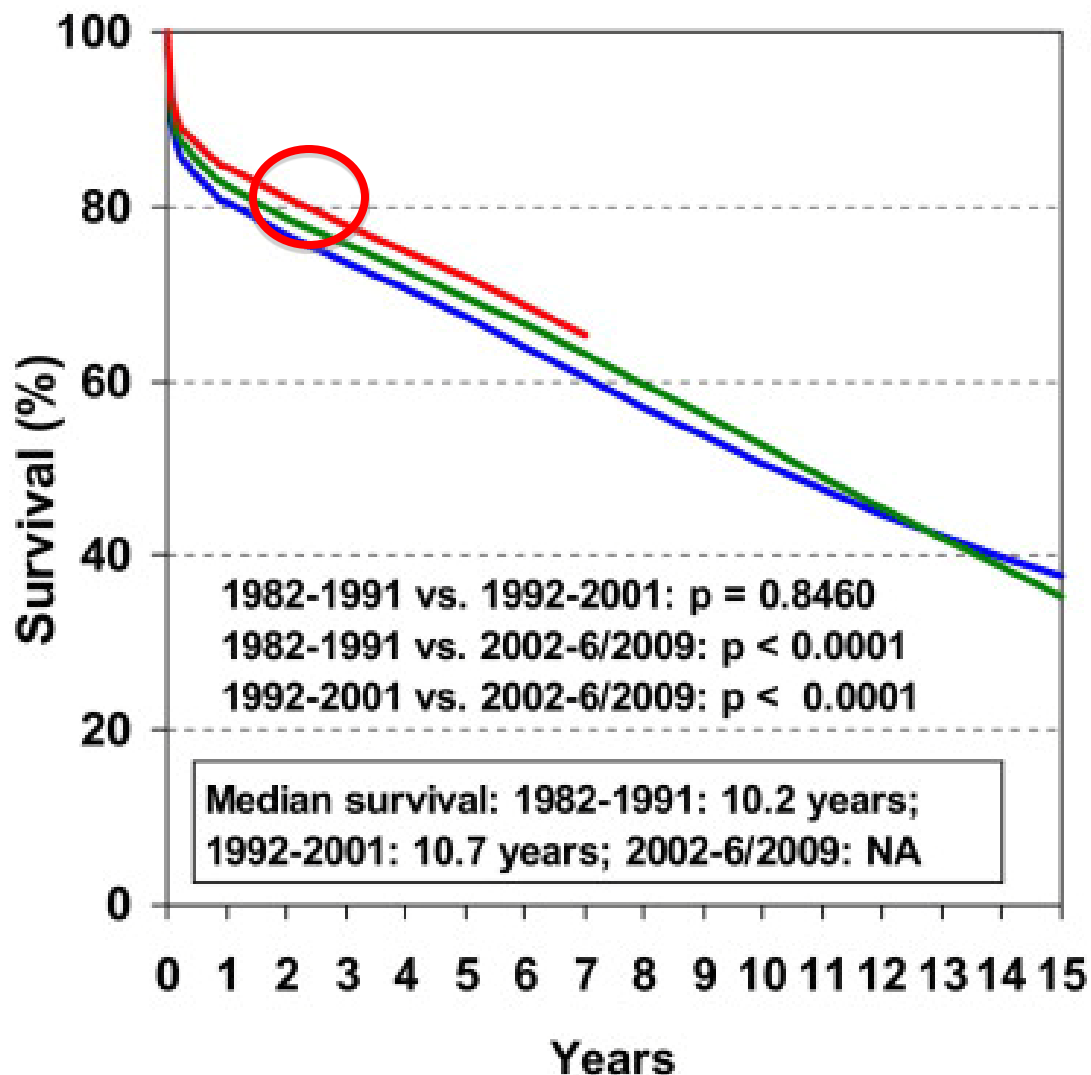
**All Patient Implants with Device Strategy at time of implant:
Destination Therapy**



LVAD Destination Therapy, n=1287

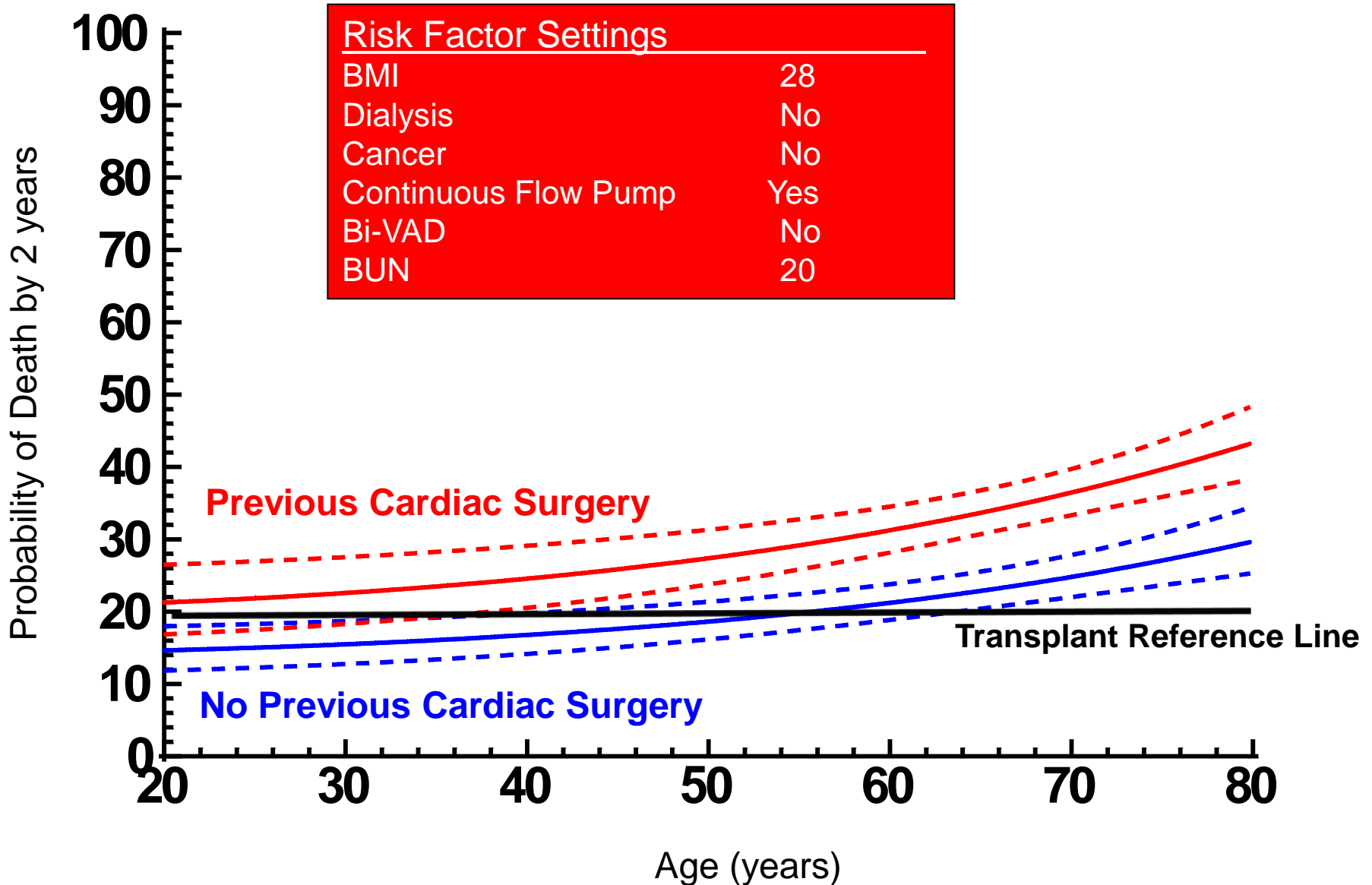


Survival to 1 Year After Transplant for Adult Heart Transplants Performed Between January 1982 and June 2009, Stratified by Era of Transplant.

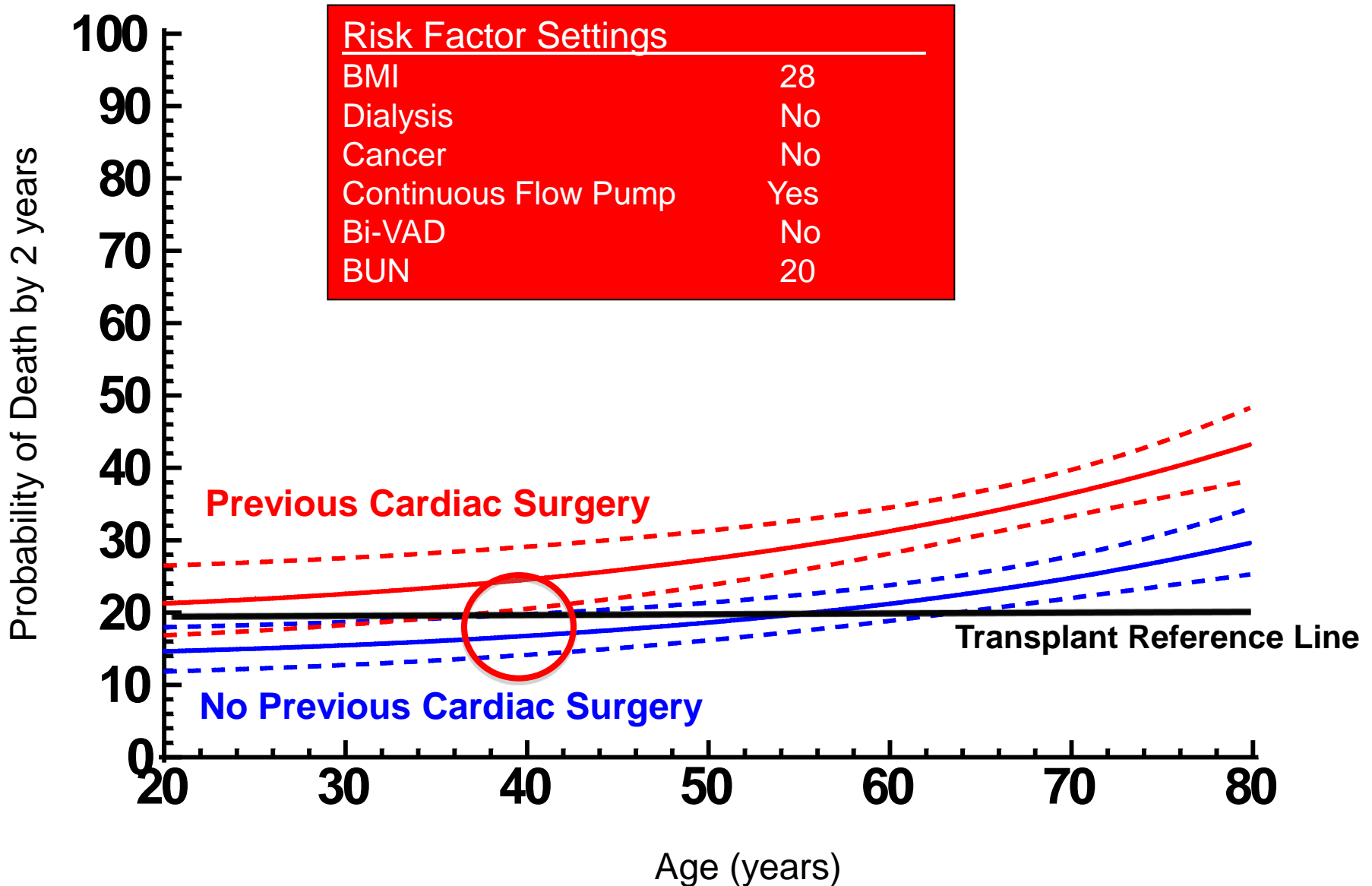


— 1982-1991 (N=20,504) — 1992-2001 (N=36,879) — 2002-6/2009 (N=22,477)

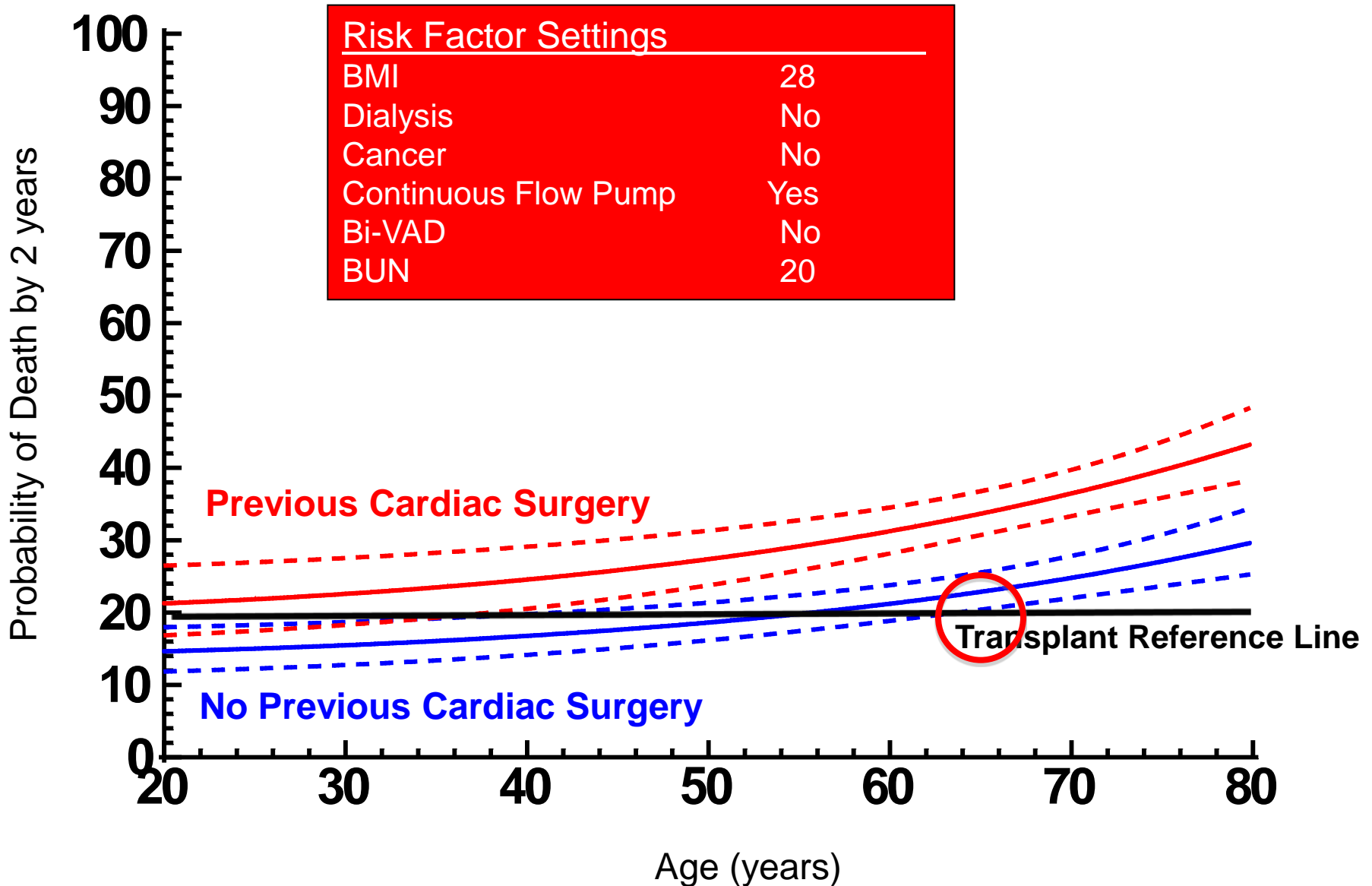
INTERMACS Patient Profile Levels 3-7



INTERMACS Patient Profile Levels 3-7



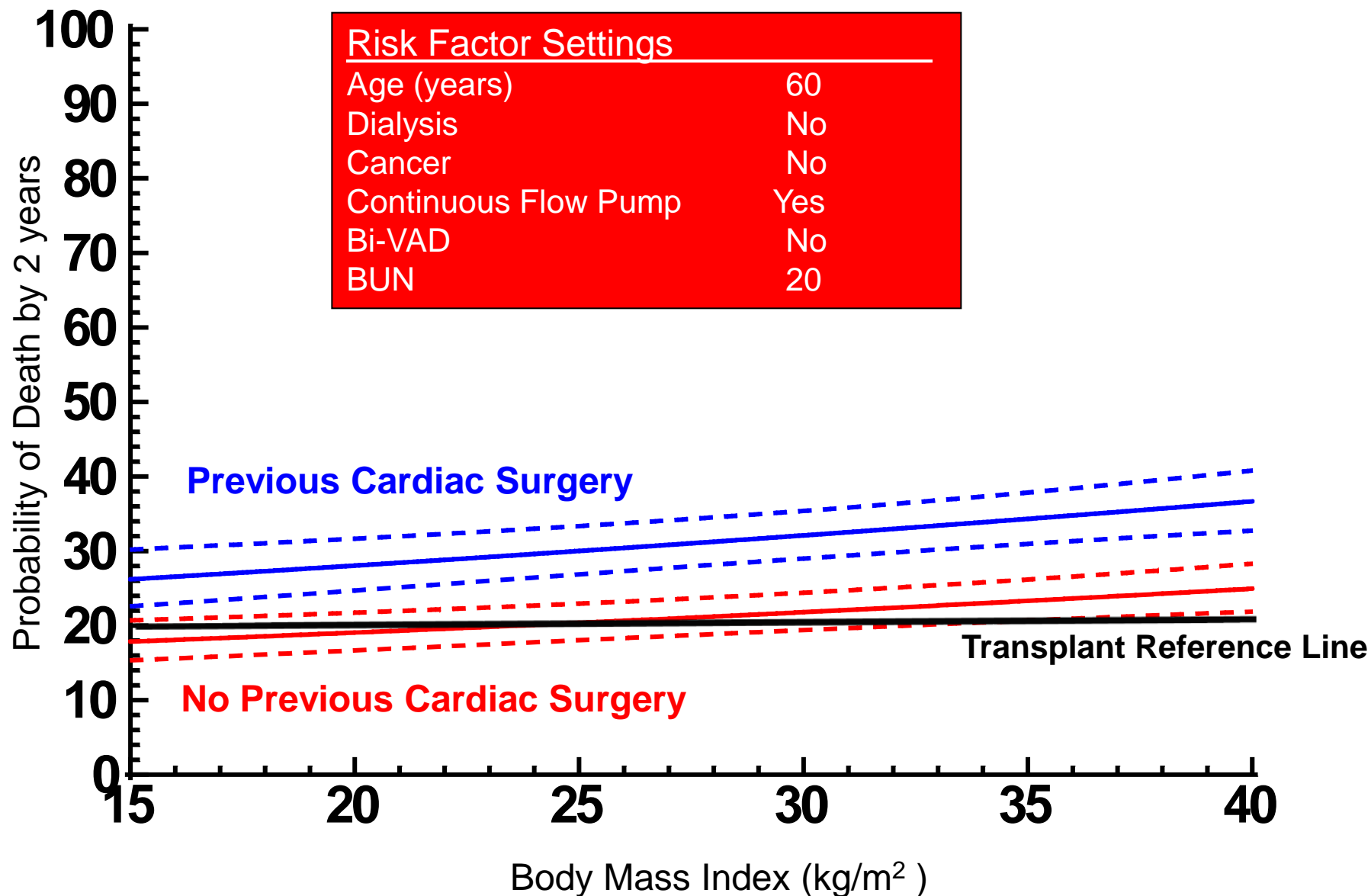
INTERMACS Patient Profile Levels 3-7



INTERMACS Patient Profile Levels 3-7

Risk Factor Settings

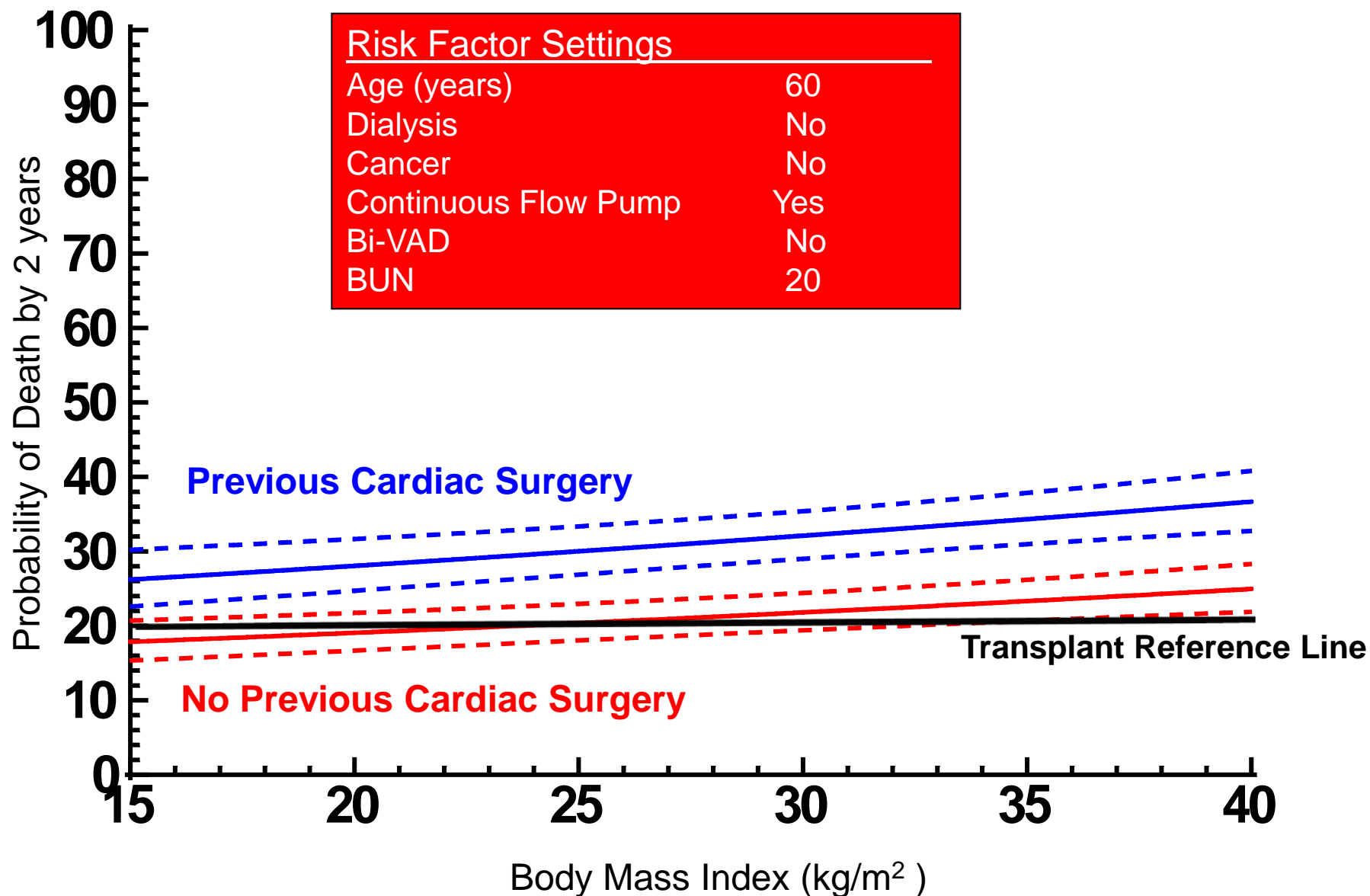
Age (years)	60
Dialysis	No
Cancer	No
Continuous Flow Pump	Yes
Bi-VAD	No
BUN	20



INTERMACS Patient Profile Levels 3-7

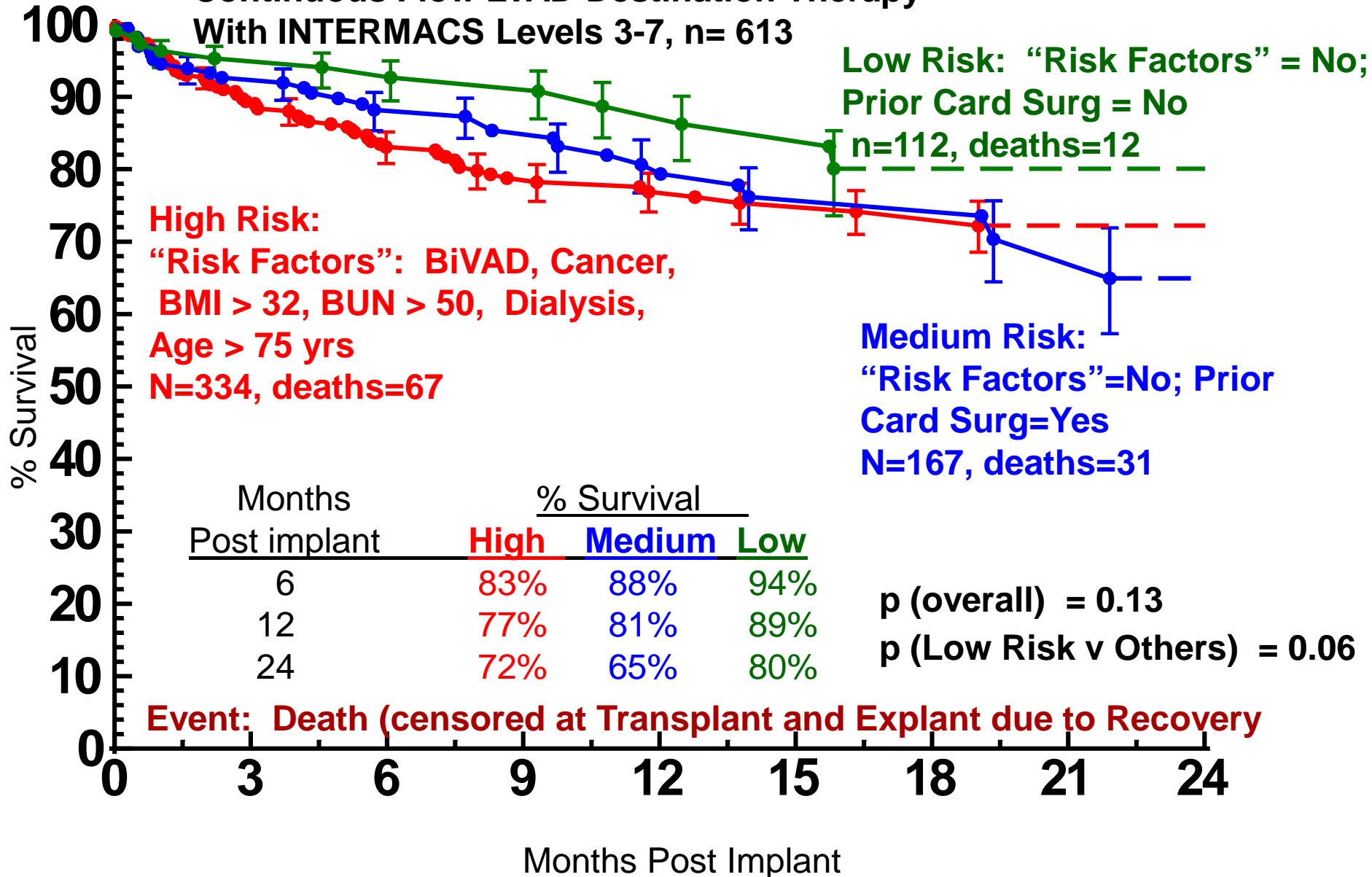
Risk Factor Settings

Age (years)	60
Dialysis	No
Cancer	No
Continuous Flow Pump	Yes
Bi-VAD	No
BUN	20



Continuous Flow LVAD Destination Therapy

With INTERMACS Levels 3-7, n= 613



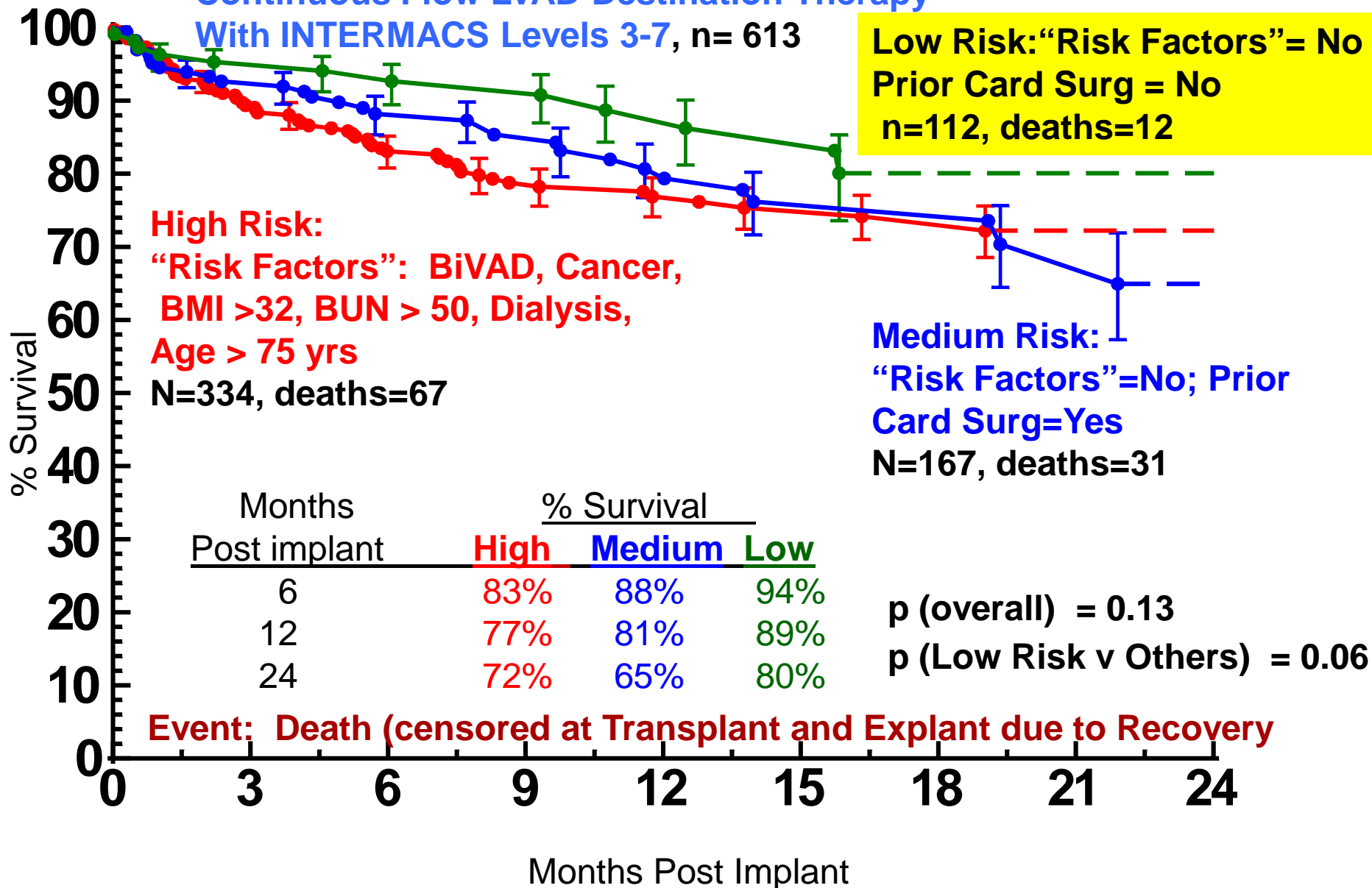
Continuous Flow LVAD Destination Therapy

With INTERMACS Levels 3-7, n= 613

Low Risk: “Risk Factors”= No
Prior Card Surg = No
n=112, deaths=12

High Risk:
“Risk Factors”: BiVAD, Cancer,
BMI >32, BUN > 50, Dialysis,
Age > 75 yrs
N=334, deaths=67

Medium Risk:
“Risk Factors”=No; Prior
Card Surg=Yes
N=167, deaths=31



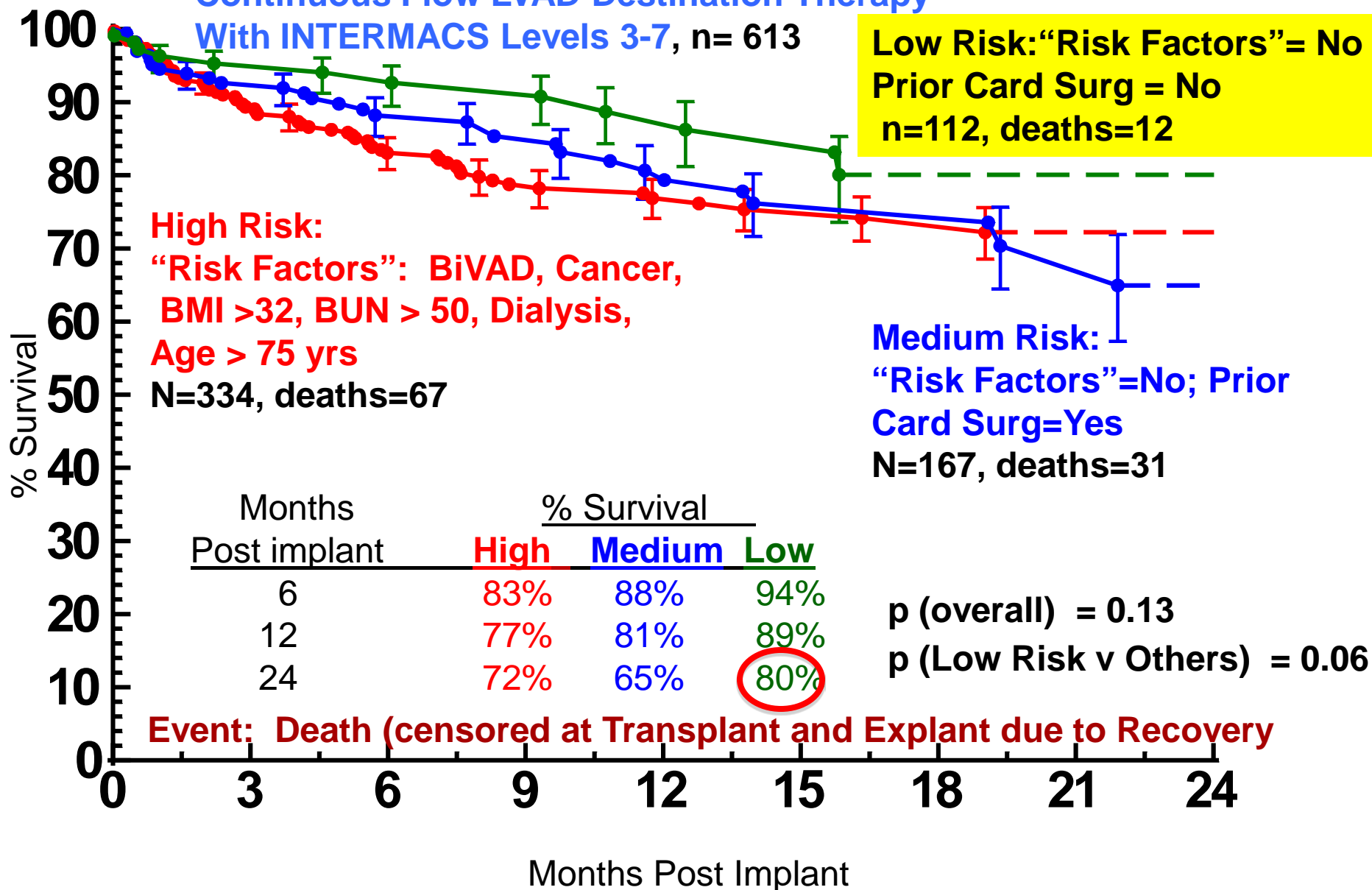
Continuous Flow LVAD Destination Therapy

With INTERMACS Levels 3-7, n= 613

Low Risk: "Risk Factors" = No
Prior Card Surg = No
n=112, deaths=12

High Risk:
"Risk Factors": BiVAD, Cancer,
BMI >32, BUN > 50, Dialysis,
Age > 75 yrs
N=334, deaths=67

Medium Risk:
"Risk Factors" = No; Prior
Card Surg = Yes
N=167, deaths=31



IV. Adverse Events

The following analyses only include patients with continuous flow pumps

Major Bleeding

An episode of **SUSPECTED INTERNAL OR EXTERNAL BLEEDING** that results in one or more of the following:

- a. Death,
- b. Re-operation,
- c. Hospitalization,
- d. Transfusion of red blood cells as follows:

If transfusion is selected, then apply the following rules:

During first 7 days post implant

- Adults (≥ 50 kg): ≥ 4 U packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.
- Pediatrics (< 50 kg): ≥ 20 cc/kg packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.

After 7 days post implant

- Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Device Malfunction

Device malfunction denotes a failure of one or more of the components of the MCSD system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure.

Device failure should be classified according to which components fails as follows:

- 1) **Pump** failure (blood contacting components of pump and any motor or other pump actuating mechanism that is housed with the blood contacting components). In the special situation of **pump thrombosis**, thrombus is documented to be present within the device or its conduits that result in or could potentially induce circulatory failure.
- 2) **Non-pump** failure (e.g., external pneumatic drive unit, electric power supply unit, batteries, controller, interconnect cable, compliance chamber)

Neurological Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). Each neurological event must be subcategorized as:

- 1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction)
- 2) Ischemic or Hemorrhagic Cerebral Accident/CVA (event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study).

In addition, to above, for patients < 6 months of age, any of the following:

- 3) New abnormality of head ultrasound
- 4) EEG positive for seizure activity with or without clinical seizure

Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

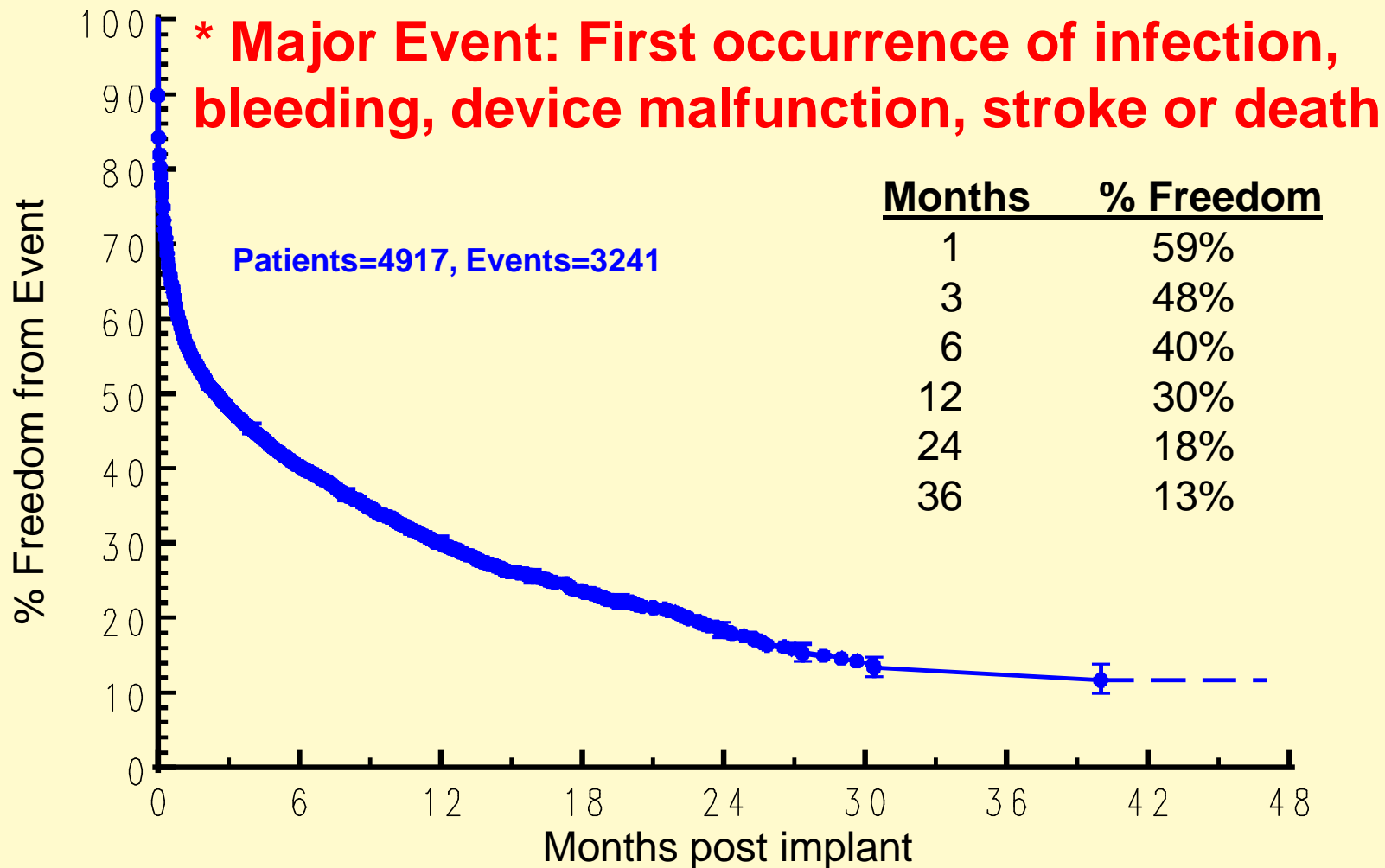
Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD).

Sepsis

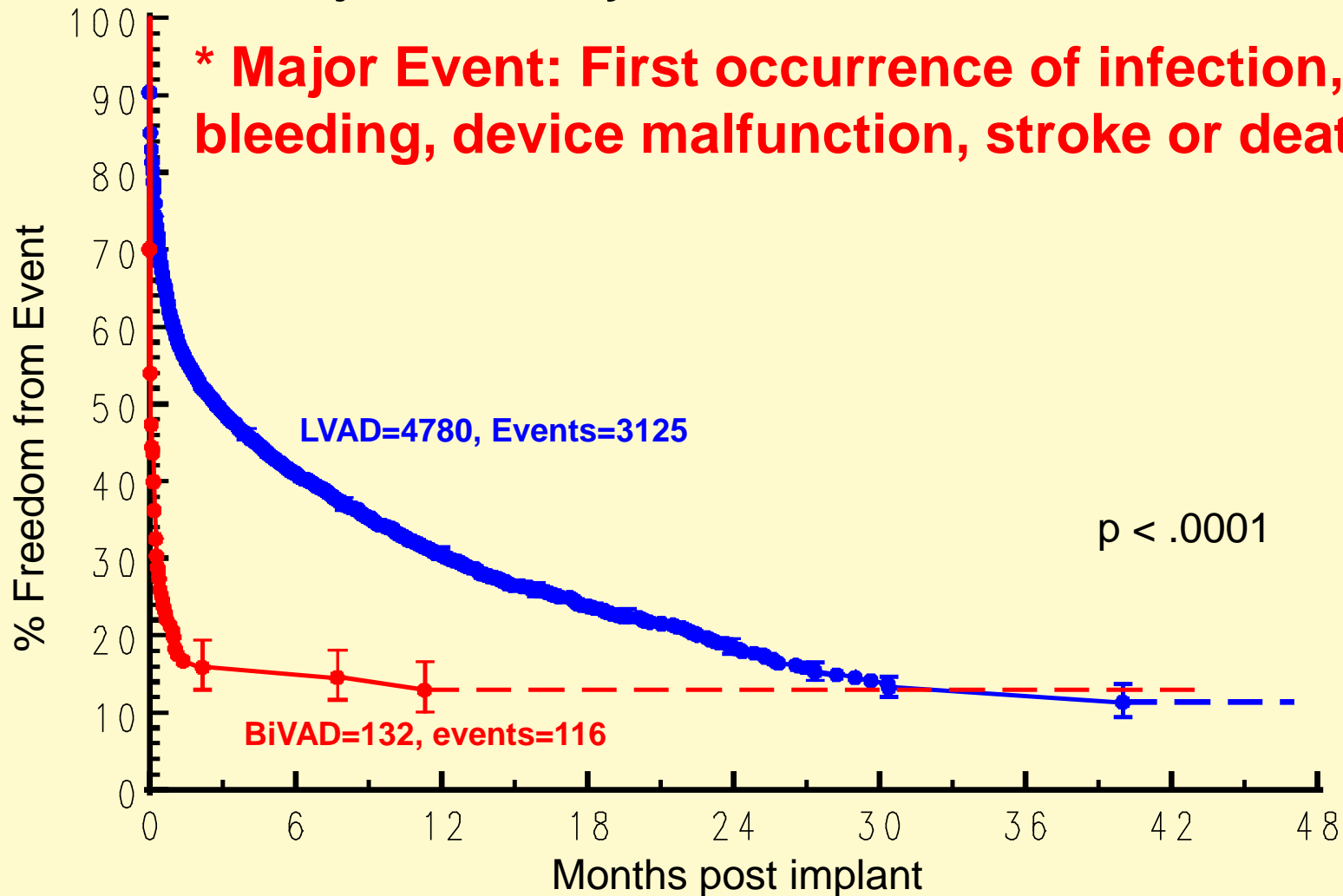
Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012 Time to First Major Event*



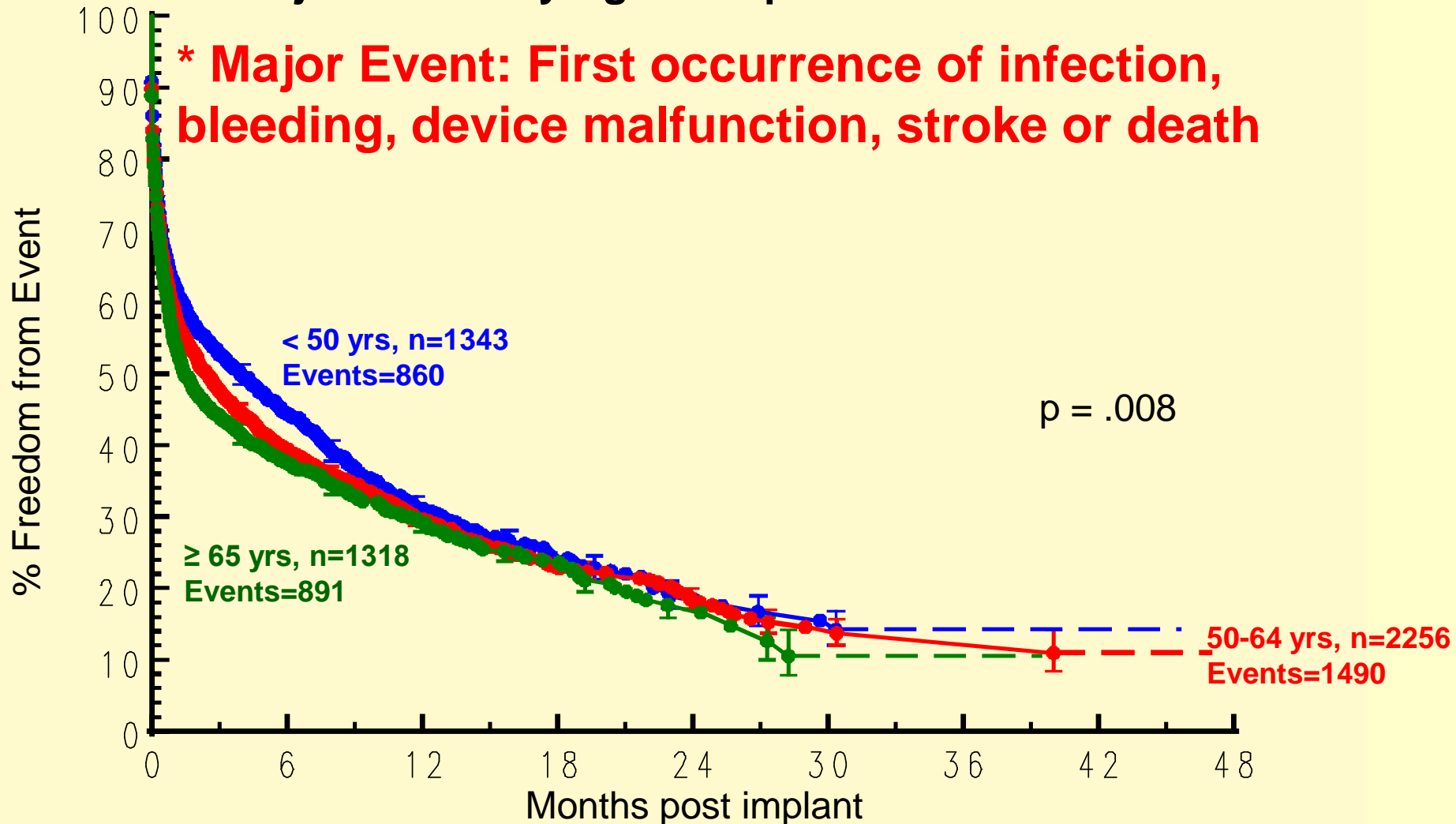
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012

Time to First Major Event* by Device Side



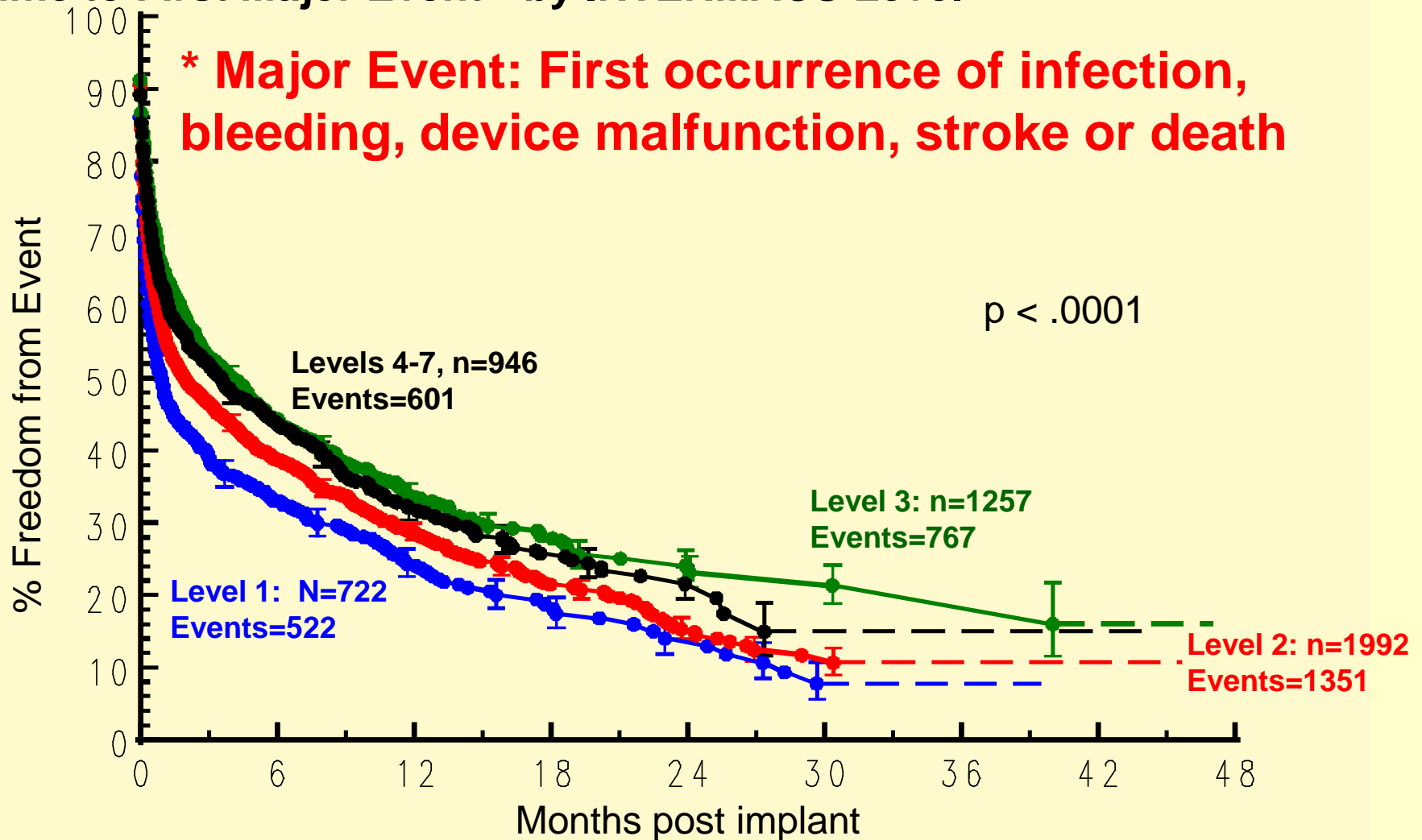
Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012

Time to First Major Event* by Age Group

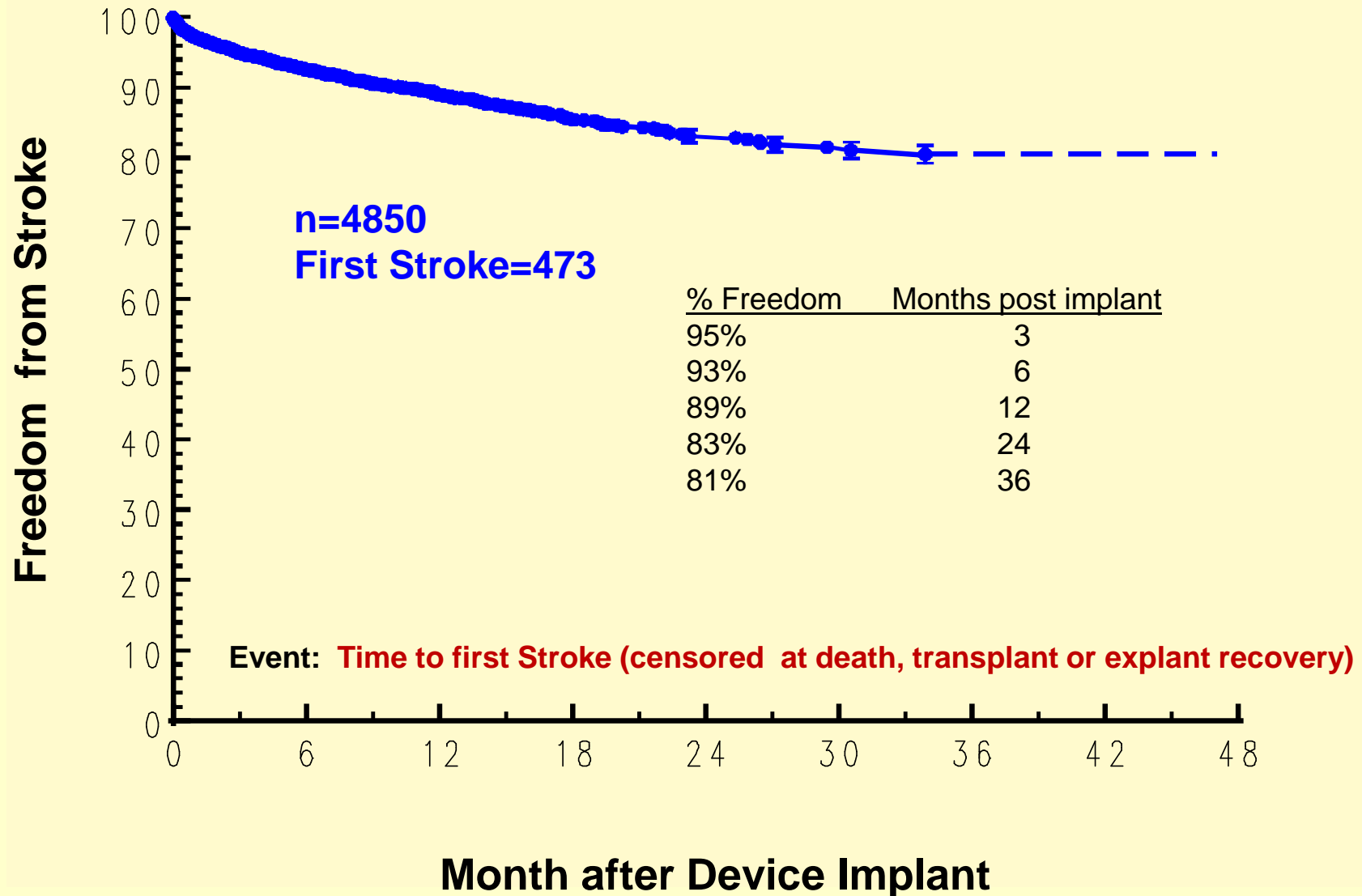


Adult Primary Continuous Flow LVADs & BIVADs, DT and BTT, n=4917 Implants: June 2006 – March 2012

Time to First Major Event* by INTERMACS Level

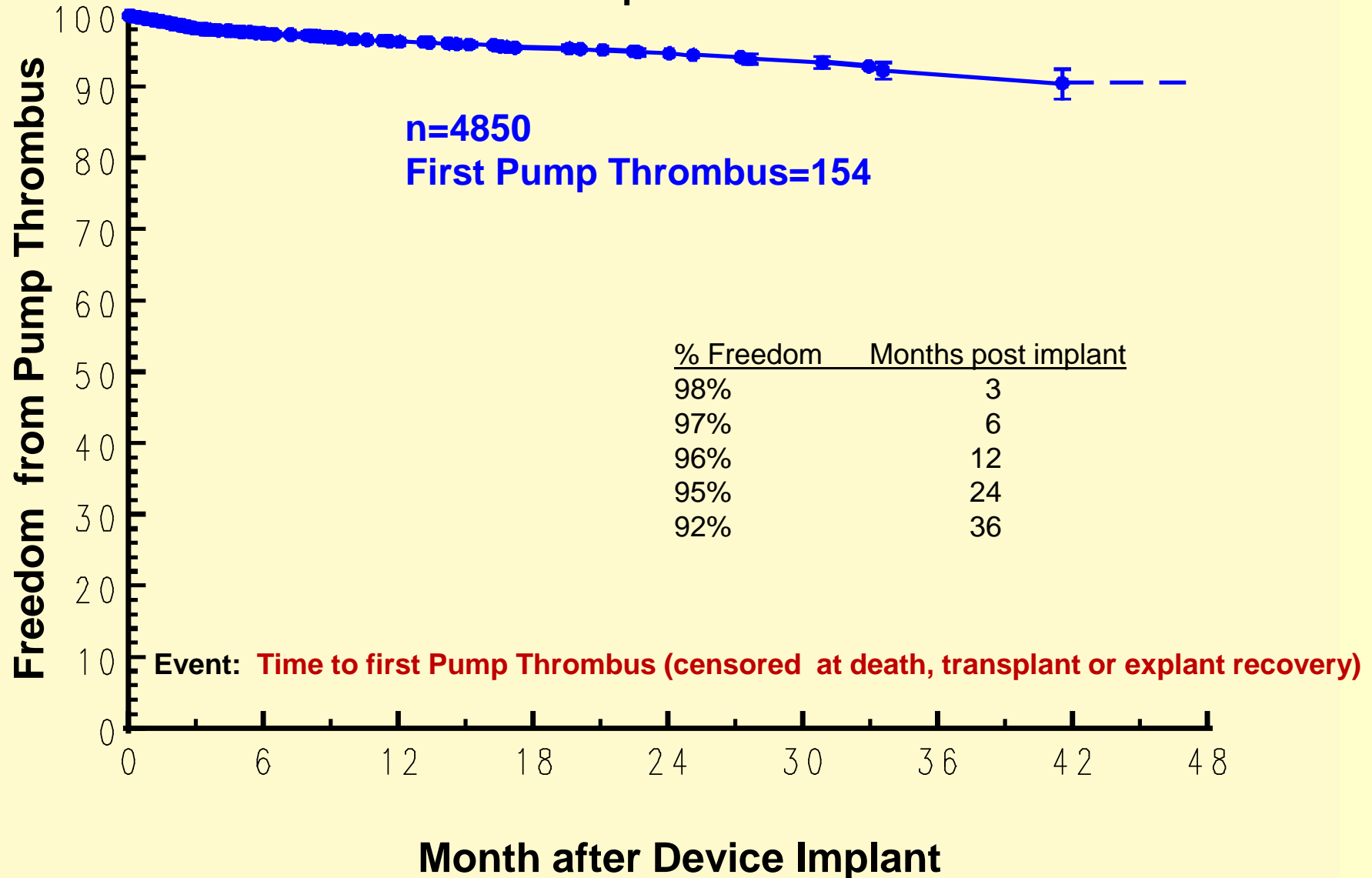


Adult primary continuous flow LVADs, n=4850 Time to First Stroke



Adult primary continuous flow LVADs, n=4850

Time to Pump Thrombus



V. Quality of Life

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

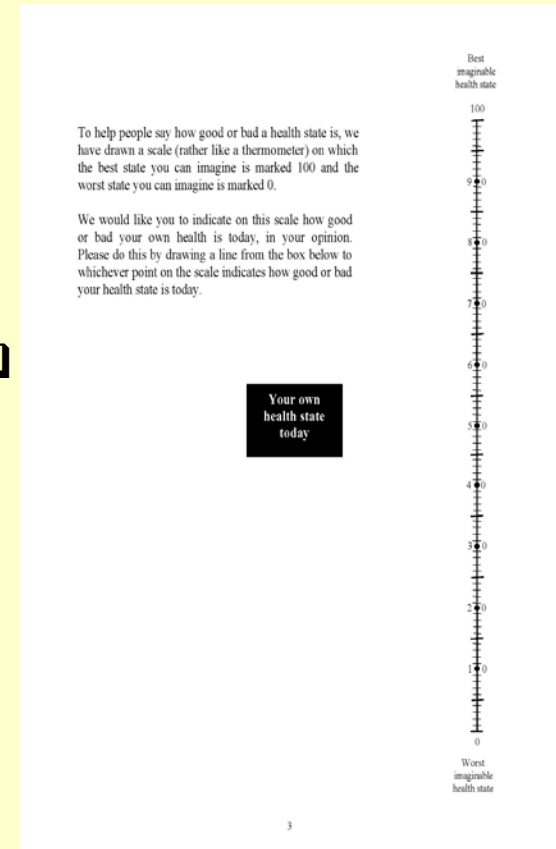
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

EQ-5D-3L

Health Questionnaire

English version for the US



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today

Best imaginable health state

100

90

80

70

60

50

40

30

20

10

0

Worst imaginable health state

EQ5D Dimension: Self Care

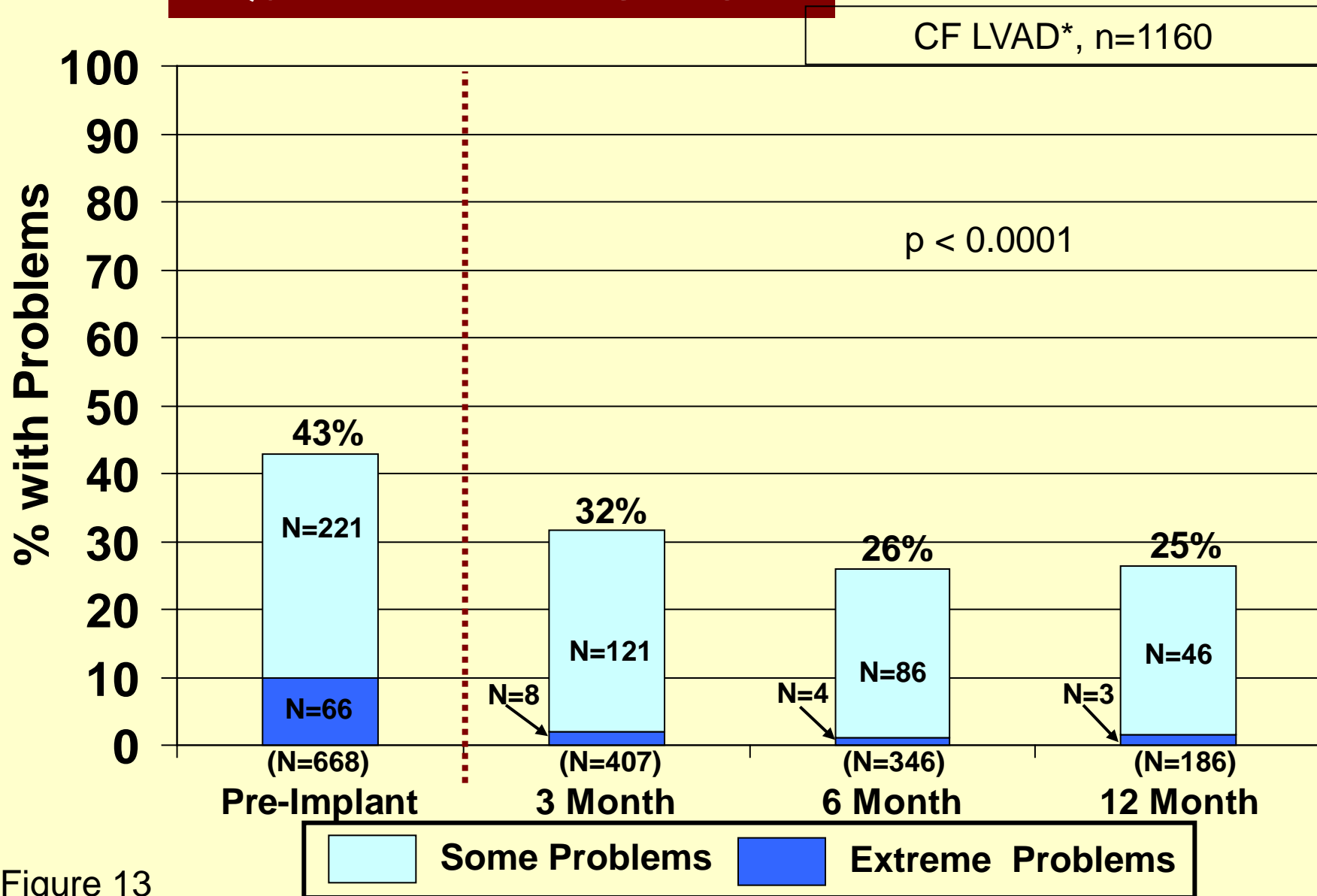


Figure 13

EQ5D Dimension: Usual Activities

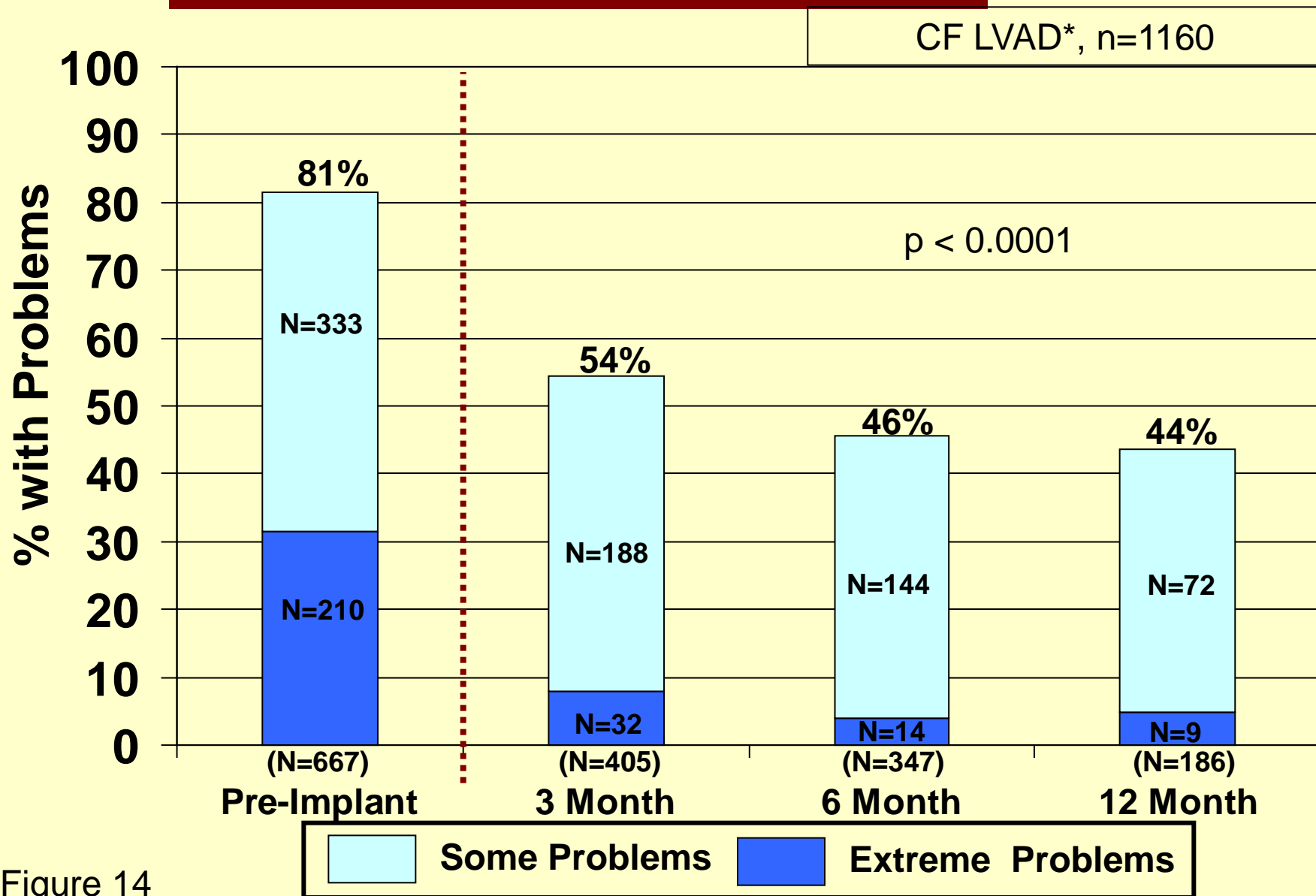


Figure 14

EQ5D Visual Analog Scale (VAS) across time (mean \pm SE)

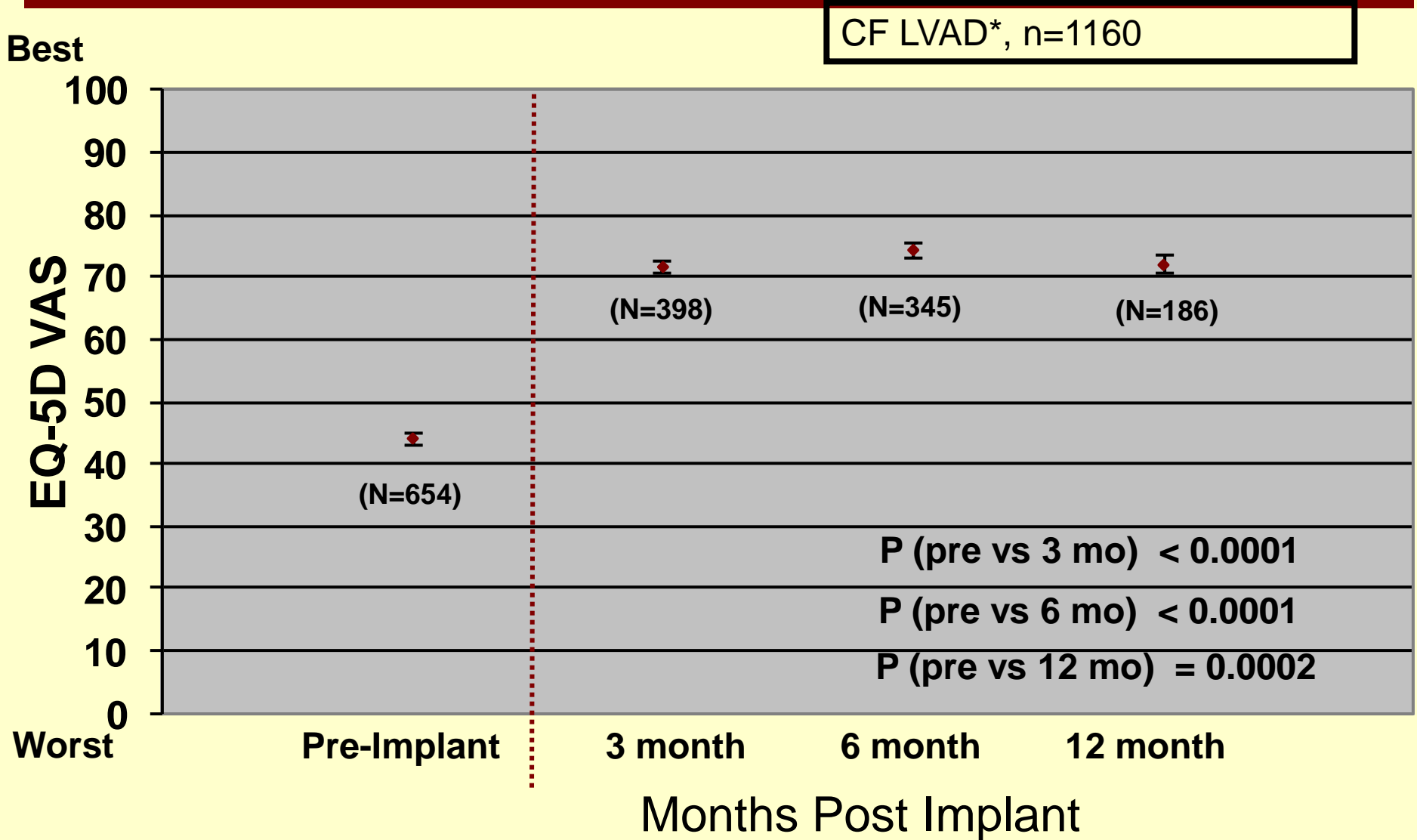


Figure 15

VI. Functional Capacity

The limitations of functional capacity data

<u>Follow-up</u>	<u>Pt Seen in Hospital/Clinic</u>	<u>6 Minute Walk</u>		<u>VO2 Max</u>		<u>R at Peak</u>	
		<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>
Pre-Implant	957	30	3.1%	58	6.1%	28	2.9%
3 Month	426	79	18.5%	14	3.3%	12	2.8%
6 Month	202	38	18.8%	10	5.0%	8	4.0%
12 Month	71	16	22.5%	1	1.4%	0	-
18 Month	16	3	18.8%	0	-	0	-
24 Month	3	1	33.3%	0	-	0	-
Total	1675	167	10.0%	83	5.0%	48	2.9%

VII. Knowledge Gaps

INTERMACS Level	Existing Information		
	MCSD (INTERMACS)	Transplant	Optimal Medical
1 Critical Cardiogenic Shock	n= 1307	Status 1	?
2 Progressive Decline	n= 2664	Status 1	?
3 Stable but Inotrope dependent	n= 1515	Status 1	?
4 Recurrent Advanced HF	n= 791	Status 2	(MEDAMACS)
5 Exertion Intolerant	n= 184	Status 2	(MEDAMACS)
6 Exertion Limited	n= 104	Status 2	(MEDAMACS)
7 Advanced NYHA Class III	n= 61	Status 2	(MEDAMACS)

Note: MEDAMACS will begin enrolling patients late fall 2012