Candidate selection for long term mechanical heart support: when is early implantantion recommended?

- ADVANCES IN CARDIAC ARRHYTHMIAS
and GREAT INNOVATIONS IN CARDIOLOGY -
XXVII Giornate Cardiologiche Torinesi
- Turin, October 23-24, 2015 -

Maria Frigerio
Director, DeGasperis CardioCenter
Director, 2nd Section of Cardiology-Heart Failure & Transplant Unit
Niguarda-Ca' Granda Hospital, Milan, Italy

Tools for Heart Failure Treatment

	Stage	A	B	C	D
All	Prevention & Lifestyle	X	X	X	X
	Physical activity	X	X	X	X
	Anti-remodeling drugs		X	X	X
	Symptomatic drugs			X	X
	ICD			X	X
Targeted	CRT			X	X
	Revascularization		X	X	X
	LV Reshaping			X	X
	MR correction			X	X
	AFib/A-V node ablation		X	X	X
	VT ablation		X	X	X
Selected	Long Term VAD				X
	Heart Transplantation				X
All	Palliation (+/- inotropes)				X

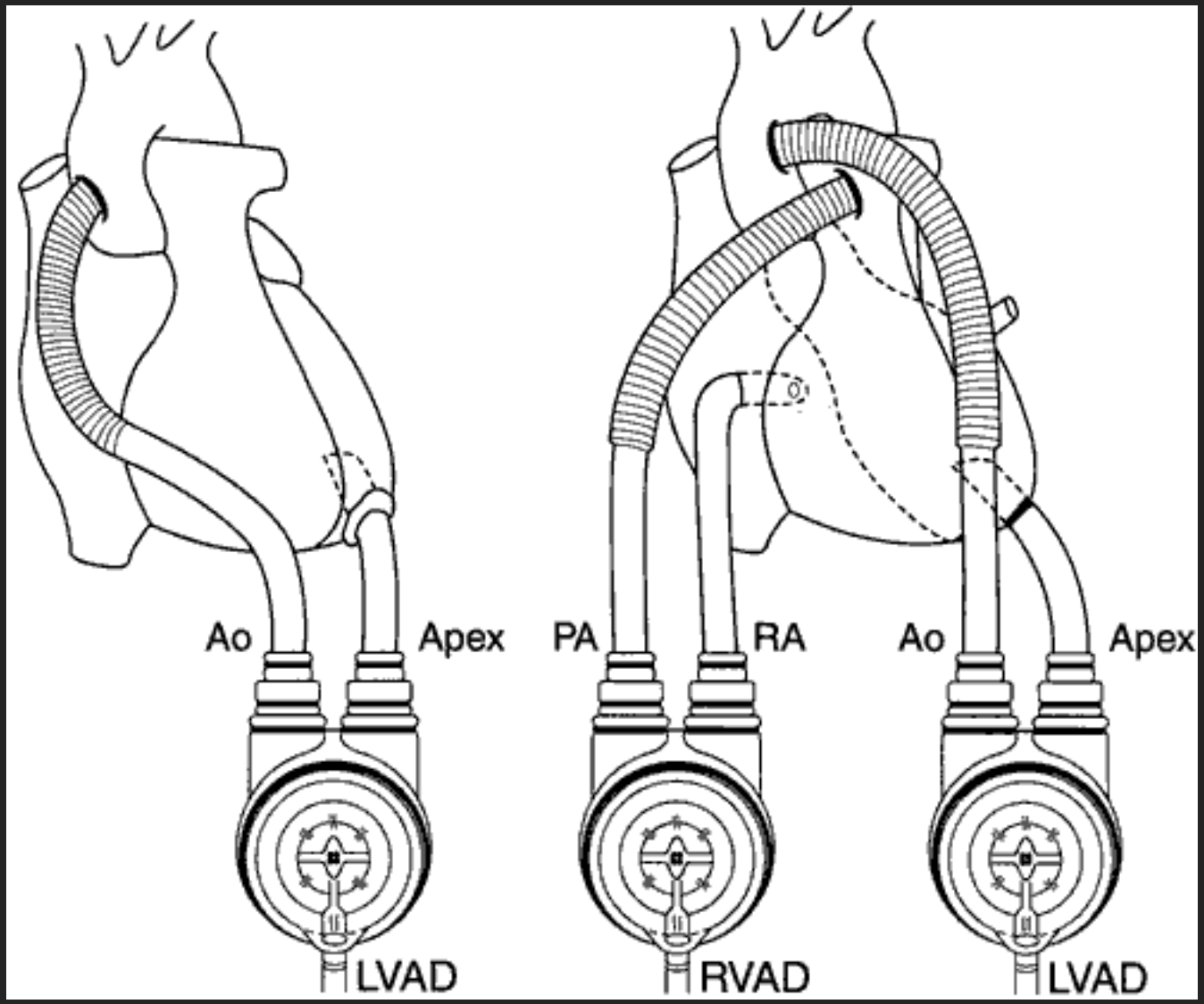
Treatment for Stage D Heart Failure

Treatment	Heart transplant	Long term VAD	Long term inotropes
Main limiting factor	Donors	Costs	Efficacy not proven
Medical/surgical contraindications	Y	Y	N/few
Complex specialized care required	Y, +++	Y, +	Ideally N
Symptomatic benefit vs standard medical therapy	Y	Y	Y, temporary
Survival benefit vs standard medical therapy	Probable	Proven	Unproven
Median survival on treatment, y	~10	1-2+ *	<1 *
	*: estimate altered by use as Bridge To Transplant (BTT)		

Long-term LVAD therapy: a short summary

- Originally designed for temporary rescue therapy or short-to mid-term Bridge To Transplant (BTT)
- Pivotal trial demonstrating superiority of LVAD therapy (Pulsatile, HeartMate I) over medical therapy in inotrope-dependent refractory HF pts, unsuitable for HTx (Destination Therapy strategy).
- Establishment of the INTERMACS Registry and definition of pt profiles
- Improved outcomes with Continuous Flow LVAD (HM-II) with respect to Pulsatile Flow.
- Increased # of pts on long-term LVAD/BTT: prolongation of HTx waiting time, especially where no priority is assigned for donor allocation to uncomplicated LVAD recipients
- Most pts implanted when Inotropes dependent (INTERMACS <3)

1989: Temporary paracorporeal MCS



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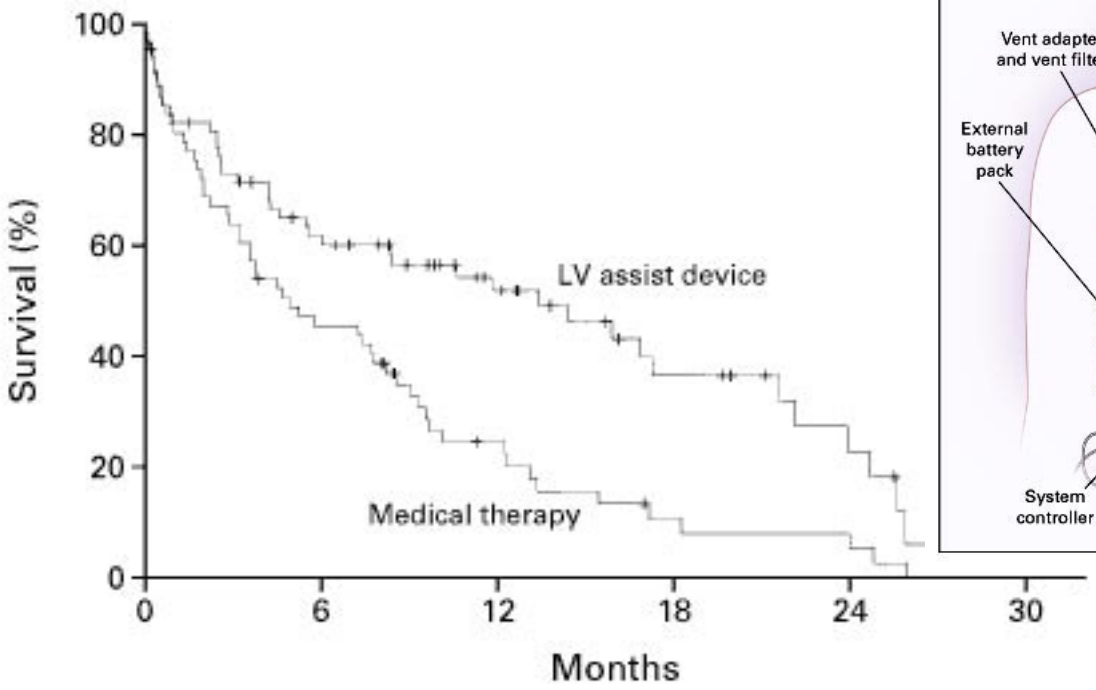
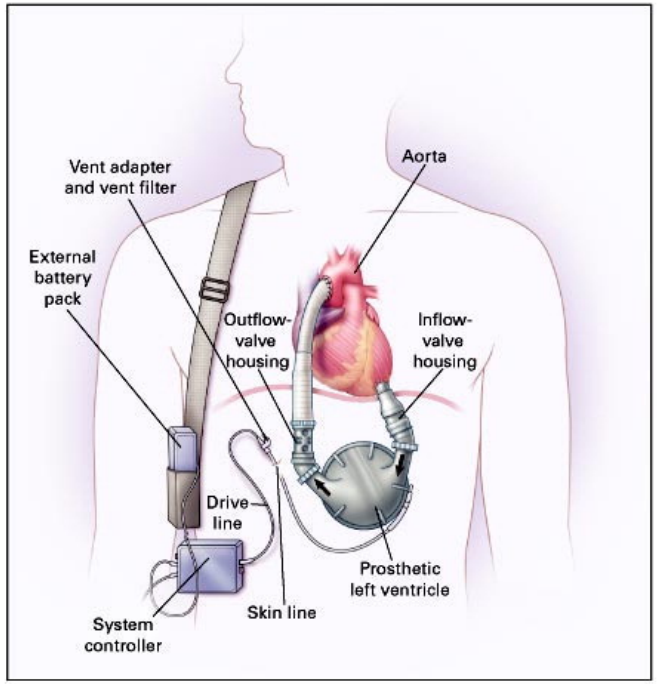
2001: The proof of concept - REMATCH Study



No. at Risk						
LV assist device	68	38	22	11	5	1
Medical therapy	61	27	11	4	3	0



Rose EA et al, N Engl J Med 2001; 345: 1435-43

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INTERMACS

Interagency Registry for Mechanically Assisted Circulatory Support

Quarterly Statistical Report
2015 2nd Quarter

Implant dates: June 23, 2006 – June 30, 2015

Prepared by:

The Data and Clinical Coordinating Center
University of Alabama at Birmingham

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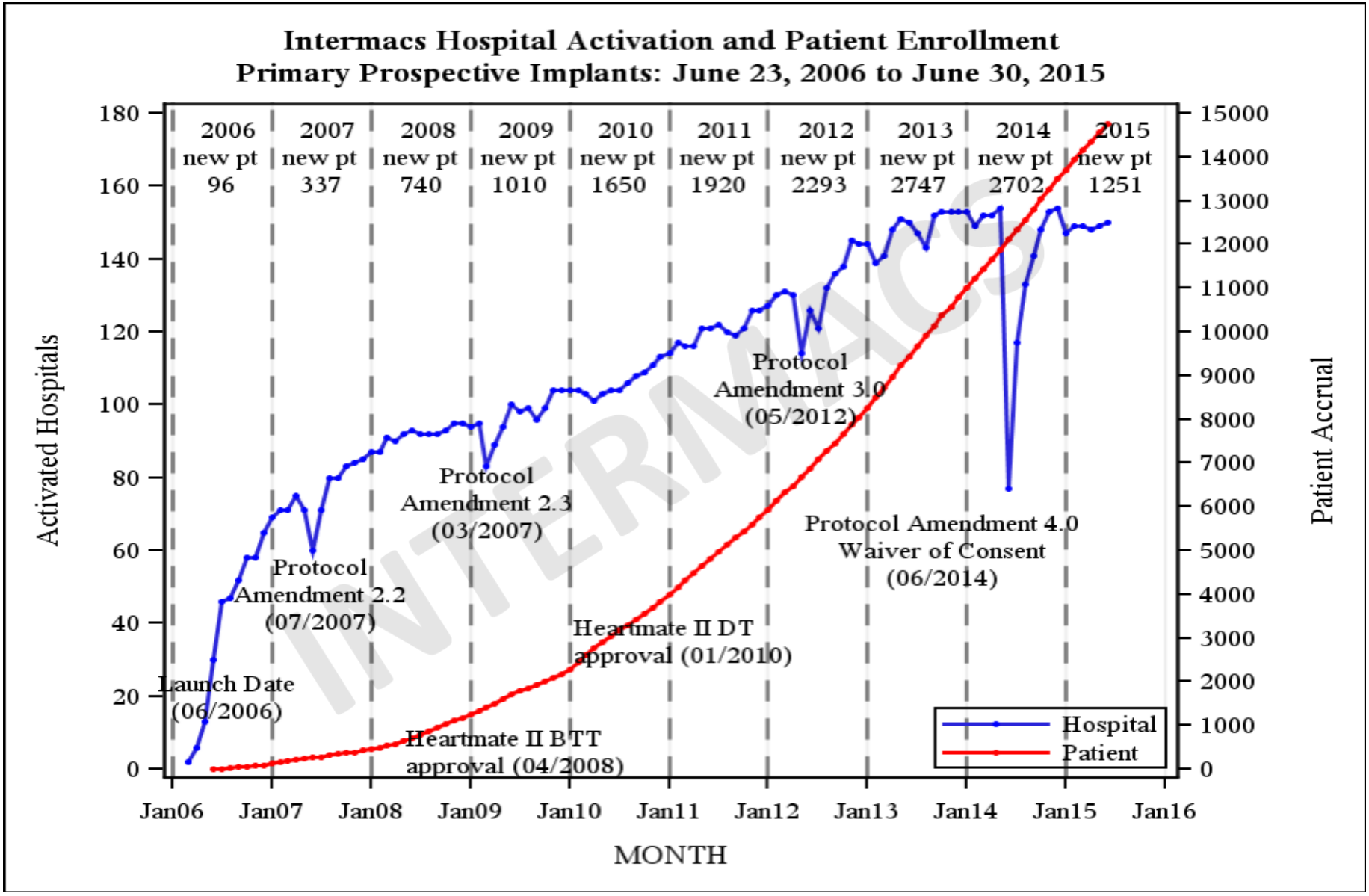
Craig Collum, MPH
Kathryn Hollifield, RN



Between June 23, 2006 and June 30, 2015, 161 hospitals participated in Intermacs and, of these, 156 hospitals actively contributed information on a total of 14746 patients. Cumulative patient accrual and the number of participating hospitals over this time period are displayed.

INTERMACS profiles

Pt Profile	Time to MCS	Benefit
1.Critical cardiogenic shock	hours	Proven
2.Progressive decline	days	
3.Stable inotrope dependent	days/weeks	
4.Resting symptoms	weeks/months	Possible
5.Exertion intolerant	variable	
6.Exertion limited	variable	Doubtful
7.Advanced NYHA III	---	

Modifiers: Frequent flyers - Arrhythmias - Temporary support

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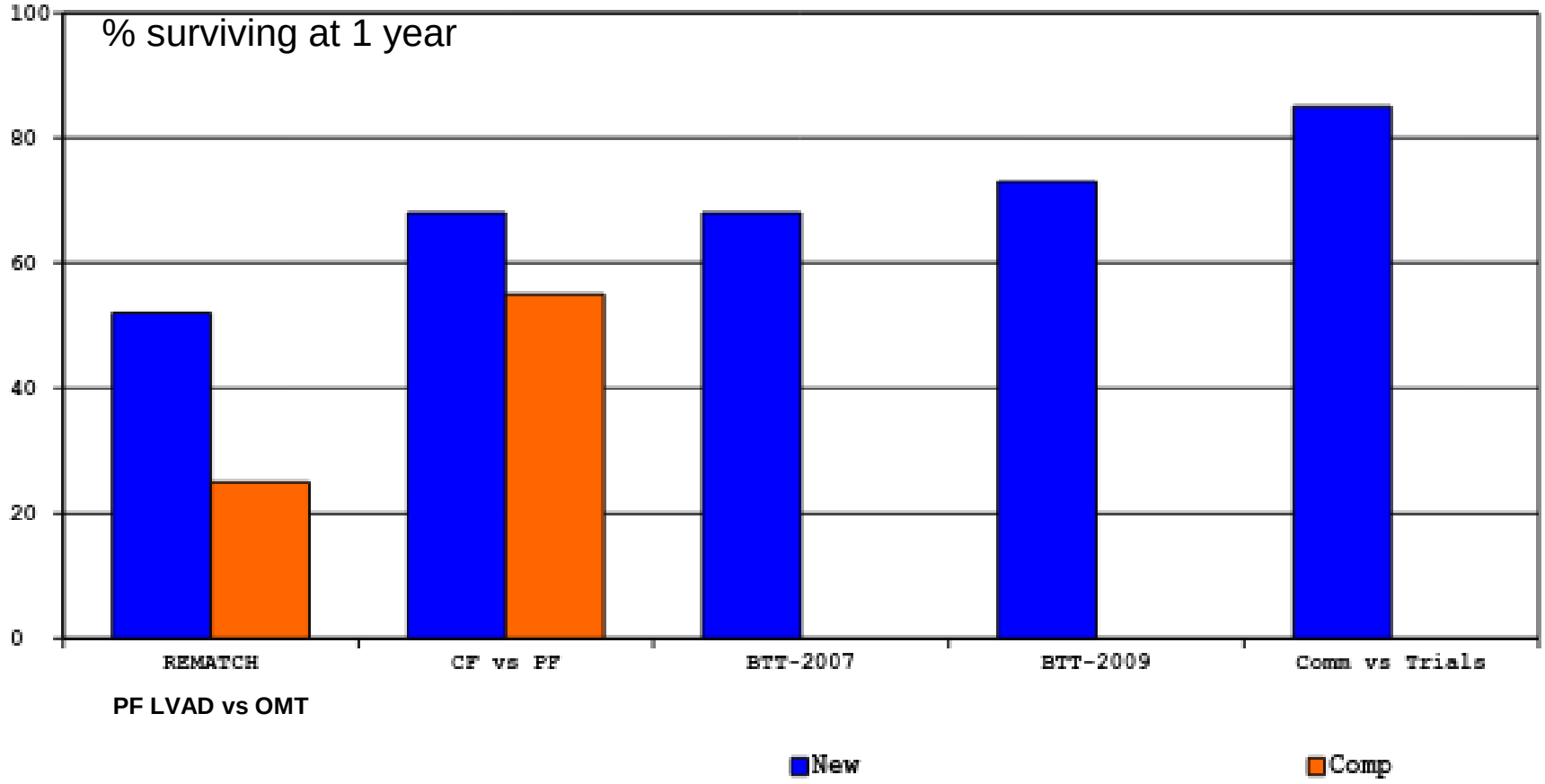
1-y survival after LVAD implantation: the rising of the machine



NEJM 2001; 345: 1435-43

NEJM 2009; 361: 2241-51

NEJM 2007; 357: 885-96

JACC 2009; 54: 312-21

AnnThoracSurg 2011;92: 1406-13

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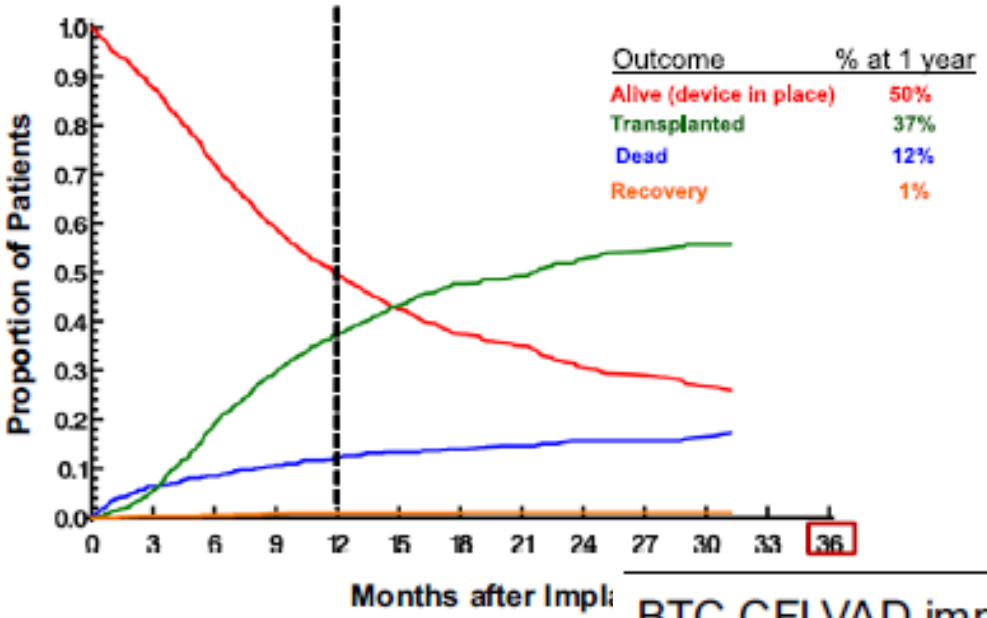
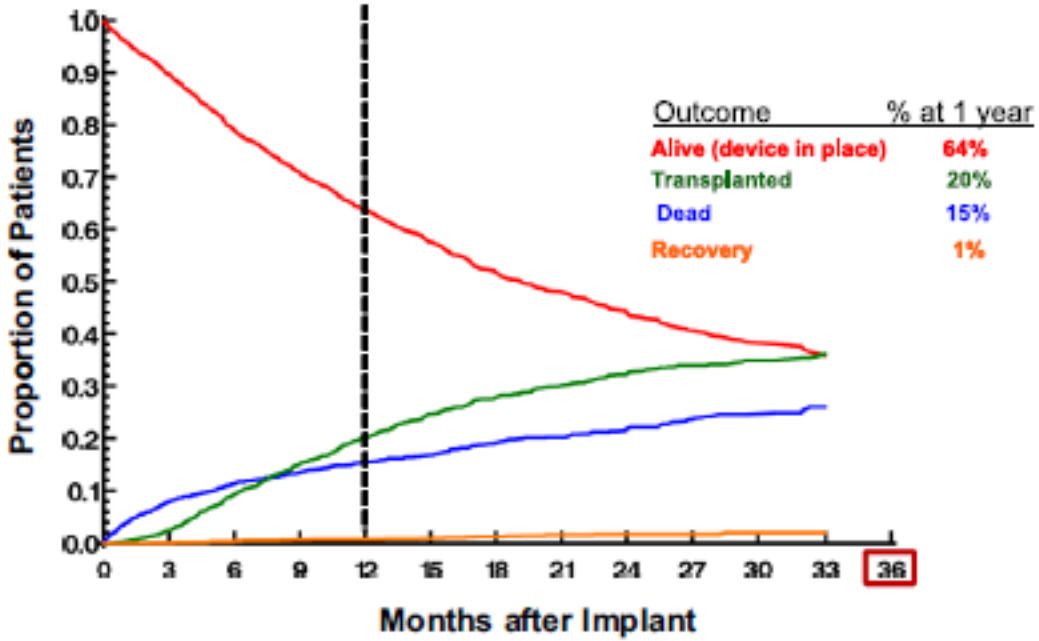
BTT: Listed CFLVAD implants 2011-2013, n=1309

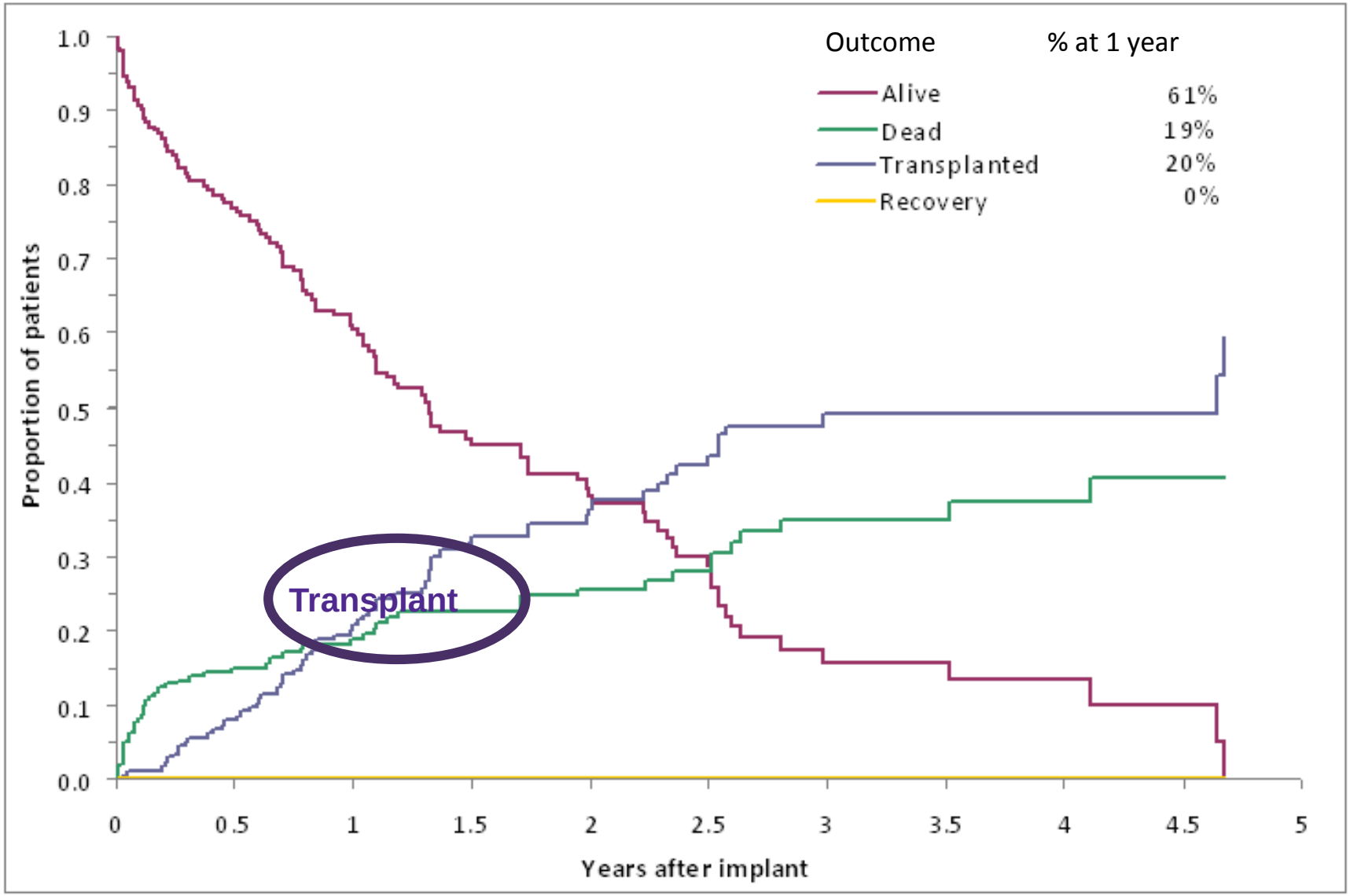


Intermacs

BTC CFLVAD implants 2011-2013, n=2205



ITAMACS, 2010-14: Competing outcomes for BTT pts



Courtesy of G. Feltrin

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- Improved outcomes with Continuous Flow LVAD (HM-II) with respect to Pulsatile Flow.
- Establishment of the INTERMACS Registry and definition of pt profiles
- Definition of subgroups of BTT indication: listed; high/low probability of listing (Bridge To Candidacy/ Bridge To Decision
- Increased # of pts on long-term LVAD/BTT: prolongation of HTx waiting time, especially where no priority is assigned for donor allocation to uncomplicated LVAD recipients
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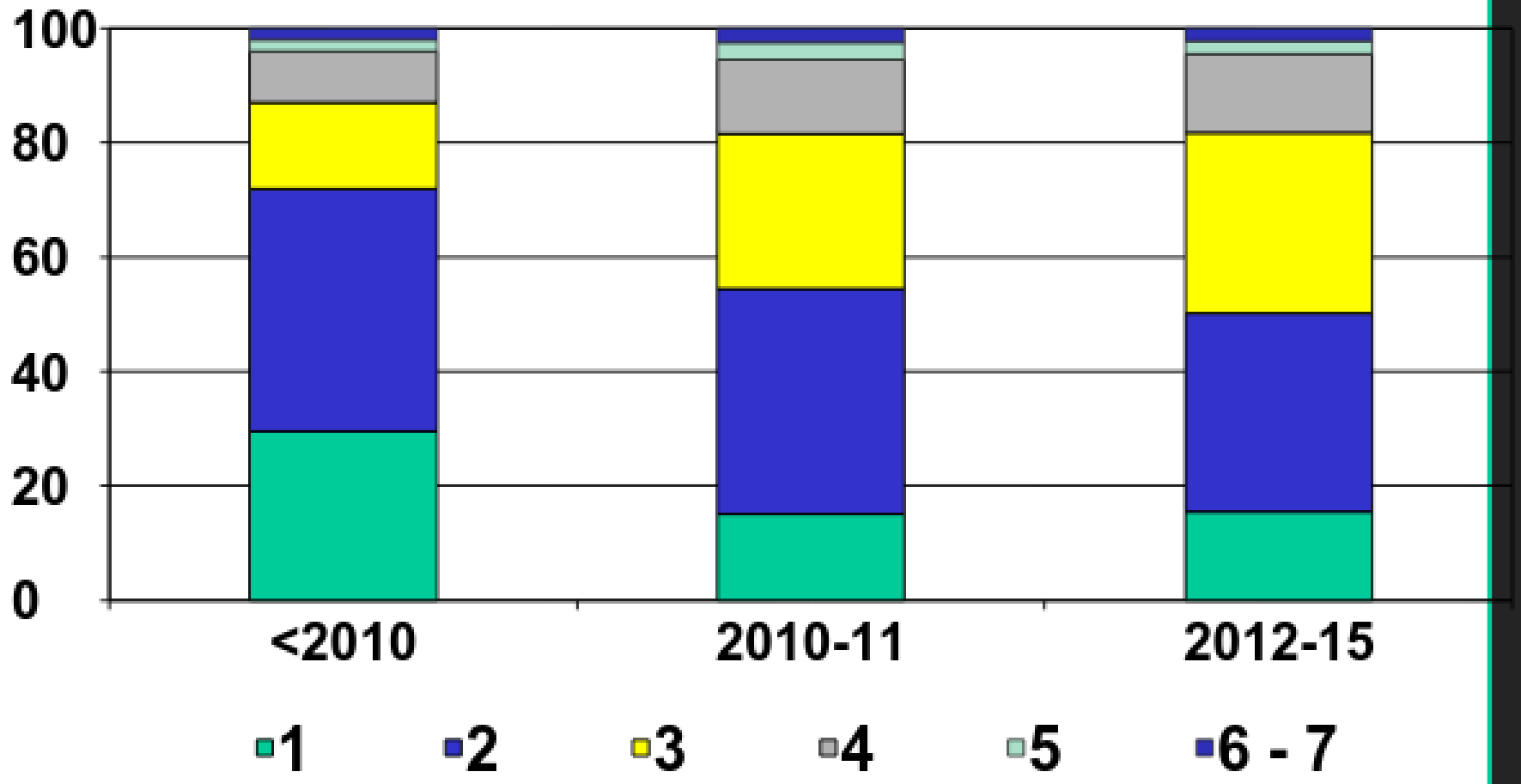
INTERMACS Profile over time



INTERMACS Report, June 2015

Early LVAD implantation

- What is it?
- Why think about it?
- When is it recommended?

Early LVAD implantation: What is it?

- Implantation in INTERMACS profile >3
- Implantation in INTERMACS profile >4 if frequent flyer modifier

Early LVAD implantation: Why think about it?

- Awareness of poor prognosis after hospitalizations with need for inotropic therapy
- Consideration for signs of refractoriness not included in INTERMACS classification
- Avoid sum of risk factors in pts with comorbidities
- Expected improvement in postop- survival

Need for inotropes as a marker of in-hospital and post-discharge poor prognosis

	80 pts needing Inotropes		
Outcome	***Not weaned, n=36 (45%)***	***Weaned, n=44 (55%)***	***All, N=90***
Death	***14 (39%)***	***6 (14%)***	***20 (25%)***
LVAD	***18 (50%)***	***1 (2%)***	***19 (24%)***
HTx	***4 (11%)***	***2 (4,5%)***	
- ***HTx- and LVAD-free 1-y survivors***		***35 (79,5%)***	***35 (44%)***

Costantinescu A et al, Eur J Heart Fail 2014; 16:435-43

Need for inotropes as a marker of in-hospital and post-discharge poor prognosis

	None	Inotropes	- Dopa	- Dobu	- Levo
Variable	n=1495	n=360	n=258	n=143	n=73
In-hospital death %	2,7	21,4*	25,2	23,1	16,4
1-y outcome %					
- mortality	17,7	50,6*	55,0	50,4	43,8
- CV mortality	11,7	41,9	46,5	42,0	38,4
- HF hosp	14,2	23,7*	19,7	25,5	26,2

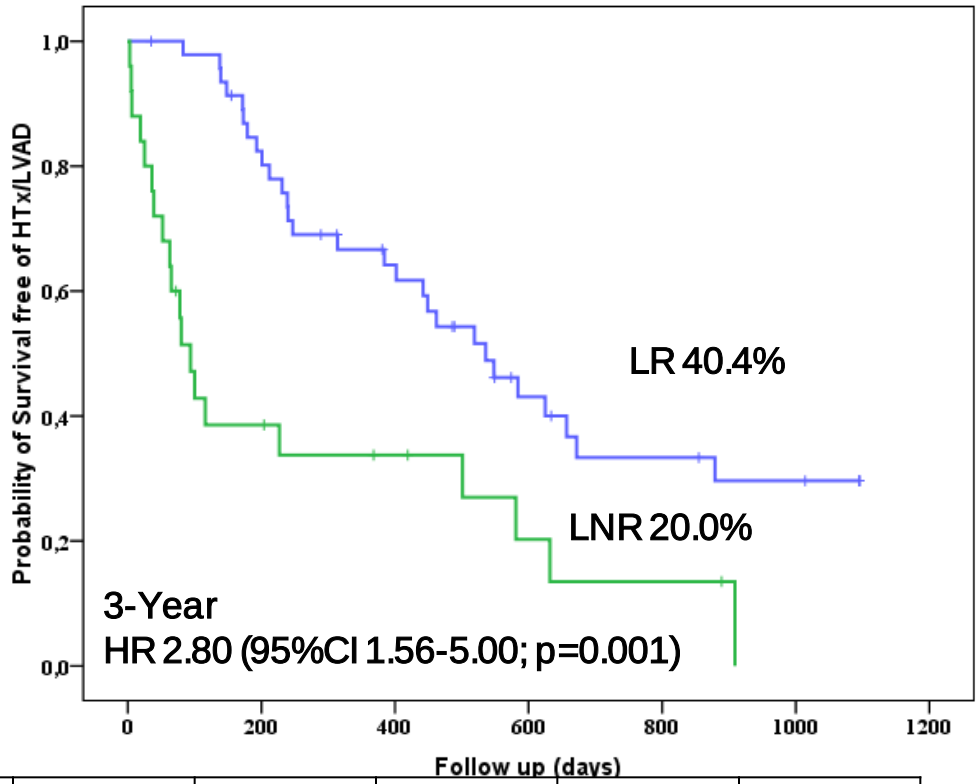
Mortara A et al, JHLT 2014; 33:1056

Need for inotropes as a marker of in-hospital and post-discharge poor prognosis

Repeated Levosimendan, Niguarda hospital, 2006-14	*Non Responders*	*Responders*	*All*
	n=25 (35%)	*n=47 (65%)*	*n=72*
Indication: weaning	*16 (64%)*	*8 (17%)*	*24 (33%)*
Indication: hemodynamics	*-*	*8 (17%)*	*8 (11%)*
Indication: maintenance	*9 (36%)*	*31 (66%)*	*40 (56%)*
Outcome - death	*1 (4%)*	*12 (25%)*	*13 (18%)*
Outcome - LVAD	*8 (32%)*	*12 (25%)*	*20 (28%)*
Outcome - HTx x	*10 (40%)*	*12 (25%)*	*22 (30.5%)*
Lost to follow-up	*2 (8%)*	*2 (4%)*	*4 (5.5%)*
INTERMACS ≤3 LVAD/HTx-free 1-y survivors	*9/25 (36%)*	*32/47 (68%)*	*41/72 (57%)*

Perna E, unpublished data

INTERMACS <3/urgent HTx-free survival in Levosimendan responders/non responders



No. at risk					
LR	*47*	*36*	*25*	*9*	*7*
LNR	*25*	*8*	*3*	*1*	*0*

Perna E, unpublished data

Early LVAD implantation: Why think about it?

- Awareness of poor prognosis after hospitalizations with need for inotropic therapy
- Consideration for signs of refractoriness not included in INTERMACS classification
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Clinical markers of deterioration in advanced chronic heart failure

- Weight loss
- Increased diuretic dose
- Hyponatremia
- Deterioration of renal function
- Liver dysfunction
- Arrhythmias
- ACE-I/BetaBlockers intolerance

8 Ottobre 2015: Gli assenteisti di Capodanno: rischiano 95 medici e 54 vigili urbani

Verso la richiesta di rinvio a giudizio per le malattie fasulle certificate dai sanitari

Giulio De Santis - Ilaria Sacchettoni

CORRIERE DELLA SERA

Ottocentonovantaquattro agenti della Municipale si diedero malati la notte di San Silvestro. Assenze giustificate. Come? In quarantanove casi, secondo l'inchiesta che si è appena conclusa, ciò sarebbe avvenuto grazie a un falso attestato medico, rilasciato sulla scorta di una semplice telefonata del paziente. Certificando, cioè, malanni vari senza neppure un'occhiata alla lingua del «moribondo». Altri colleghi di quei medici, poi, avrebbe fatto di più. E, da semplici sostituti del vero titolare, sarebbero entrati abusivamente nel sistema informatico per compilare la diagnosi, in qualche caso vera ma pur sempre abusiva..

In sintesi, a conclusione delle indagini sull'emergenza vigili di Capodanno, la procura si prepara a chiedere il rinvio a giudizio di 149 persone, di cui 95 sono medici di base o loro sostituti, e un terzo, 54 per la precisione, sono vigili urbani, che per gli investigatori sarebbero responsabili di una truffa (articolo 640 del codice) ai danni del Comune

Case study 1: the local policeman that wanted to go to work

- Male, 56 yrs, 186 cm, 76 kg (- 8 kg last year)
- DCM diagnosed in 2007, NYHA II/III, never admitted for acute/decompensated HF
- EKG: NSR 68/min, LV hypertrophy, no LBBB (no ICD)
- Echo: LVEDD 79mm, LVEVD 421ml, LVEF 18%, MR2+, TR2+, PAP 65mmHg, TAPSE 14 mm
- Lab: BUN 70 mg/dl, Creat 1.4 mg/dl, eGFR 53, Bil 1.4 mg/dl, cholesterol 110 mg/dl, NT-proBNP 6200 ng/ml, Sodium 131 mEq/l
- SysBP 85 mmHg
- VO2max 10.3, AT 60%, VE/VCO2 slope 52.
- Therapy: Furosemide 37.5mg, Ramipril 5 mg, Carvedilol 25 mg, Spironolactone 25 mg
- Right heart cath: RAP 12, PAP 68/24/40, PCWP 28 mmHg, IC 1.4 l/min/m2

Case study 1: estimating prognosis in ambulatory HF patients

- 3C-HF score: 1-year survival 83%
- Seattle Heart Failure : 1-year survival 85%
- MECKI score: 2-year urgent HTx free survival 42%
- HFSS score: high-risk, 1-year survival 43%

UNSUITABLE FOR HTx (Pulmonary hypertension)

RISK FACTORS FOR LVAD: RV dysfunction, end-organ dysfunction

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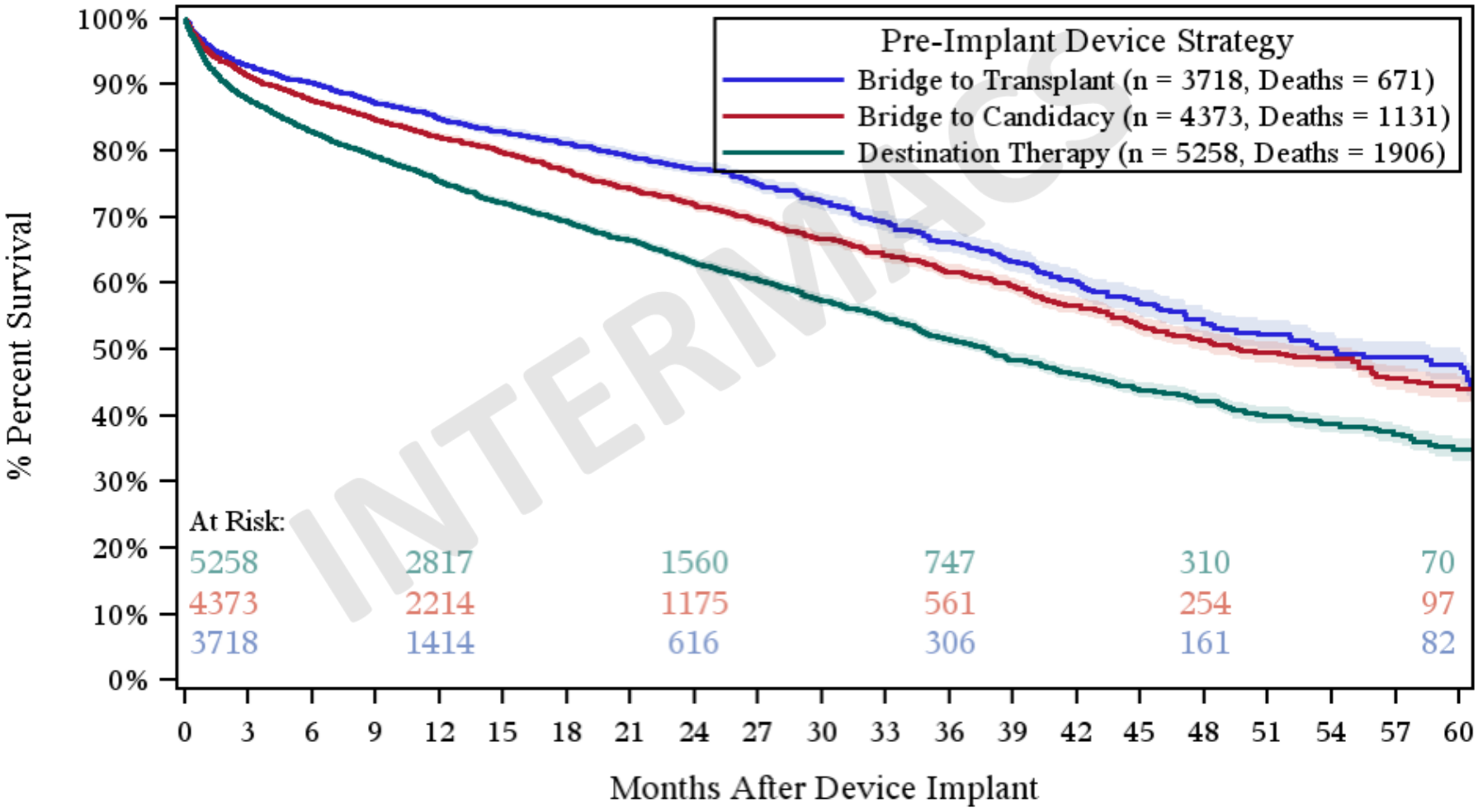
Intermacs - Kaplan-Meier Survival for Continuous Flow LVADs (with or without RVAD implant at time of LVAD operation) by Pre-Implant Device Strategy

Primary Prospective Implants: June 23, 2006 to June 30, 2015



Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death (censored at transplant or recovery)

Intermacs

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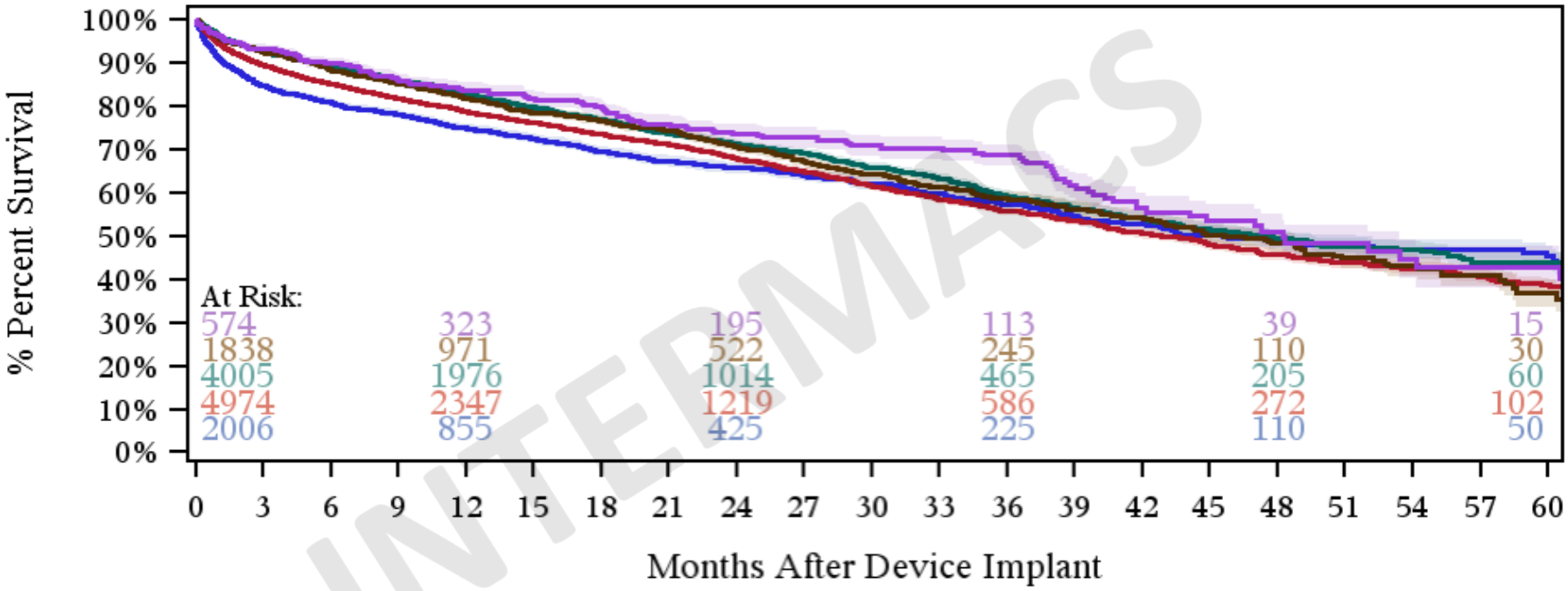

Pre-Implant Patient Profile

- Level 1 - Critical Cardiogenic (n = 2006, Deaths = 605)
- Level 2 - Progressive Decline (n = 4974, Deaths = 1457)
- Level 3 - Stable but Inotrope (n = 4005, Deaths = 995)
- Level 4 - Resting Symptoms (n = 1838, Deaths = 515)
- Levels 5,6,7 - All Others (n = 574, Deaths = 154)

Shaded areas indicate 70% confidence limits

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Event: Death (censored at transplant or recovery)

Intermacs

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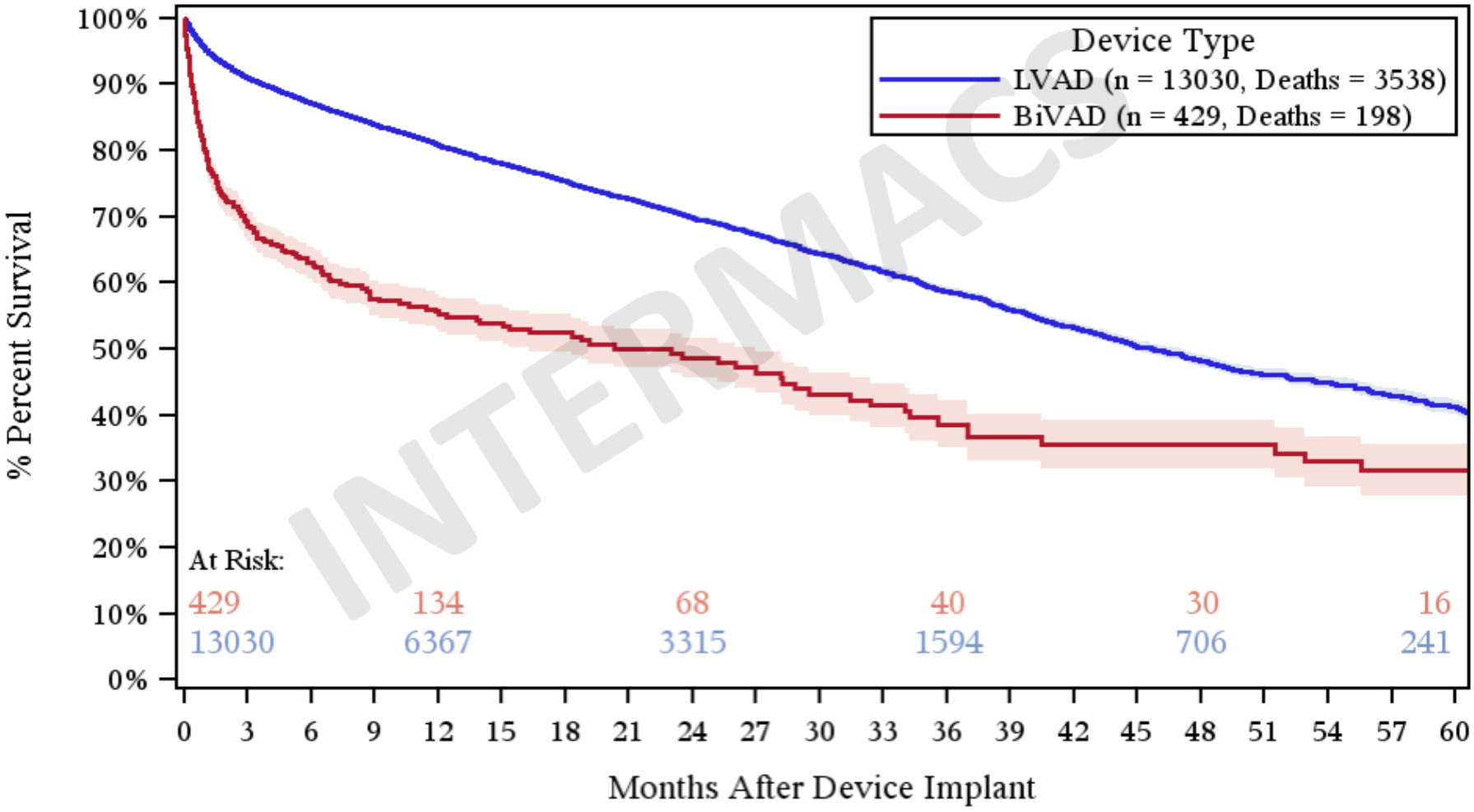

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Intermacs

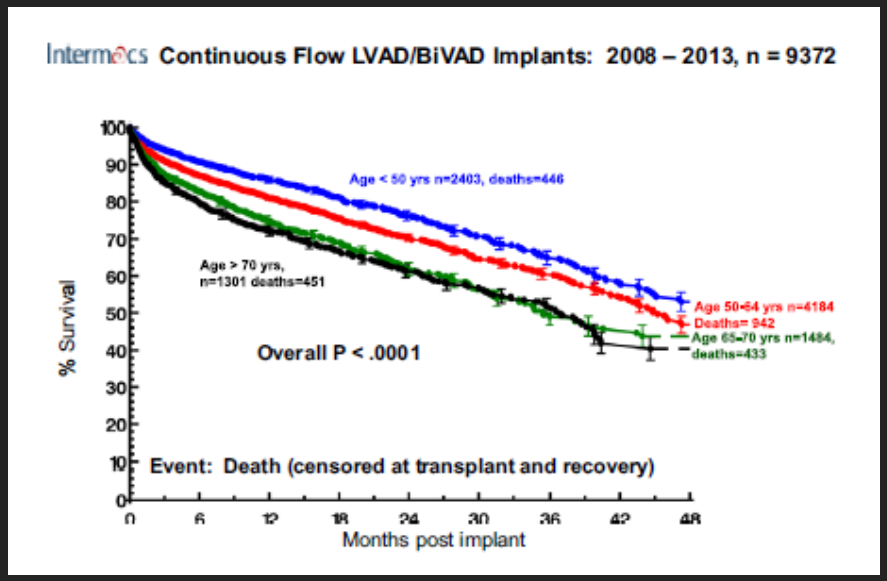
INTERMACS 6th annual report: Risk Factors for postoperative death

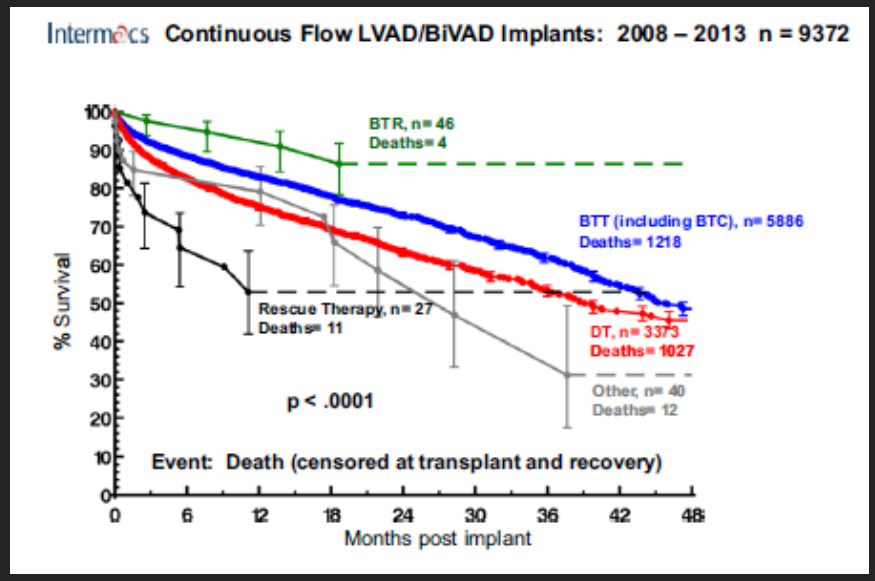
Table 6 Adult Primary Continuous-flow LVAD and BiVAD Implants: June 2006 to December 2013 ($N = 9,372$)

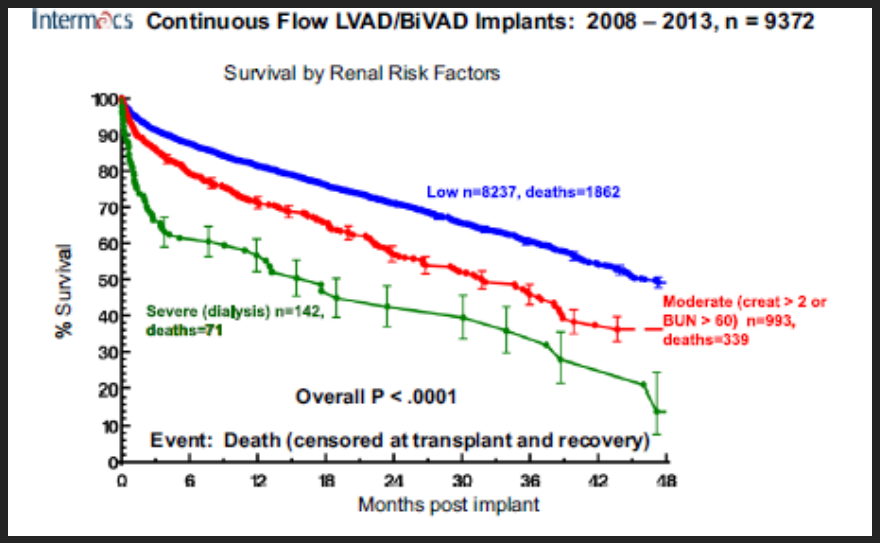
J Heart Lung Transplant 2014;33:555–564

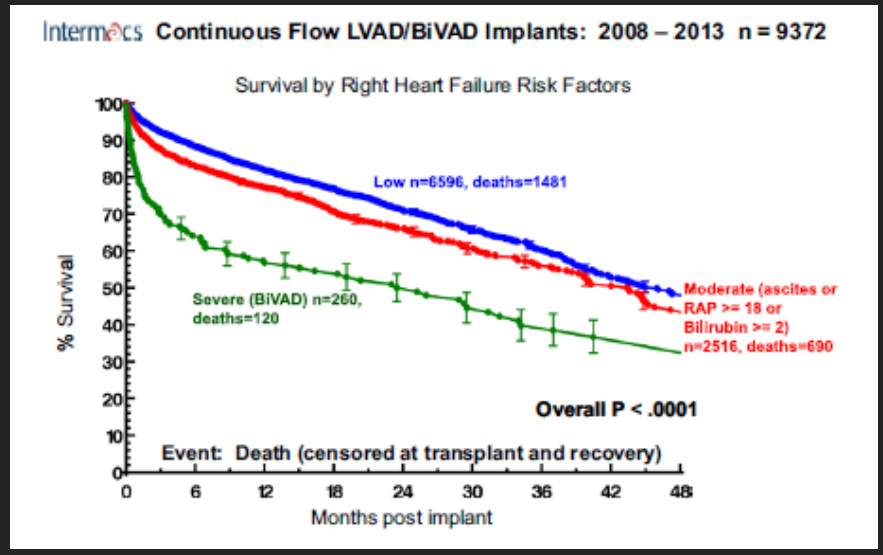
	Early hazard		Late hazard	
Risk factors for death	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Demographics				
Age (older)	1.36	<0.0001		
Female	1.20	0.007		
BMI (higher)	1.13	<0.0001		
Clinical status				
History of stroke	1.30	0.03		
INTERMACS Level 1	1.69	<0.0001		
INTERMACS Level 2	1.44	<0.0001		
Destination therapy	1.24	0.0005		
Non-cardiac systems				
Albumin (lower)	0.90	0.02		
Creatinine (higher)			1.05	0.0003
Dialysis	2.37	<0.0001		
BUN (higher)	1.06	<0.0001	1.06	0.01
Right heart dysfunction				
Right atrial pressure (higher)	1.11	0.02		
RVAD in same operation	2.45	<0.0001		
Bilirubin (higher)	1.21	<0.0001		
Ascites	1.27	0.01		
Surgical complexities				
History of cardiac surgery	1.43	<0.0001		
Concomitant cardiac surgery			1.21	0.0008

INTERMACS 6th annual report: Risk Factors for postoperative death









Case study 2: the VIP who didn't want privileges

- Male, 66 yrs, 172 cm, 80 kg, type 2 diabetes, COPD
- post-MI cardiomyopathy, prior CABG
- EKG: NSR 86/min, prior anterior MI, LBBB --> CRT-D
- Hospitalised for acute cholecystitis, stop baseline HF therapy
- Admission for AHF requiring ventilation and inotropes
- Echo: LVEDD 69 mm, LVEVD 350 ml, LVEF 21%, MR2+, TR 0, PAP 48 mmHg, TAPSE 17 mm
- Lab: BUN 50 mg/dl, Creat 2.1 mg/dl, eGFR 44, Bil 1.6 mg/dl, cholesterol 160 mg/dl, NT-proBNP 4000 ng/ml, Sodium 133 mEq/l
- SysBP 95 mmHg
- VO2max 11.4, AT 65%, VE/VCO2 slope 45.
- Therapy: Furosemide 100 mg, ACE-I not tolerated, Bisoprolol 2.5 mg, Spironolactone 25 mg
- Right heart cath: RAP 8, PAP 48/20/33, PCWP 22 mmHg, IC 1.5 l/min/m2.

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- Seattle Heart Failure : 1-year survival 85%
- MECKI score: 2-year urgent HTx free survival 65%
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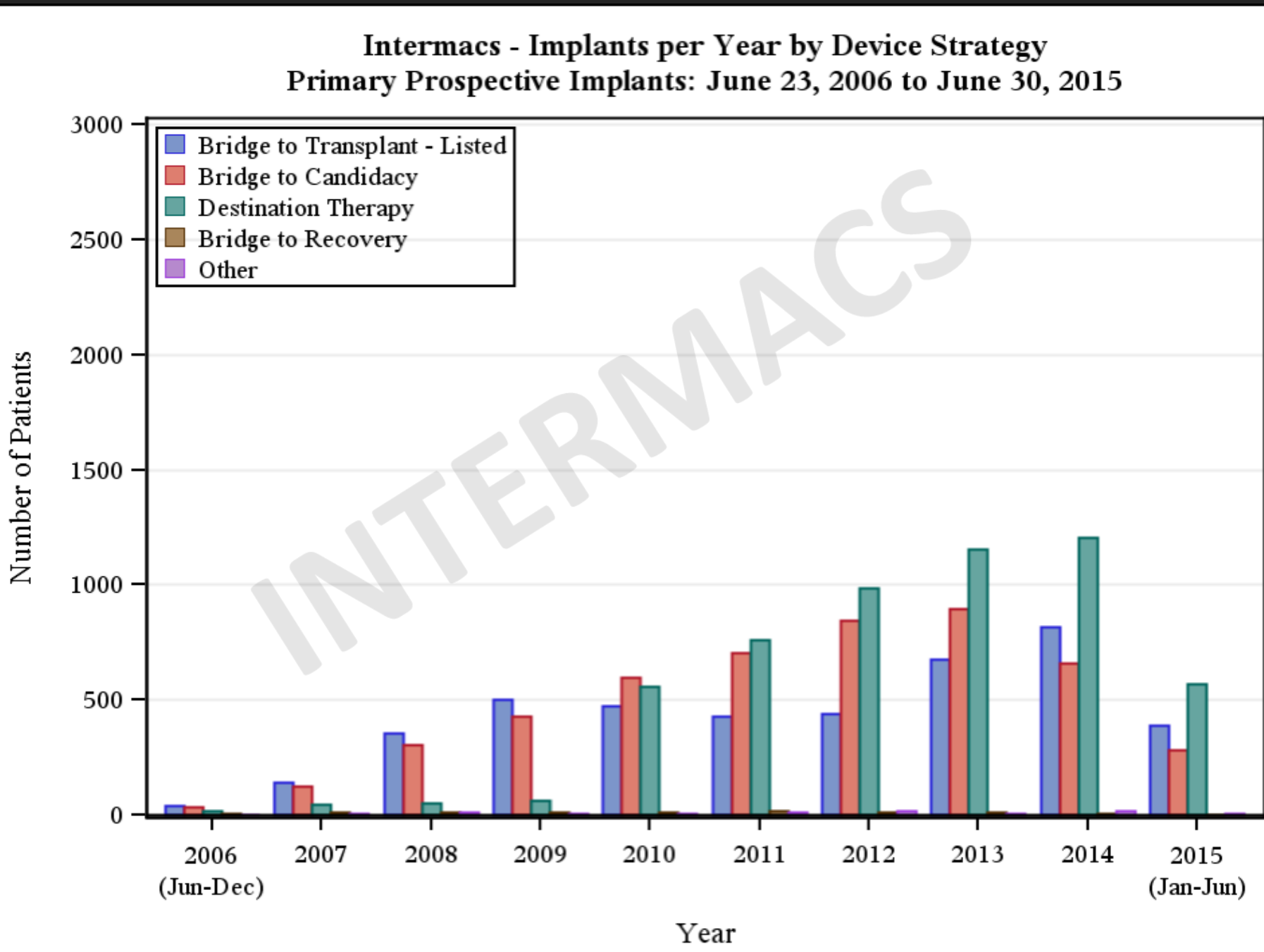
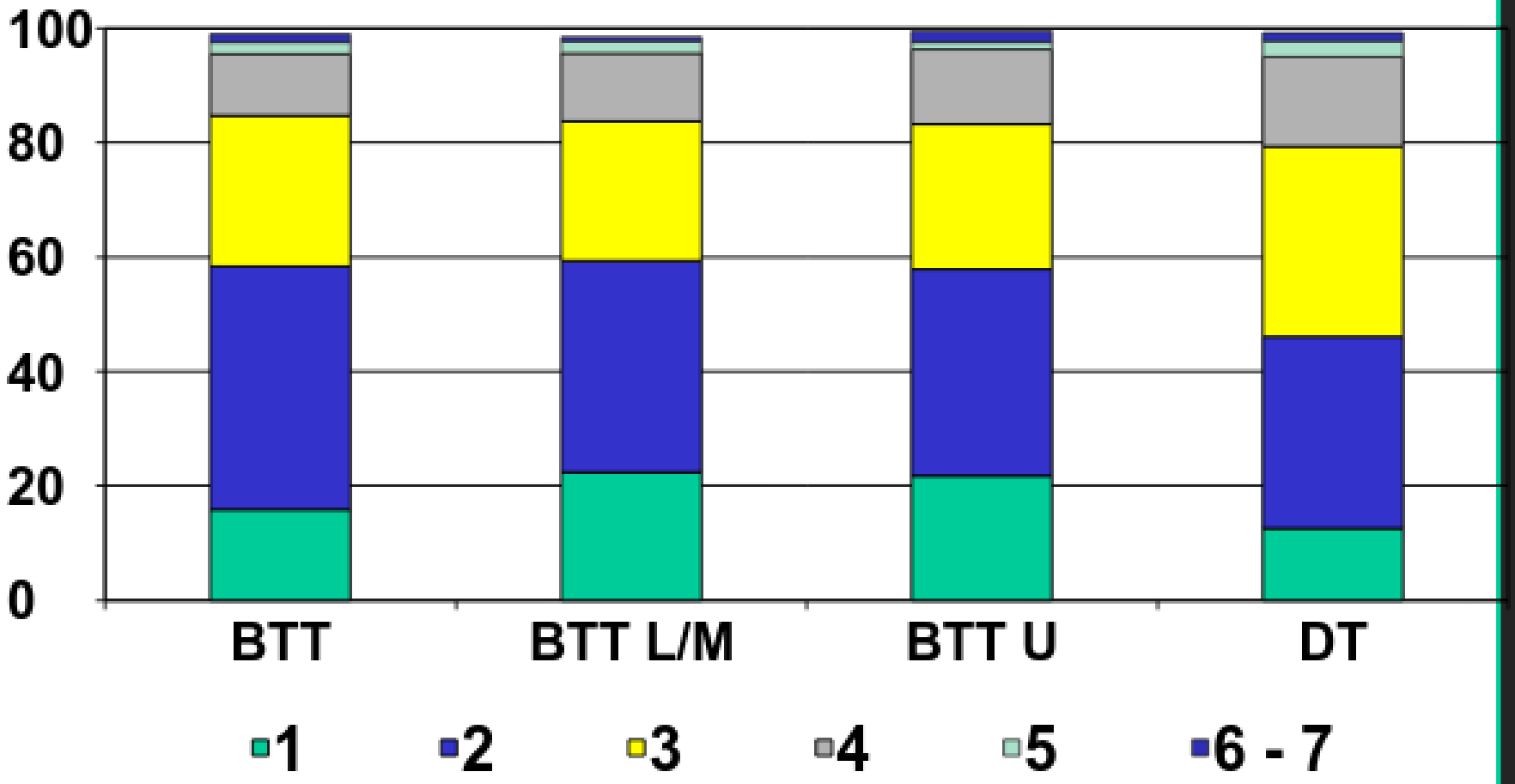
RISK FACTORS FOR HTx: age, renal insufficiency, diabetes, redo

RISK FACTORS FOR LVAD: renal insufficiency, diabetes, redo


Intermacs - Implants per Year by Device Strategy
Primary Prospective Implants: June 23, 2006 to June 30, 2015
Bridge to Transplant - Listed
Bridge to Candidacy
Destination Therapy
Bridge to Recovery
Other
Number of Patients
3000
2500
2000
1500
1000
500
0
2006 (Jun-Dec)
2007
2008
2009
2010
2011
2012
2013
2014
2015 (Jan-Jun)
Year
INTERMACS

INTERMACS Profile vs Indication



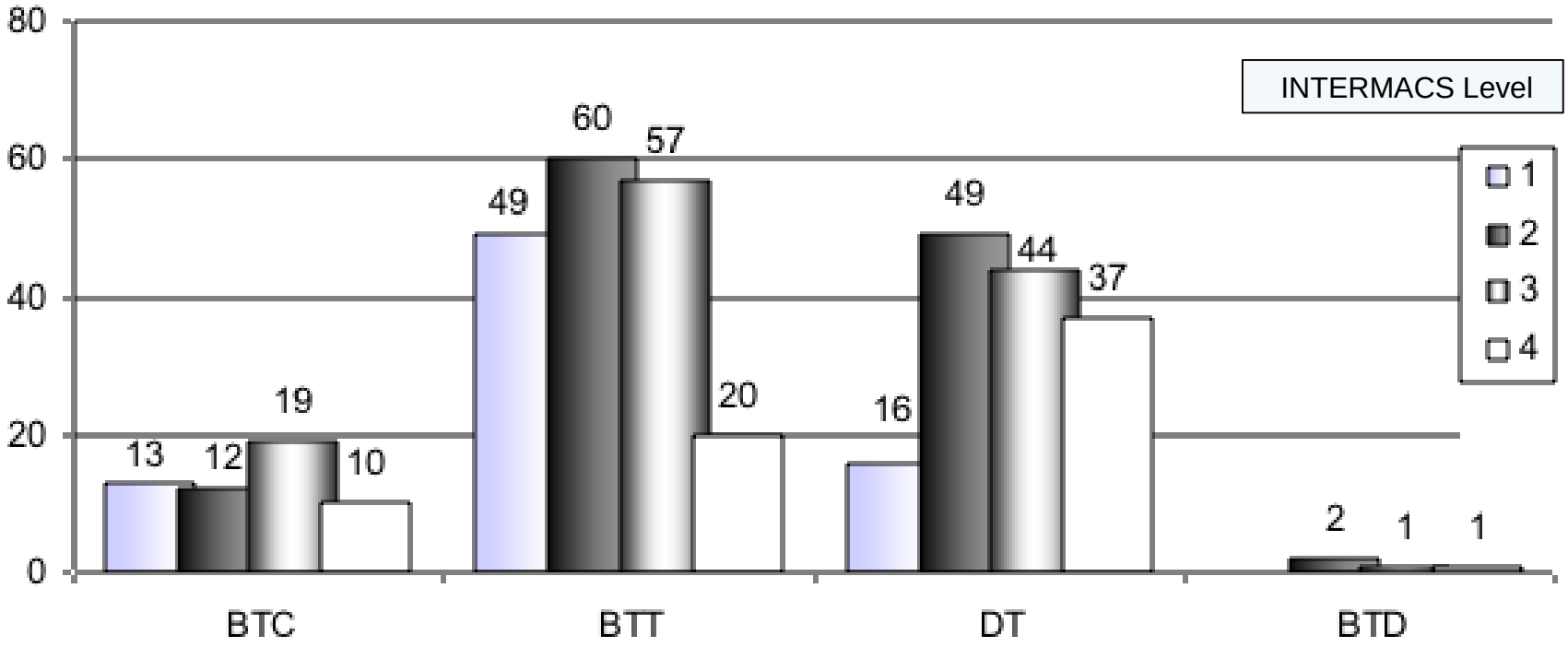
INTERMACS Quarterly Report, June 2015

C.F. LVAD implants by age and level

	INTERMACS LEVEL				
AGE N %	1	2	3	4	TOT
< 50	26 32.9	31 39.2	16 20.3	6 7.6	79 100
50 –64	38 18.4	58 28.0	74 35.7	37 17.9	207 100
65 – 69	10 13.9	22 30.6	22 30.6	18 25.0	72 100
70 +	4 12.5	12 37.5	9 28.1	7 21.9	32 100
TOT	78 20.0	123 31.5	121 31.0	68 17.4	390 100

Frequency Missing = 2

C.F. LVAD
implants by strategy and level



Courtesy of G. Feltrin

Early LVAD implantation: Why think about it?

- Awareness of poor prognosis after hospitalizations with need for inotropic therapy
- Consideration for signs of refractoriness not included in INTERMACS classification
- Avoid sum of risk factors in pts with comorbidities
- Expected improvement in postop- survival

Early LVAD implantation: When is it recommended?

- Expected increase in probability of postop-survival
- Expected increase in overall life expectancy
- Expected improvement in symptoms & QoL
- Expected prevention of irreversible pulmonary hypertension
- Expected prevention of irreversible end-organ damage

To allow HTX

- Expected prevention of irreversible right ventricular dysfunction

Before LVAD is precluded

2015, ROADMAP study: The new proof of concept?

Inclusion and Exclusion Criteria

- **Key Inclusion Criteria**
  - Meets FDA Approved DT Indication
    - NYHA Class IIIB or IV; Age 18 to 85
    - Left ventricular ejection fraction (LVEF) ≤ 25%
    - Not listed (or planned) for heart transplantation
    - On optimal medical management (OMM)
  - 6MWD < 300 meters
  - At least 1 hospitalization for HF in last 12 months, or 2 unscheduled ED or infusion clinic visits for HF in last 12 months
- **Key Exclusion Criteria**
  - Any inotrope use within 30 days
  - Inability to perform 6MWT
  - Any ongoing MCS (including IABP & temporary devices) at enrollment
  - CRT or coronary revascularization within 3 months

Rogers JG et al: ROADMAP Trial Design: Am Heart J. 2015 Feb;169(2):205-210

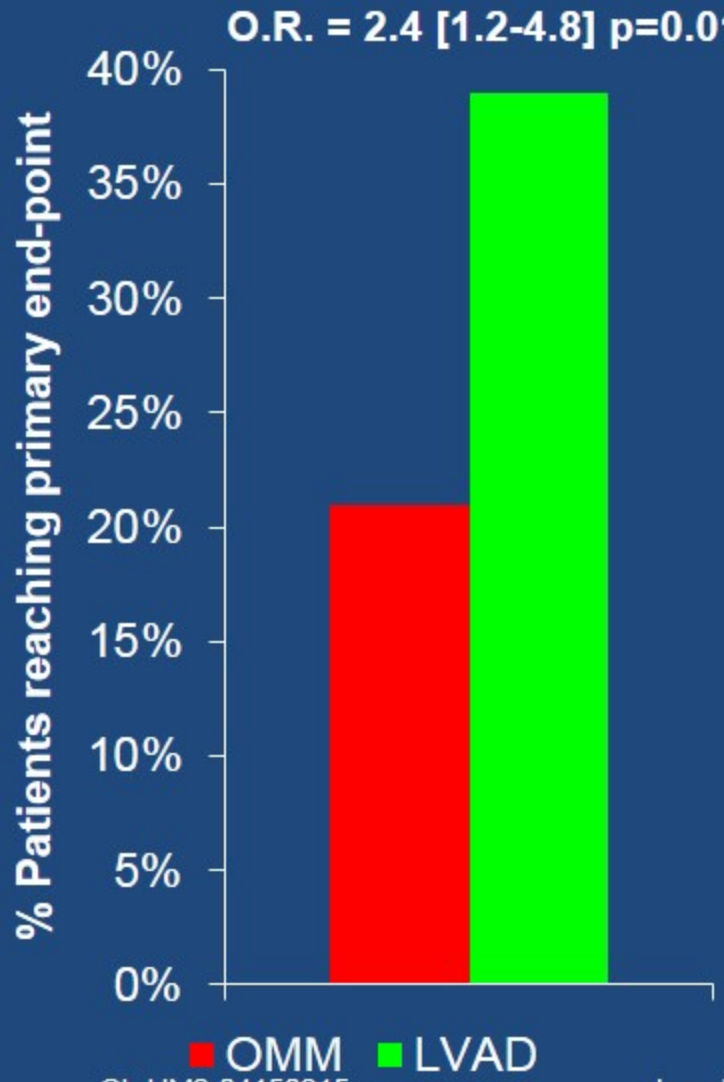
Baseline Data

Parameter[1]		OMM (n=103)	LVAD (n=97)	P
NYHA[2]	Class IIIB (%)	77 (75%)	47 (48%)	<0.001
	Class IV (%)	26 (25%)	50 (52%)	
INTERMACS[2]	Profile 4 (%)	35 (34%)	63 (65%)	<0.001
	Profile 5 (%)	29 (28%)	21 (22%)	
	Profile 6 (%)	35 (34%)	10 (10%)	
	Profile 7 (%)	2 (2%)	0 (0%)	
6MWD (m)		219 [157-269] (n=103)	182 [122-259] (n=97)	0.057
VO2, RER≥1.1		10.9 [9.6-12.7] (n=23)	10.2 [8.8-11.3] (n=27)	0.131
EQ5D VAS[3]		55 [45-75] (n=99)	50 [30-60] (n=93)	<0.001
PHQ-9[4]		7 [3-10] (n=101)	10 [6-15] (n=96)	<0.001
SHFM predicted 1 yr survival		84 [73-91] %	78 [63-89] %	0.012
HMRS Score		1.16 [0.57-1.94] (n=88)	1.40 [0.93-1.81] (n=93)	0.312

[1]Median [IQR]
[2]As determined at the site by an advanced practice practitioner other than principal investigator
[3]VAS score 0 -100 = worst to best health, 41 = mean VAS in DT post approval study (Jorde UP et al JACC 2014)
[4]PHQ-9 score 5-9 = mild depression, 10-14 = moderate depression

Primary Endpoint

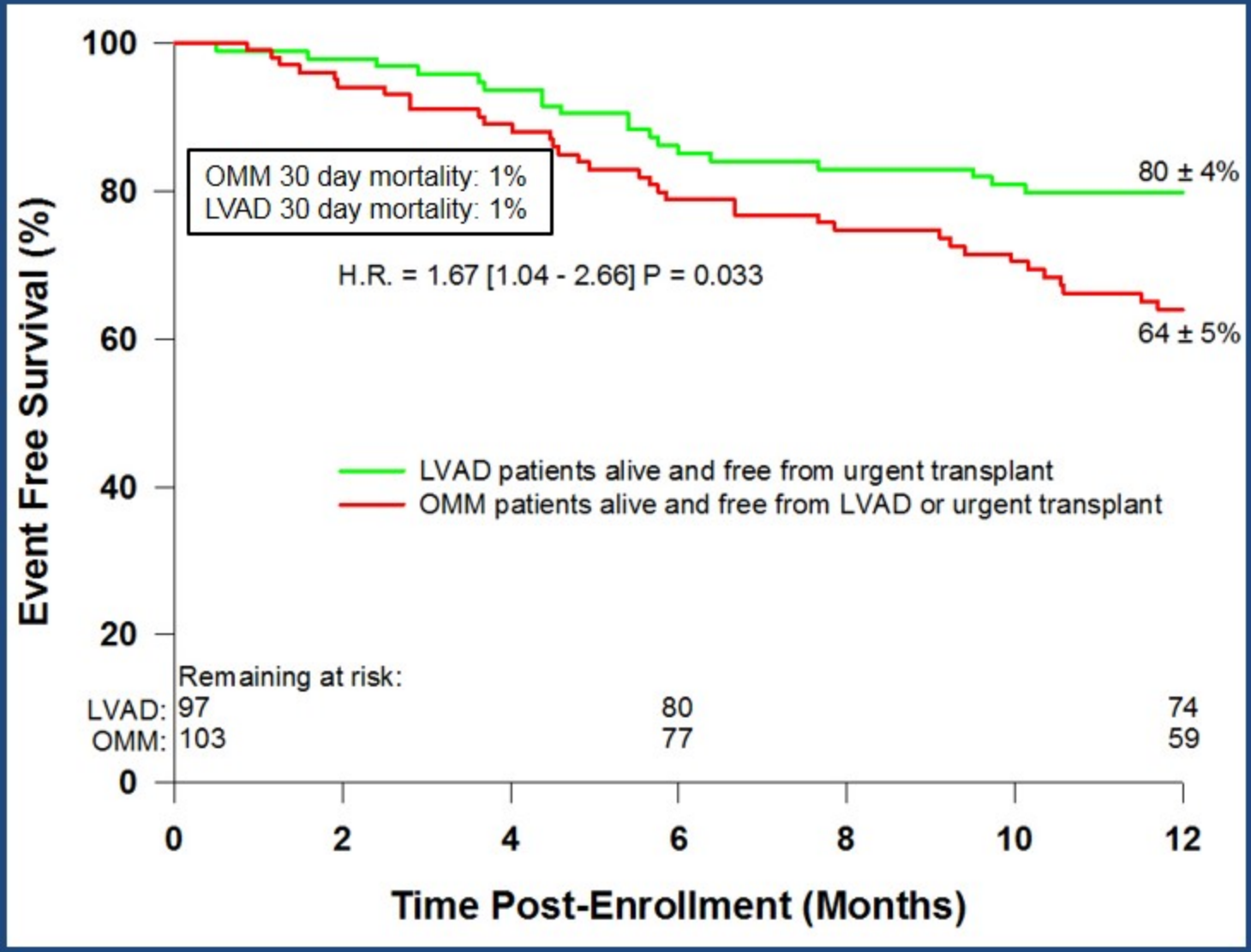
Alive at 12 months on original therapy with increase in 6MWD by 75m



End Point	OMM (n=81)[1]	LVAD (n=85)[2]
Alive at 12 months on original therapy with increase in 6MWD by 75m	17 (21%)	33 (39%)
		P=0.017
First event that prevented success:	N=64 (79%)	N=52 (61%)
Death within 1 year	17 (21%)	17 (20%)
Delayed LVAD	18 (22%)[3]	NA
Delta 6MWT<75m	29 (36%)	33 (39%)
Urgent Tx	0 (0%)	2 (2%)

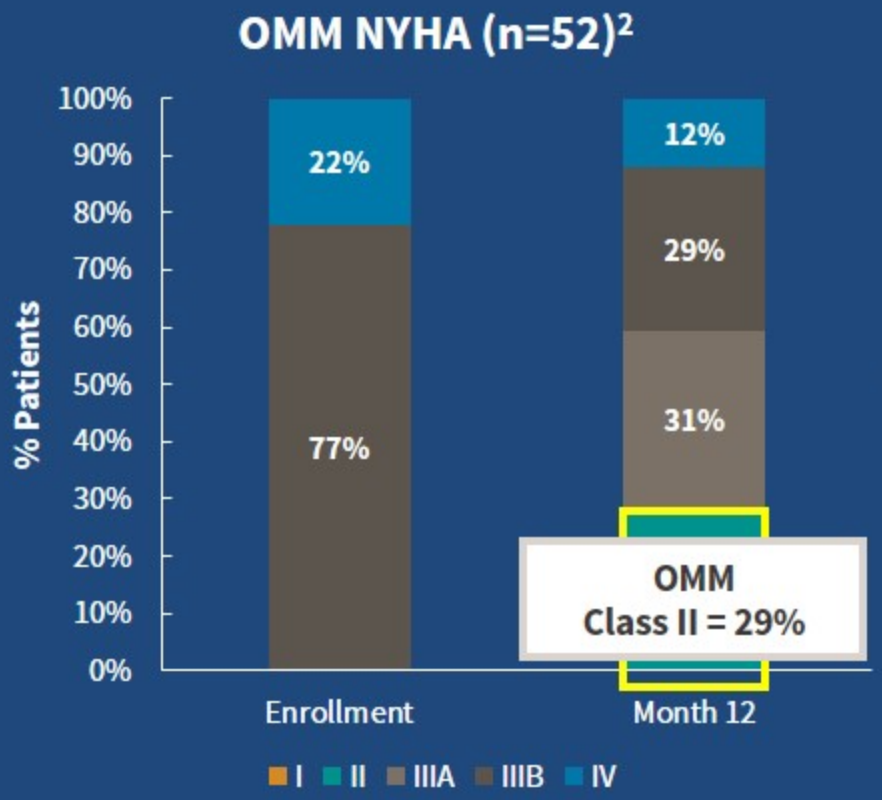
[1]Excluded OMM patients: 9 withdrawn, 13 missing 6MWD
[2]Excluded LVAD patients: 3 withdrawn, 8 missing 6MWD, 1 elective HTx
[3]Including 1 TAH

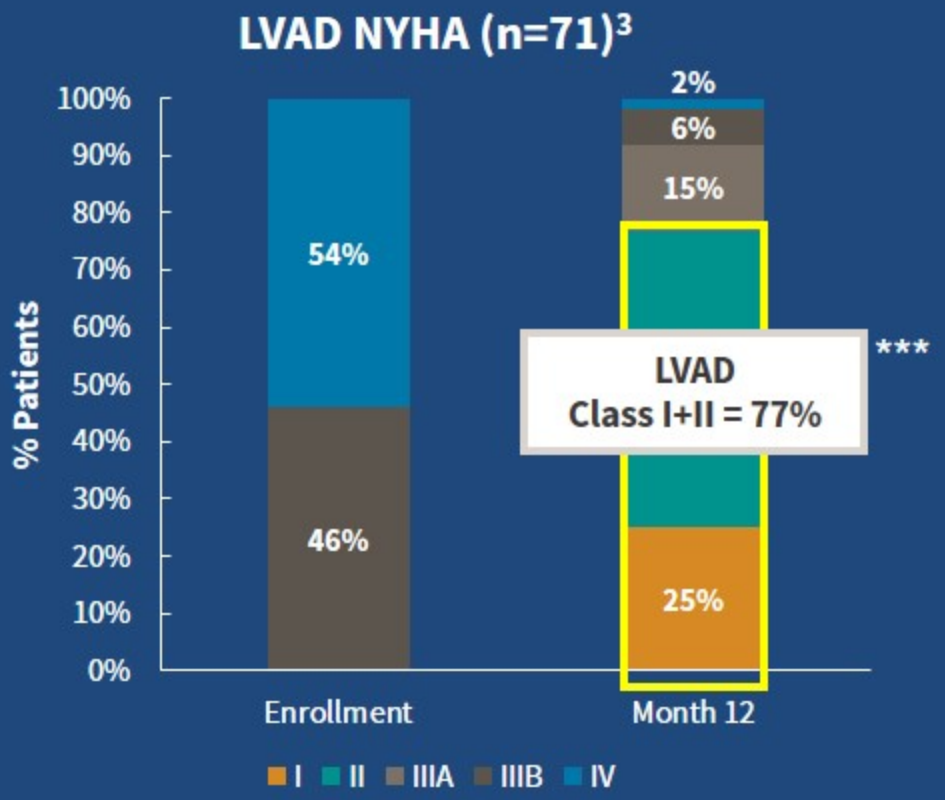
Survival As-Treated on Original Therapy



Changes in NYHA Classification[1]

1 Year Survivors on Original Therapy





[1]As determined at the site by an advanced practice practitioner other than principal investigator
[2]Excluded OMM patients: 7 missing NYHA classification
[3]Excluded LVAD patients: 3 missing NYHA classification
***P<0.001 LVAD vs. OMM

GL-HM2-04150215

Jerry D. Estep, MD – Presented on April 17

ROADMAP Clinical Study

Adverse Events

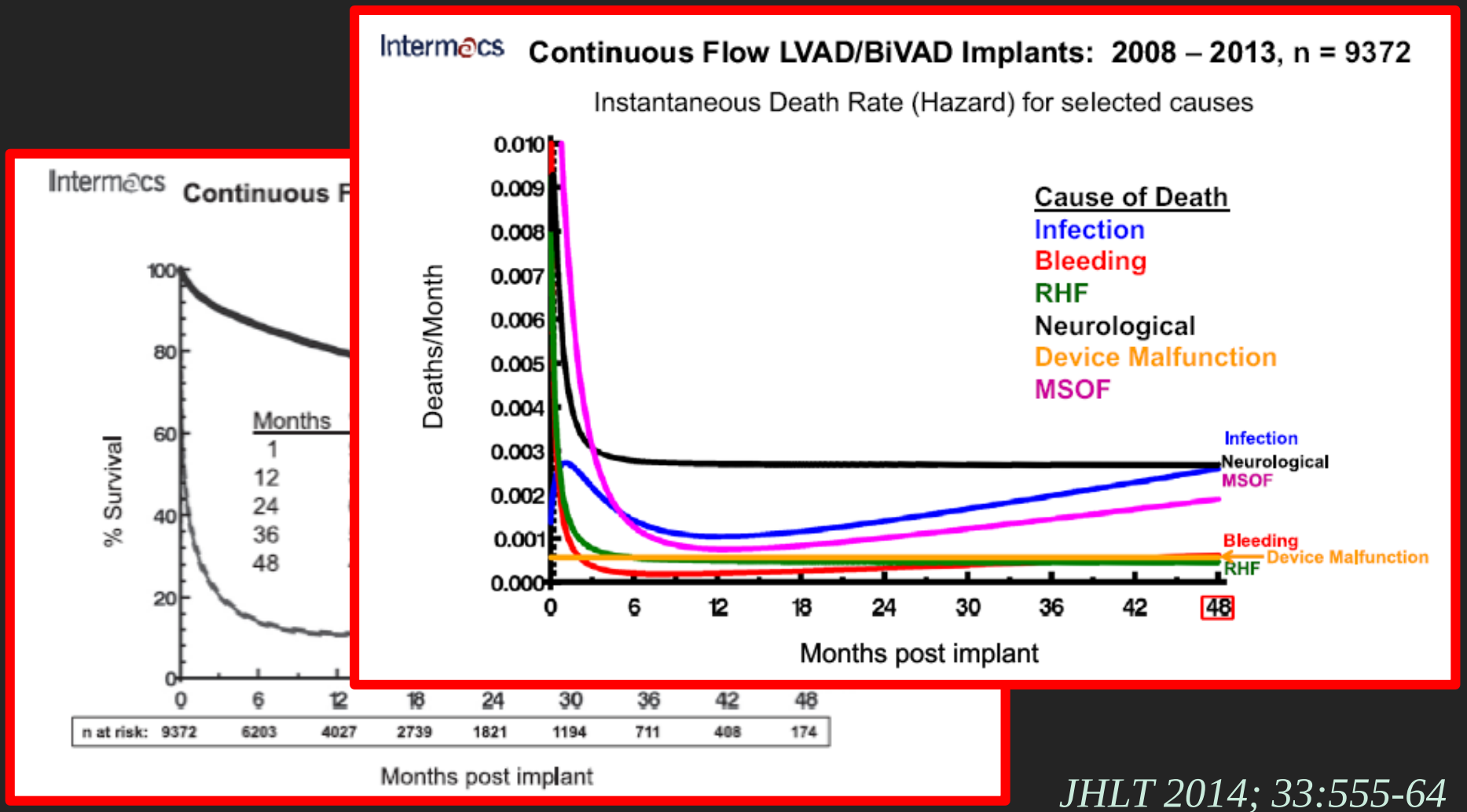
Prevalence:% of patients within 12 months; Incidence: events/pt-yr (eppy) on all data

Adverse Event	OMM (n=103) pts (%) (eppy)	LVAD (n=94) pts (%) (eppy)	DT Trial as reference (eppy) (Park et al)[1]
Bleeding GI bleeding	1 (1%) (0.02) 1 (1%) (0.02)	44 (47%) (1.22) *** 29[2] (31%) (0.76) ***	1.13 NA
Driveline Infection	NA	9 (9.6%) (0.14) ***	0.22
Pump Thrombus Within 90 days Pump replacement year 1	NA	6 (6.4%) (0.08) ** 1 (1.1%) 4 (4.3%)	0.07[3] 2.1%
Stroke Ischemic Hemorrhagic	2 (2%) (0.02) 1 (1%) (0.01) 1 (1%) (0.01)	9 (9.6%) (0.10) * 5 (5.3%) (0.06) * 5 (5.3%) (0.04) ns	0.08 0.05 0.03
Arrhythmias VT/VF	6 (5.8%) (0.12)	17 (18.1%) (0.23) ***	0.46
Worsening Heart Failure[5]	36 (35%) (0.68)	10 (10.6%) (0.12) *	NA
Re-hospitalizations	64 (62%) (1.42)	75 (79.8%) (2.49) ***	2.64[4]
"Composite" event rate[6]	39 (38%) (0.83)	62 (66%) (1.89) ***	2.09
Relative Risk [95% CI]	OMM/LVAD: 0.44 [0.34, 0.55] ***		

[1] Park et al, Circ Heart Failure 2012; 5:241-248
[2] Four patients had 50% of all GI bleeding events
[3] thrombus + hemolysis
[4] Slaughter et al NEJM 2009;361:2241-51
[5] Worsening HF: Symptoms resulting in unexpected hospitalization, ER visit, or urgent clinic visit requiring IV therapy for HF
[6] sum of bleeding, infection, thrombus, stroke, arrhythmias, and worsening HF

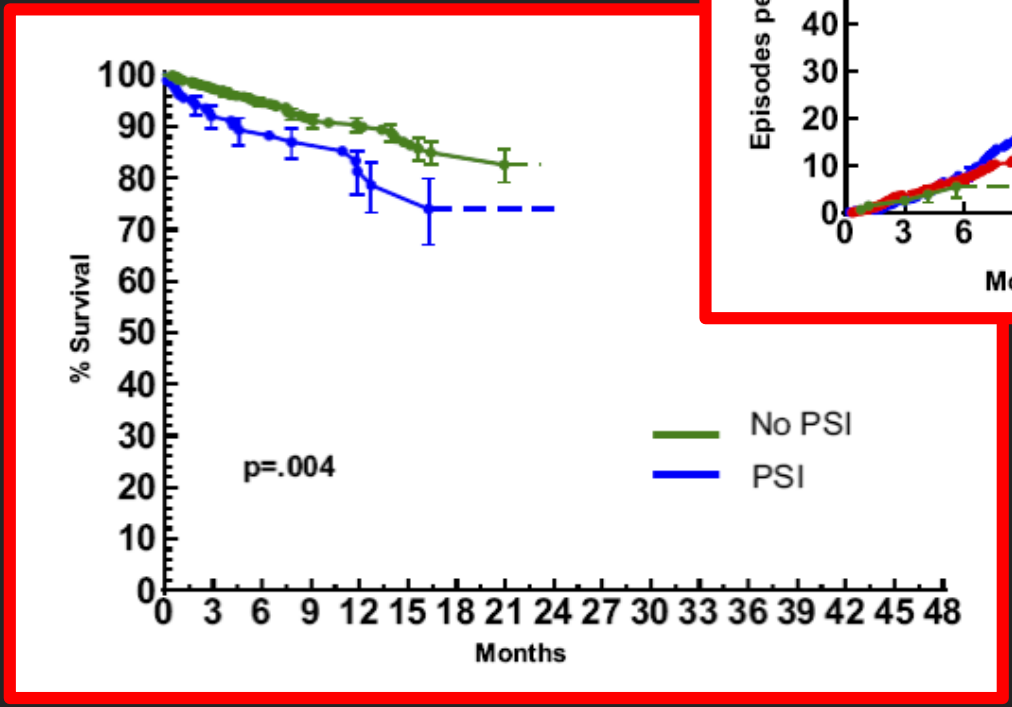
*p<0.05 , **p<0.01, ***p<0.001

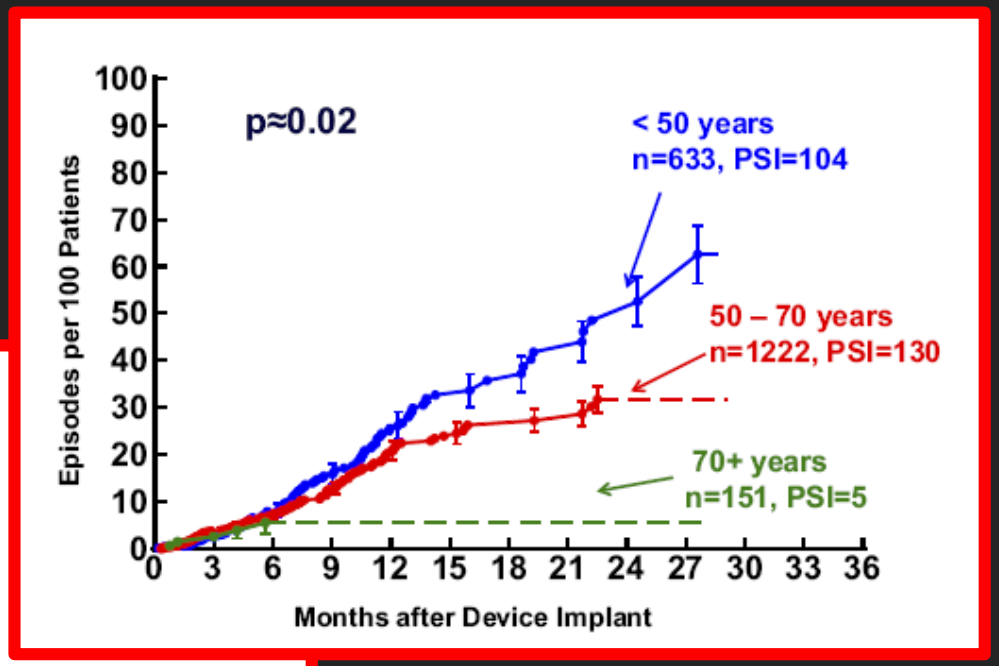
LVAD pts are permanently exposed to specific risks



JHLT 2014; 33:555-64

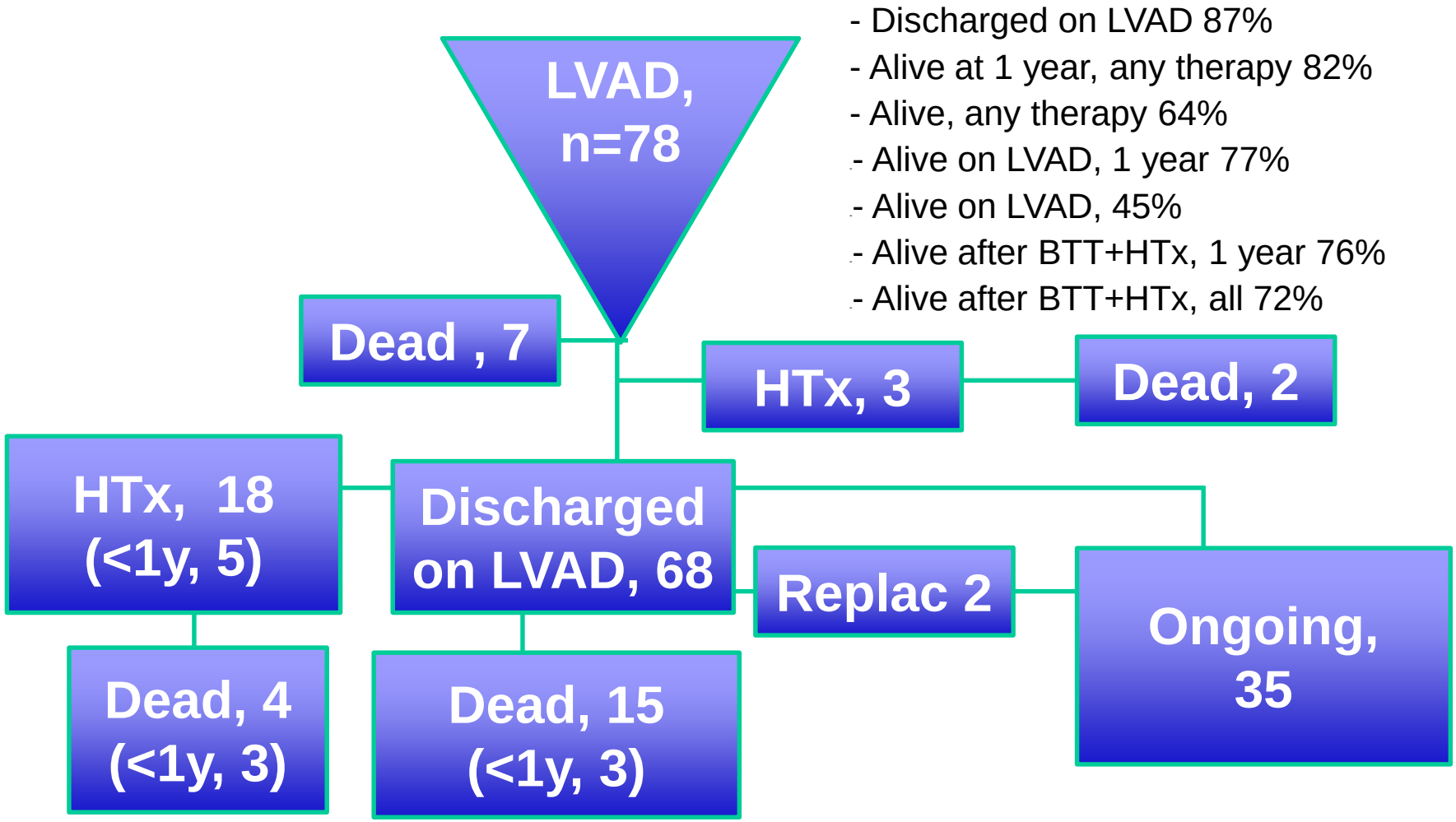
Infections: Incidence & Outcome





JHLT 2012; 31:1151-7

Niguarda LVAD patients- 2010 -15



LVAD Indication & Timing: The new paradigm