Lessons learned from ENDURANCE, ROADMAP, MedaMACS, and how to go forward?

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What could you learn from “Roadmap”

1) Thromb Res. 2016 Apr;140 Suppl 1:S196. doi: 10.1016/S0049-3848(16)30186-4. Epub 2016 Apr 8.

PO-53 - Prospective evaluation of risk assessment models and biological markers of hypercoagulability for the identification of high VTE risk patients with lung adenocarcinoma. The ROADMAP study.

2) Sex Dev. 2016;10(2):59-65. doi: 10.1159/000445398. Epub 2016 Apr 15.

Using ROADMAP Data to Identify Enhancers Associated with Disorders of Sex Development.

3) PDA J Pharm Sci Technol. 2016 May-Jun;70(3):282-92. doi: 10.5731/pdajpst.2015.006395. Epub 2016 Mar 28.

A Roadmap for the Implementation of Continued Process Verification.

4) Astrobiology. 2016 Mar;16(3):201-43. doi: 10.1089/ast.2015.1441.

AstRoMap European Astrobiology Roadmap.

5) JMIR Med Inform. 2016 May 19;4(2):e16. doi: 10.2196/medinform.4553.

Putting Meaning into Meaningful Use: A Roadmap to Successful Integration of Evidence at the Point of Care.

6) J Am Coll Cardiol. 2015 Oct 20;66(16):1747-61. doi: 10.1016/j.jacc.2015.07.075.

Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients: Results From the ROADMAP Study.

What could you learn from “Roadmap”

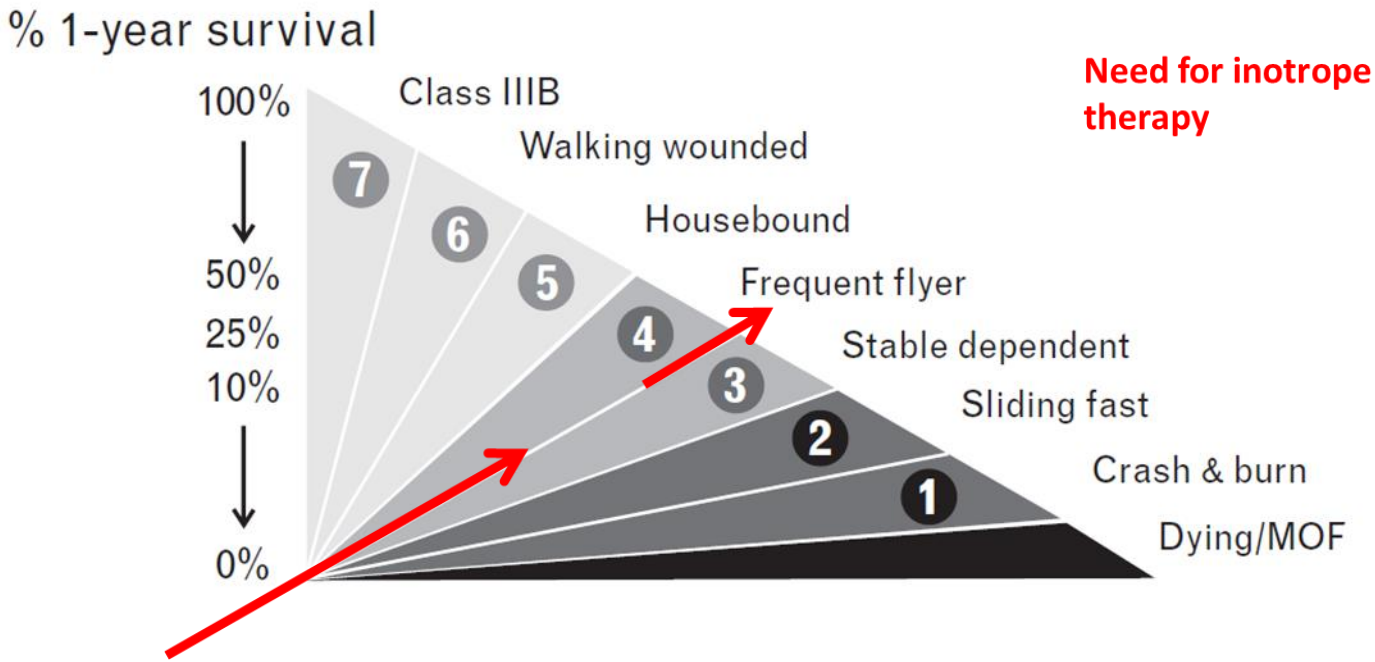
1)Depends on what scientific meeting I was attending

2)“Roadmap” was a real stretch from the actual words that described the trial

Risk Assessment and Comparative Effectiveness **o**f Left Ventricular **A**ssist **D**evice and **M**edical Management in **A**mbulatory Heart Failure **P**atients

3)As an acronym, it did not help them distinguish a potentially important heart failure trial from cancer, meaningful use, astronomy or just about anything else!

INTERMACS Patient Profiles

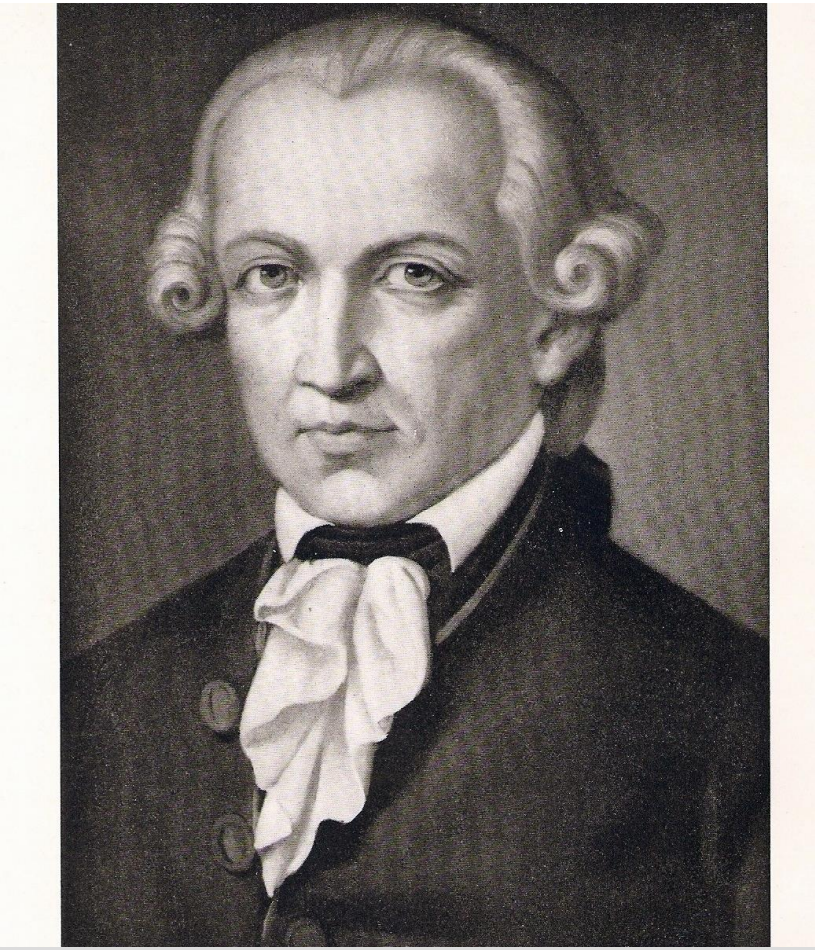


Need for inotrope therapy

Intermacs level	Survival	VAD benefit
5–7	Months to years	Not established
3–4	Weeks to months	Yes
1–2	Hours to weeks	Yes
MOF	Hours to days	Bridge to decision in selected cases

How to go forward?

Immanuel Kant
1724-1804

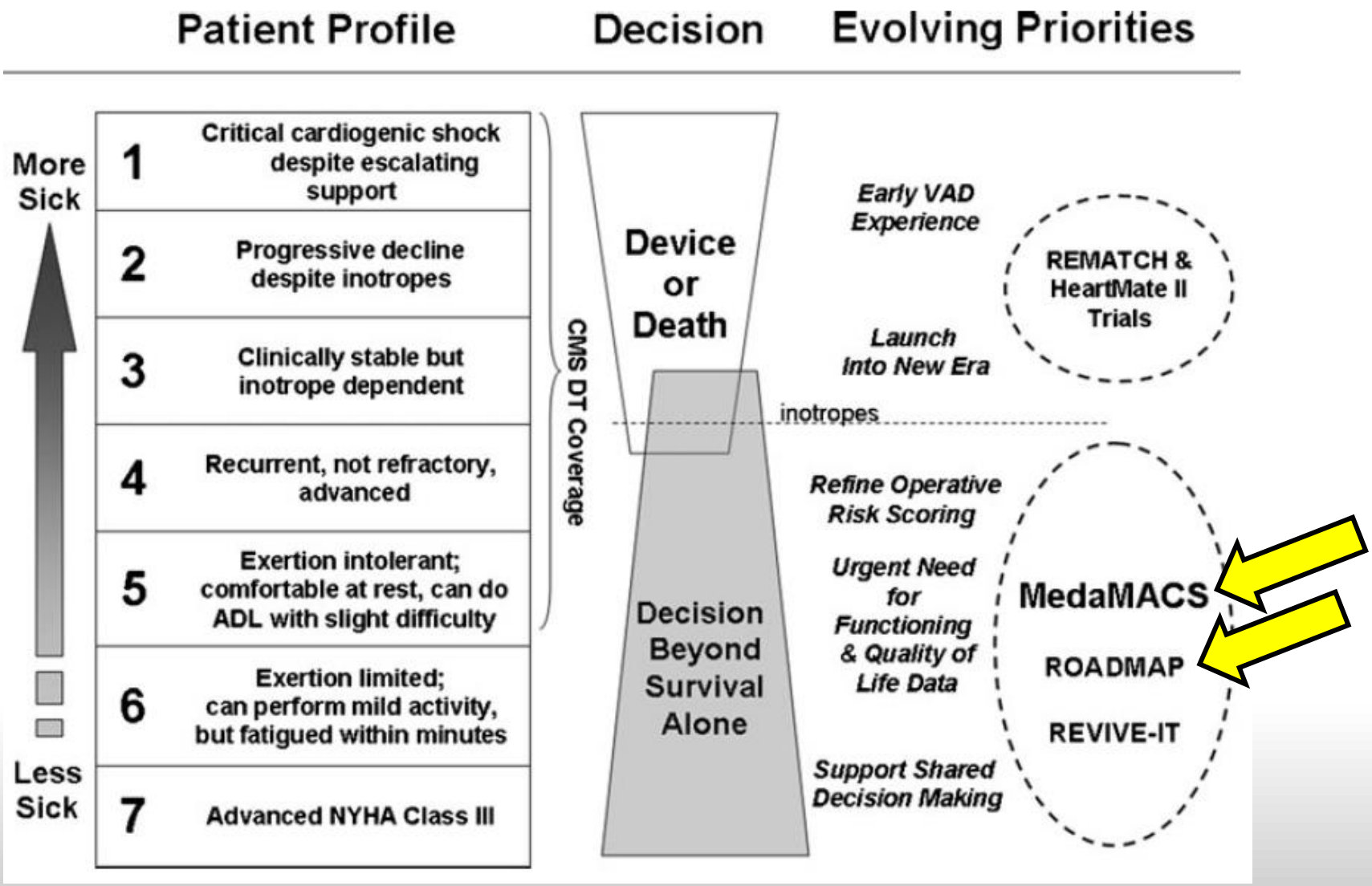


The Principle Question of Propagation

“Every answer given on a principle of experience begets a fresh question”

“Experience without theory is blind, but theory without experience is mere intellectual play.”

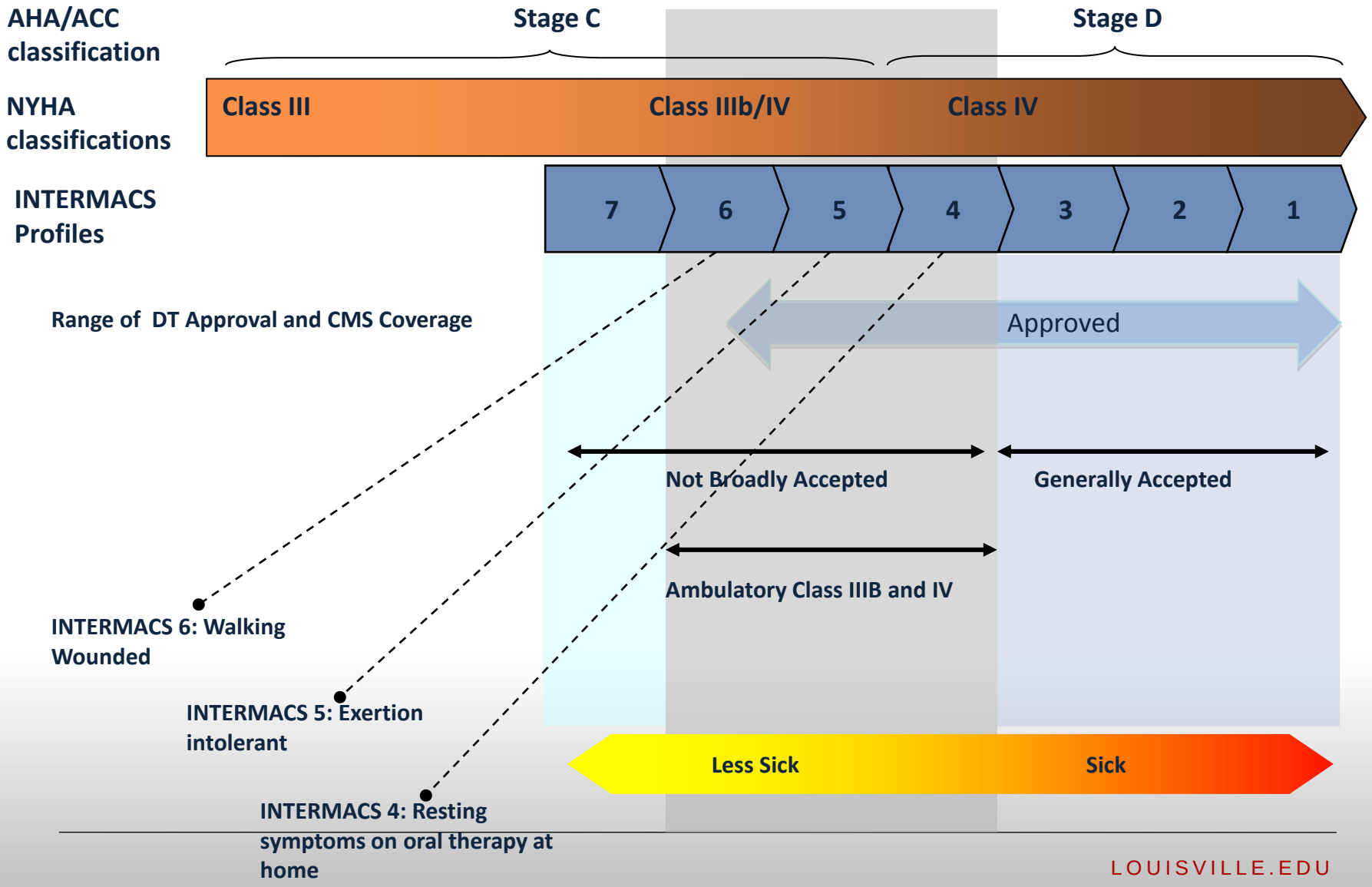
Overview



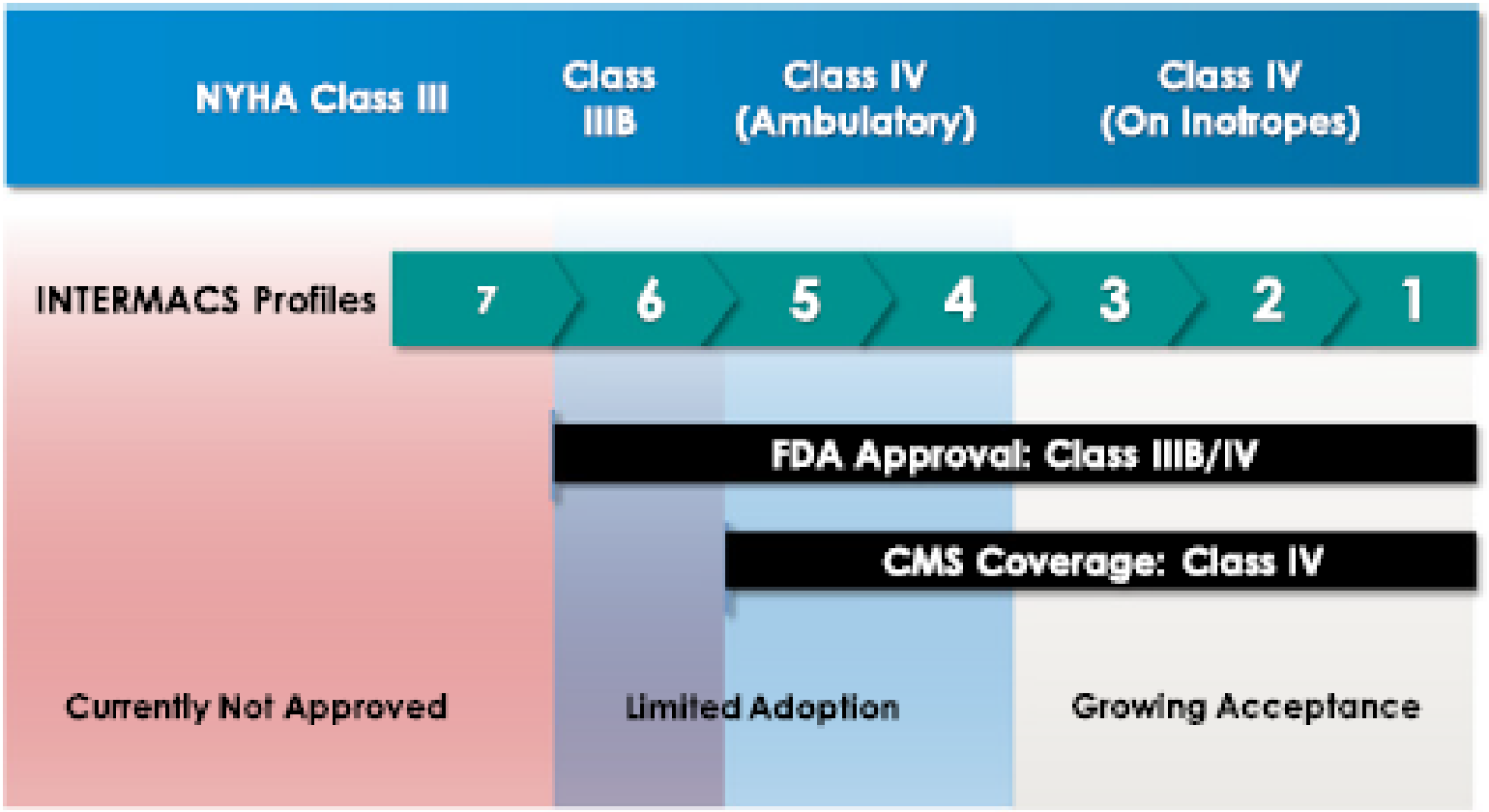
Stewart GC et al. Curr Cardiol Rep. 2013 Sep;15(9):394.

Assessing Heart Failure Prognosis

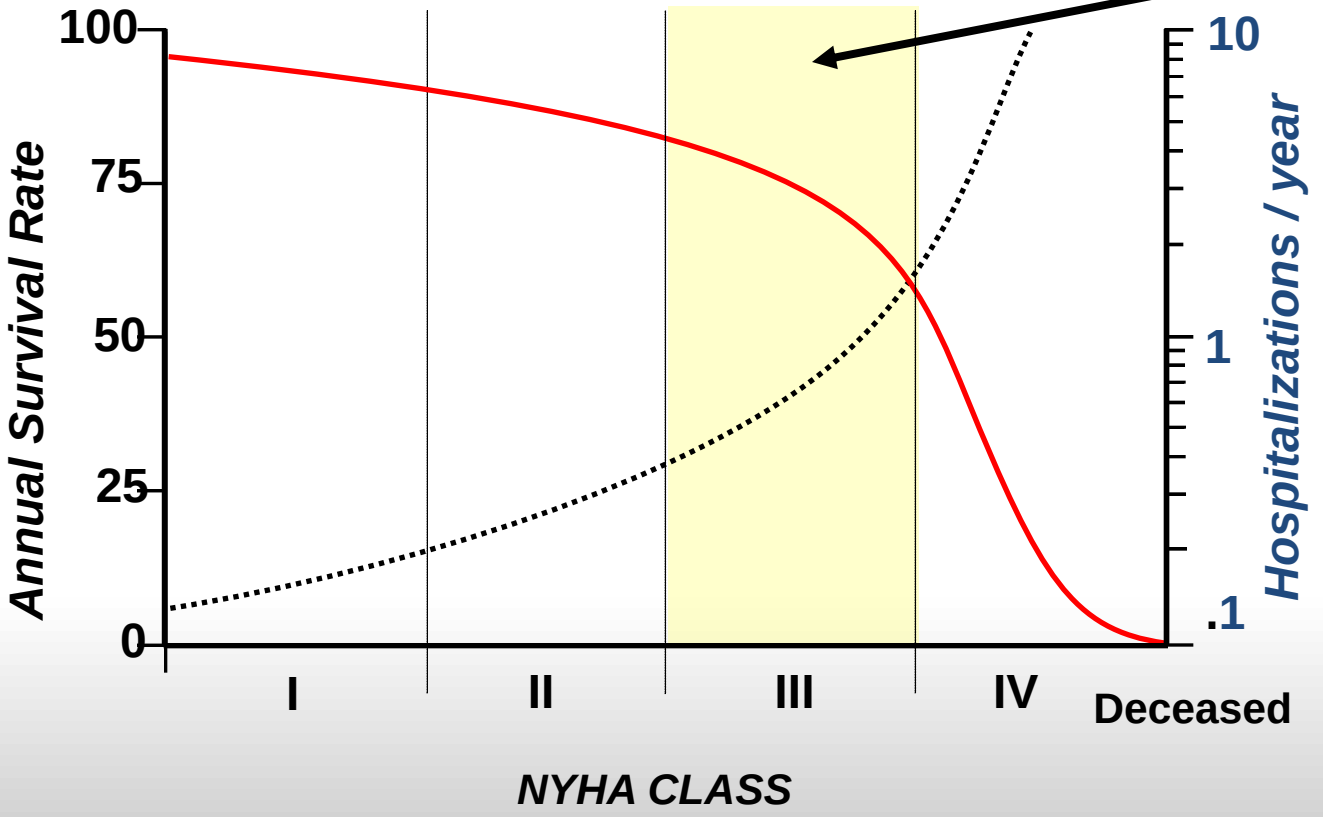
intermacs



Overlay of NYHA Class, INTERMACS Profile, FDA Approval and CMS Coverage for HeartMate II



Natural History of Heart Failure



Class III

- 25% of HF Patients
- Frequent hospitalizations
- Worsening symptoms despite drug therapy
- Significant opportunity for new therapies

Survival Rate
Hospitalizations

Adapted from Bristow, MR Management of Heart Failure, Heart Disease: A Textbook of Cardiovascular Medicine, 6th edition, ed. Braunwald et al.

High-risk VAD patients

INTERMACS 1 Classification

Table 3 CF LVAD/BiVAD Implants: April 2008 to December 2014 (n = 12,030)

	Implant date era					
	2008 to 2011		2012 to 2014		Total	
Patient profile at time of implant	*N*	%	*N*	%	*N*	%
1—Critical cardiogenic shock	465	16.0%	961	14.3%	1,803	15.0%
2—Progressive decline	1,249	43.0%	2,416	36.0%	4,507	37.5%
3—Stable but inotrope-dependent	660	22.7%	1,987	29.6%	3,471	28.8%
4—Resting symptoms	372	12.8%	968	14.5%	1,646	13.7%
5—Exertion-intolerant	83	2.9%	198	3.0%	331	2.7%
6—Exertion-limited	48	1.6%	81	1.2%	141	1.2%
7—Advanced NYHA Class III	29	1.0%	44	0.7%	76	0.6%
Not specified[a]	0	0%	46	0.7%	55	0.5%
Totals	2,906	100%	6,701	100%	12,030	100%

CF, continuous flow; NYHA, New York Heart Association.
[a]Due to change in web-based data entry capture in Protocol v3.0 (May 2012).

7th INTERMACS annual report

Kirklin JK et al. JHLT. 2015 Dec;34(12):1495-504.

Table 1. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Levels[8]

Level[a]	Hemodynamic status
1 "Crash and burn"	Persistent hypotension despite rapidly escalating inotropic support and eventually IABP, and critical organ hypoperfusion.
2 "Sliding on inotropes"	Intravenous inotropic support with acceptable values of blood pressure and continuing deterioration in nutrition, renal function, or fluid retention.
3 "Dependent stability"	Stability reached with mild to moderate doses of inotropes but demonstrating failure to wean from them due to hypotension, worsening symptoms, or progressive renal dysfunction.
4 "Frequent flyer"	Possible weaning of inotropes but experiencing recurrent relapses, usually fluid retention.
5 "Housebound"	Severe limited tolerance for activity: comfortable at rest with some volume overload and often with some renal dysfunction.
6 "Walking wounded"	Less severe limited tolerance for activity and lack of volume overload. Fatigue easily.
7 "Placeholder"	Patient without current or recent unstable fluid balance. NYHA class II or III.

Alba AC et al. J Heart Lung Transplant. 2009 Aug;28(8):827-33.

Usefulness of the INTERMACS Scale to Predict Outcomes After Mechanical Assist Device Implantation

Ana C. Alba, MD,[a] Vivek Rao, MD, PhD,[b] Joan Ivanov, PhD,[b] Heather J. Ross, MD, MHSc,[a] and Diego H. Delgado, MD, MSc[a]

- This study assessed the usefulness of the INTERMACS scale to predict outcomes in advanced heart failure patients undergoing MCS.
- 54 patients underwent MCS implantation from 2001-2007. Group A included 27 patients at INTERMACS level 1 and 2. Group B included 27 at INTERMACS level 3 and 4. Patient characteristics pre-MCS implant, incidence of complications during support, and survival between groups were compared.
- Before MCS implantation, Group A had significantly lower CI, MAP, systolic PAP, higher CVP, and lower urine output ($p < .05$). After MCS, Group A had a lower incidence of infections and a higher incidence of liver injury. Mortality at 30 days was higher in Group A; however, the mortality after 30 days post-MCS support was significantly higher in Group B. Cox model showed overall survival was poorer in Group A.
- INTERMACS levels identified patients at risk for developing complications after MCS support. INTERMACS is a valid score system that should be considered as a tool to assess patient profile and predict complications and mortality after MCS implantation.

Alba AC et al. J Heart Lung Transplant. 2009 Aug;28(8):827-33.

Intermacs Continuous Flow LVAD/BiVAD Implants: 2008 – 2014, n=12030

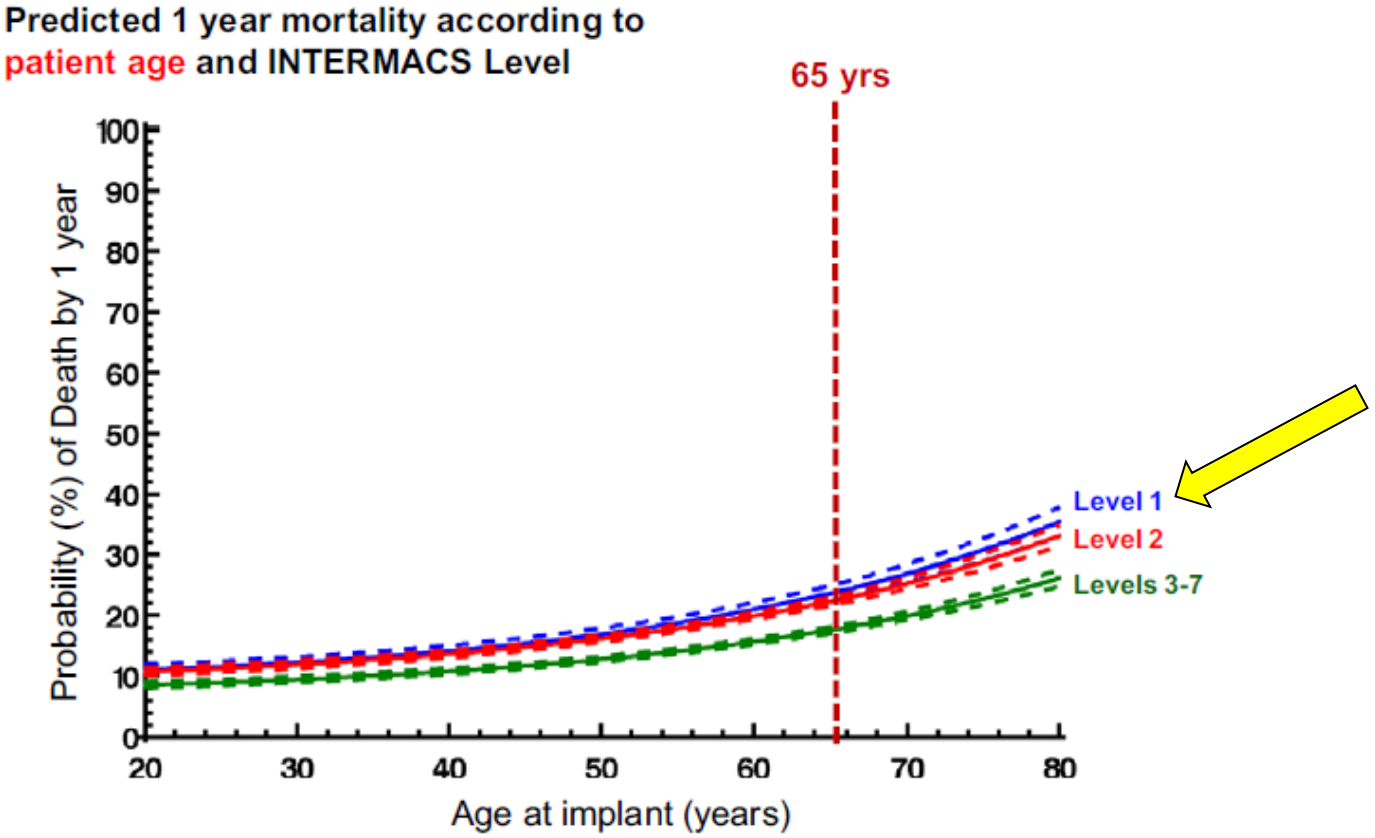


Figure 16 Nomogram depicting the solution to the multivariable equation for death by 1 year, depicting the interaction between patient age and INTERMACS level.

7th INTERMACS annual report

Kirklin JK et al. JHLT. 2015 Dec;34(12):1495-504.

Intermacs CF-LVAD/BiVAD Implants: January 2008 – December 2014, n=12030

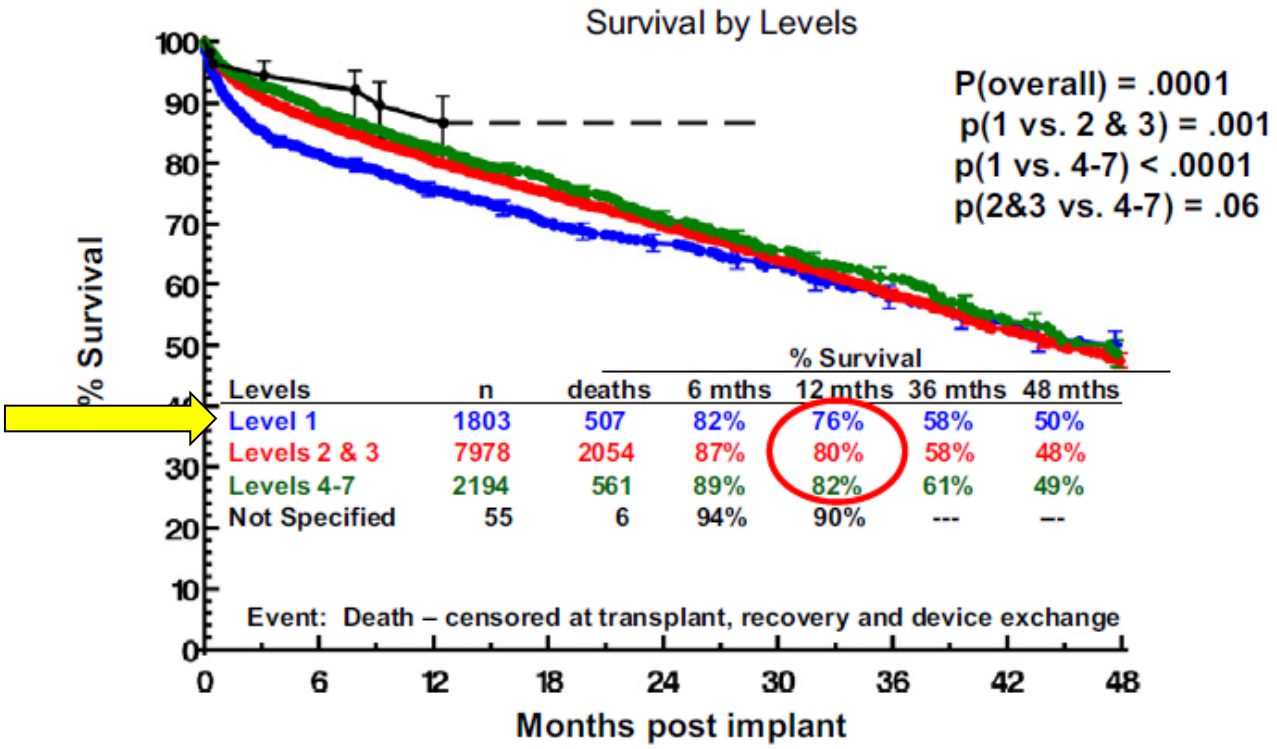


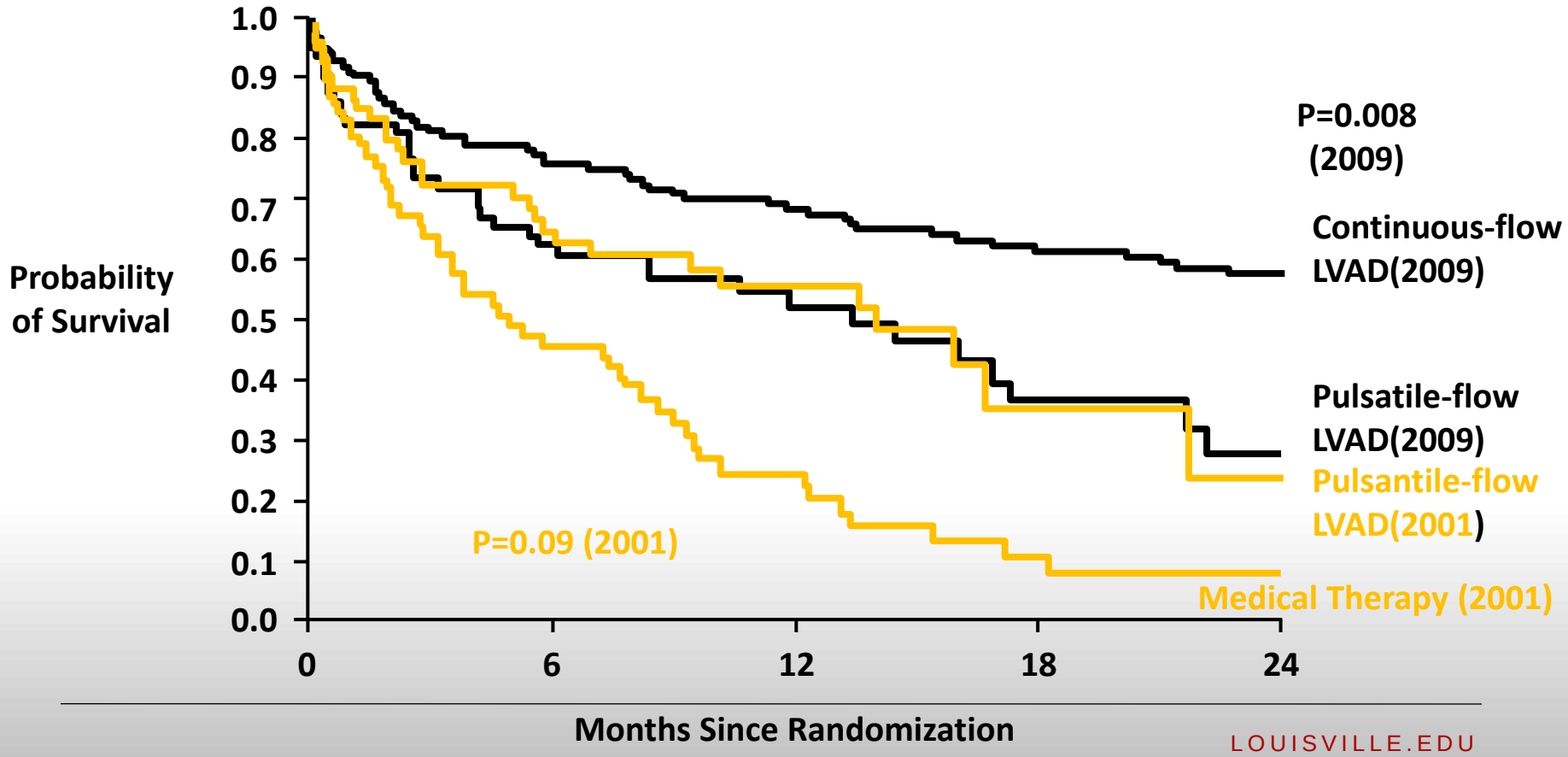
Figure 15 Actuarial survival after continuous-flow VAD implant, stratified by INTERMACS level at the time of implant. The depiction is as shown in Figure 6.

7th INTERMACS annual report

Kirklin JK et al. JHLT. 2015 Dec;34(12):1495-504.

Destination Therapy Trials

Survival Rates in Two Trials of Left Ventricular Assist Devices (LVADs) as Destination Therapy



Fang JC NEJM 2009

HeartMate II DT Trial

Exploring the Differences Between Class IIIB and IV Patients

	Class IIIB (n=160)	Class IV (n=407)	p
Mean Age (yrs)	63 ± 11	63 ± 12	0.87
Female (%)	16	25	0.02
Ischemic (%)	59	62	0.63
Treatment (%)			
Digoxin	55	42	0.006
Beta blocker	63	46	0.0003
CRT	62	61	0.85
Inotropic Therapy	68	81	0.002
IABP	10	25	<0.0001
Serum sodium (mmol/L)	135	135	0.31
Pre-albumin (mg/dl)	20.5	18.0	0.001
Creatinine (mg/dl)	1.5	1.5	0.84
Hct (%)	35.6	34.4	0.02
WBC (x10^3 /ml)	7.2	8.0	0.001

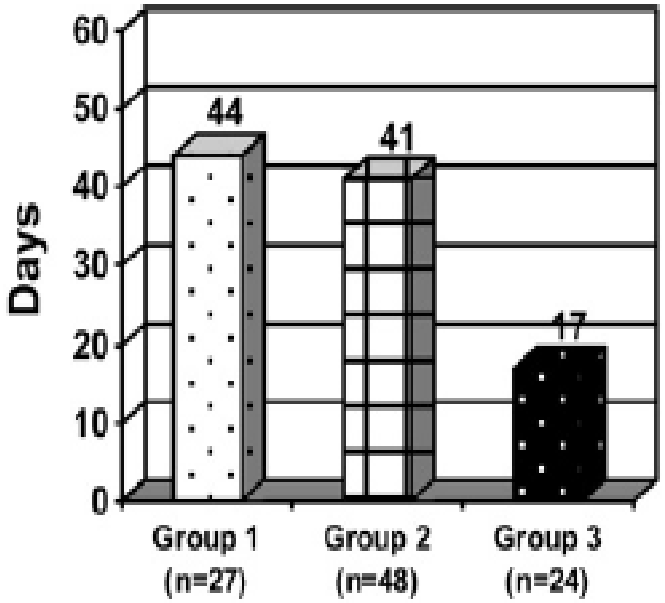
HeartMate II DT Trial

Exploring the Differences Between Class IIIB and IV Patients

Natural History of Heart Failure	
Patients Discharged on Support (%)	
Class IIIb	**96**
Class IV	**78**
Median days to Discharge	
Class IIIb	**23.5**
Class IV	**28.0**
Median Duration of Support (days)	
Class IIIb	**650**
Class IV	**570**

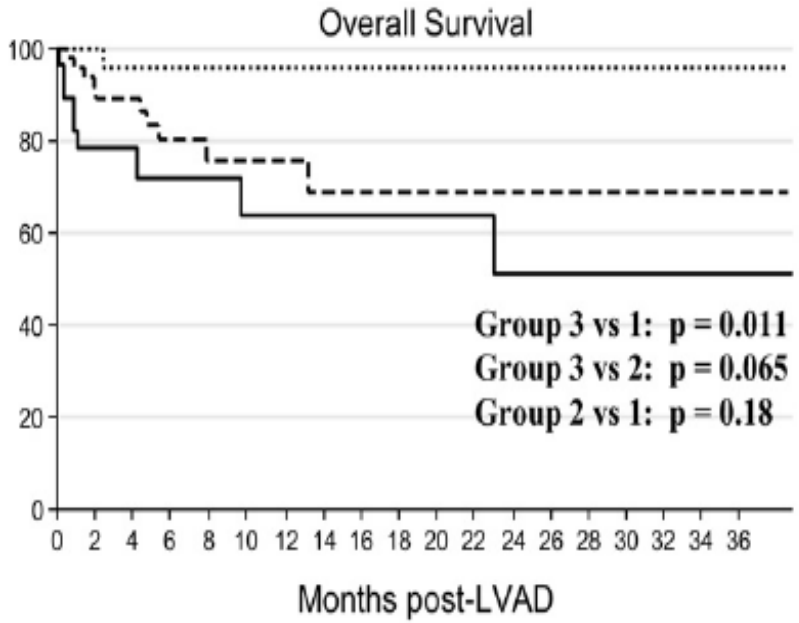
Clinical Outcomes Based on INTERMACS Profile

Length of Stay Post-VAD



Group 1: 1
Group 2: 2 or 3
Group 3: 4-7

Actuarial Survival Post-VAD



Less acutely ill, ambulatory patients in INTERMACS profiles 4-7 had better survival and reduced length of stay compared to patients who were more acutely ill in profiles 1-3.

Boyle, Ascheim, Russo, et.al. *JHLT*. 2011; 30:4,

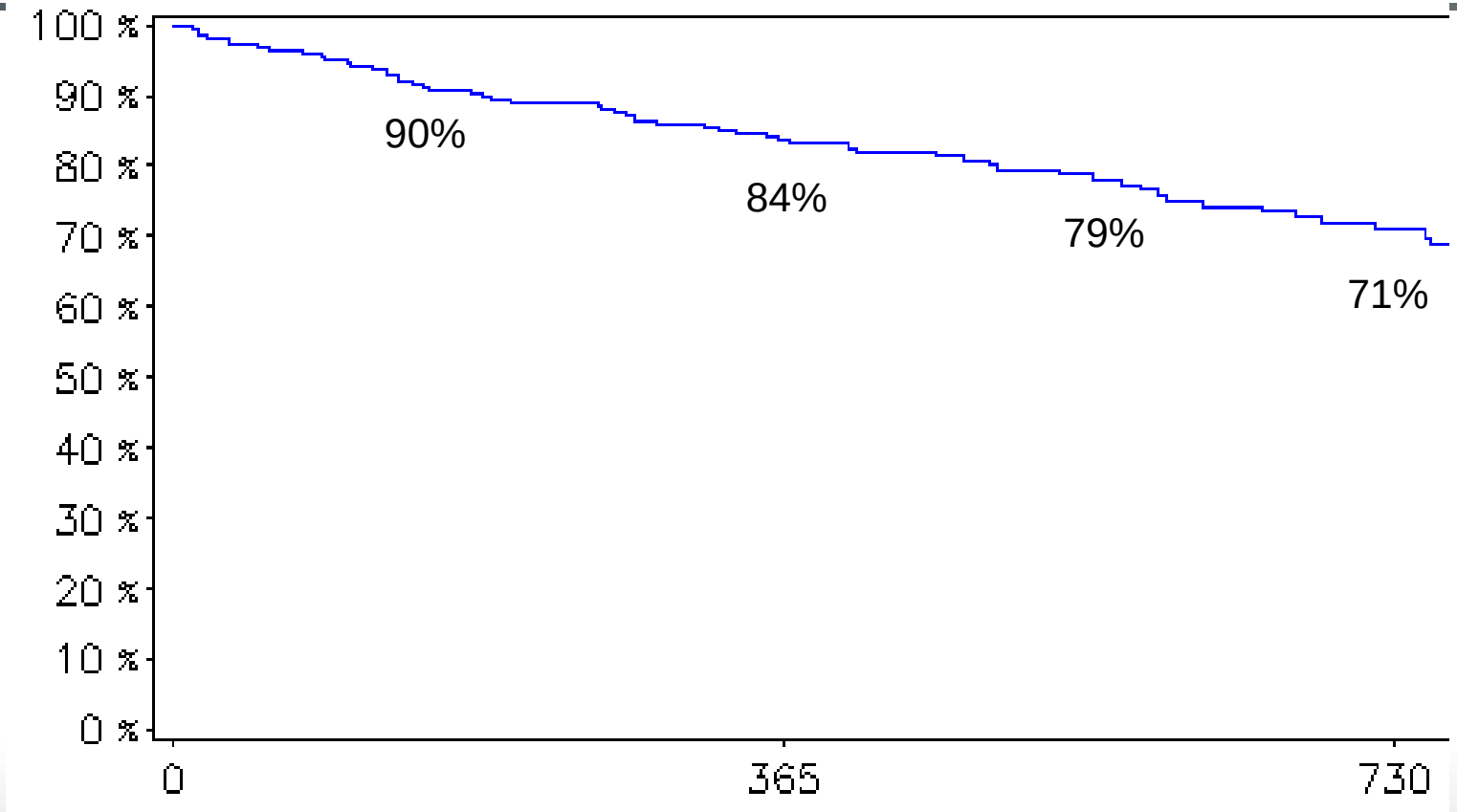
Long-term mechanical circulatory support (destination therapy): On track to compete with heart transplantation?

James K. Kirklin, MD,[a] David C. Naftel, PhD,[a] Francis D. Pagani, MD, PhD,[b] Robert L. Kormos, MD,[c] Lynne Stevenson, MD,[d] Marissa Miller, DVM, MPH,[e] and James B. Young, MD[f]

Conclusions: (1) Evolution from pulsatile to continuous flow technology has dramatically improved 1- and 2-year survivals; (2) DT is not appropriate for patients with rapid hemodynamic deterioration or severe right ventricular failure; (3) important subsets of patients with continuous flow DT now enjoy survival that is competitive with heart transplantation out to about 2 years. (J Thorac Cardiovasc Surg 2012;144:584-603)

1) Evolution from pulsatile to continuous flow technology has dramatically improved 1 and 2 year survivals
2) Important subsets of patients with continuous flow DT now enjoy survival that is competitive with heart transplantation out to 2 years

Kaplan Meier Survival in HVAD BTT+CAP Clinical Trial

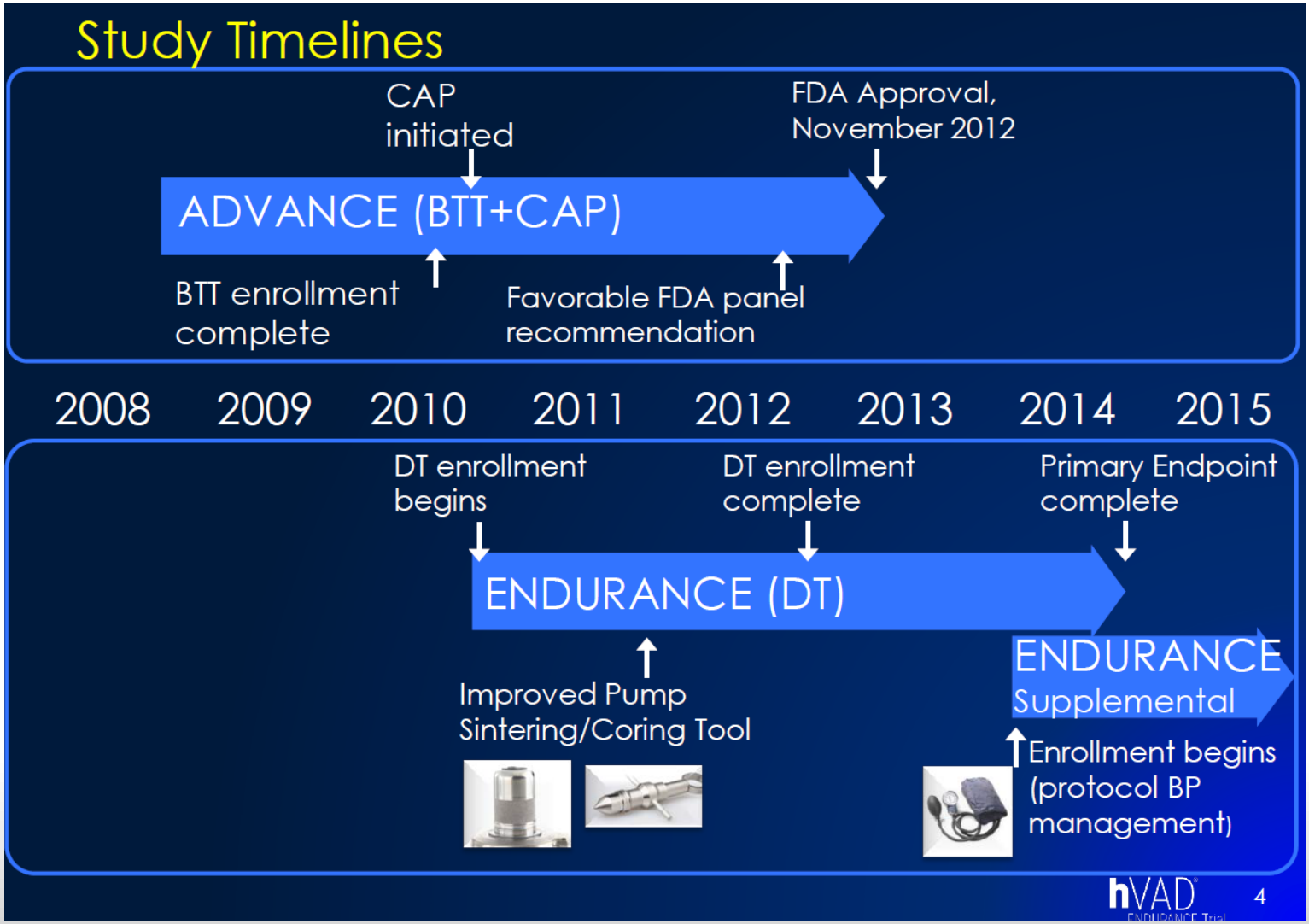


Month	0	2	4	6	8	10	12	18	24
Patient at risk	382	356	305	261	218	191	165	114	74
Survival	100%	97%	94%	90%	89%	86%	84%	79%	71%

What Do We Already Know?

1) VAD or transplant better than medical therapy in patients with advanced heart failure
2) VAD outcomes in BTT candidates equivalent to transplant out to about 3 yrs
3) VAD outcomes in DT equivalent to transplant in appropriate patients
4) NYHA Class IIIB is the same as IV (i.e IV is IV)
5) Long term outcomes limited by:
    - Medical Therapy: PHT, renal dysfunction, right heart failure
    - Transplant: rejection, infection, CAV, malignancy
    - VAD: bleeding/thrombosis, infection, stroke

ENDURANCE Trial



Pagani FD et al. Presented at the ISHLT 35th Annual Meeting and Scientific Sessions, April 15-18, 2015, Nice, France

ENDURANCE Trial

Determine safety and effectiveness of the HeartWare Ventricular Assist System in patients with chronic Stage D/NYHA Class IIIB/IV HF who have received and failed optimal medical therapy and who are ineligible for heart transplant.

Two LVADs in this study:

- HeartWare HVAD – investigational

- HeartMate II - approved by the FDA for use in patients who cannot receive a heart transplant as well as patients waiting for transplant

https://clinicaltrials.gov/ct2/show/NCT01166347

ENDURANCE Trial

Primary Outcome

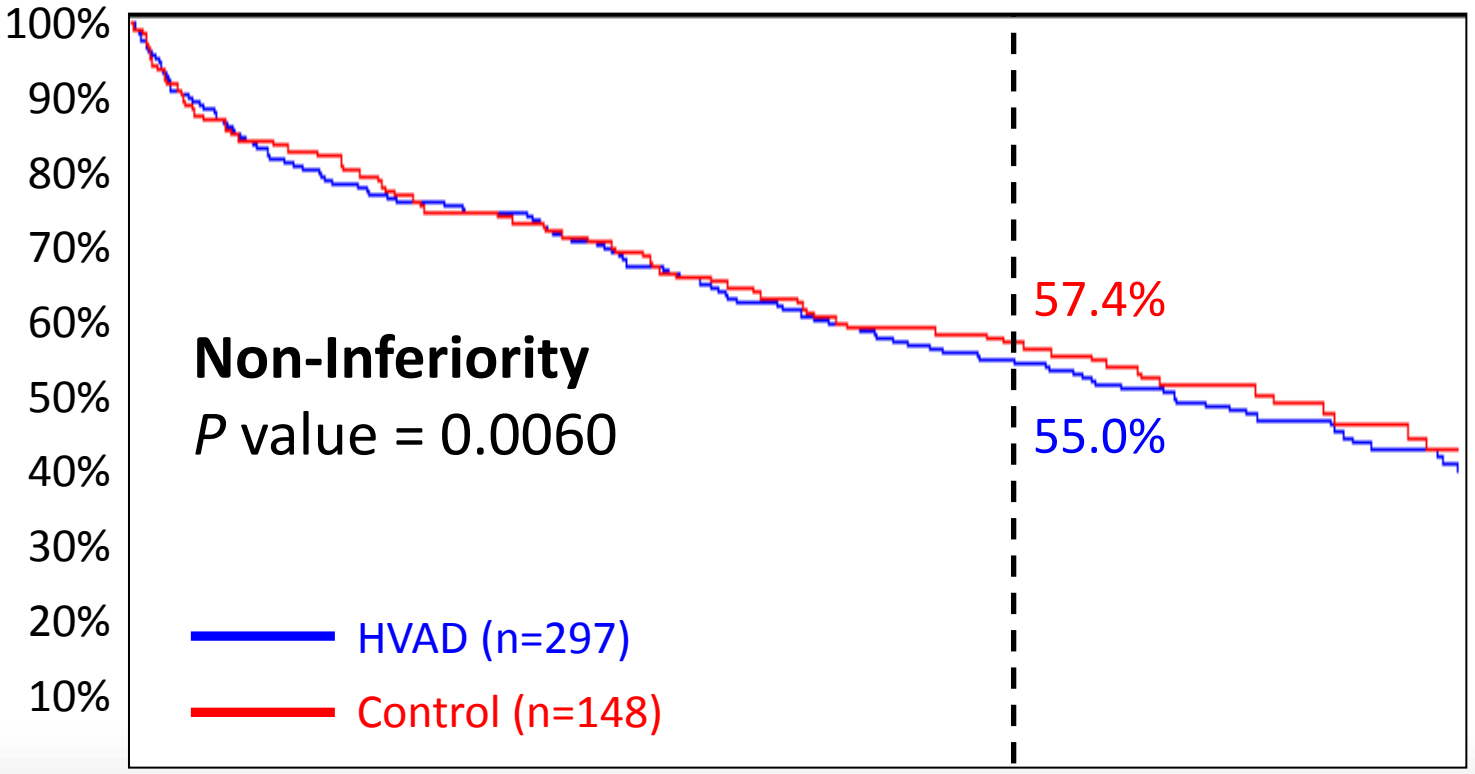
- Stroke-free survival at two years

Secondary Outcomes

- At two years, incidence of bleeding, incidence of major infection, incidence of device failures and device malfunctions, time to death, health status improvements measured by KCCQ and EuroQol EQ-5D), and functional status improvement measured by (NYHA)class and 6-minute walk test.

https://clinicaltrials.gov/ct2/show/NCT01166347

Primary Endpoint - Achieved



Days	0	365	730	1095
HVAD	297	210	156	33
Control	148	106	80	19

ENDURANCE Trial

August 2010 to May 2012
446 patients were enrolled at 48 U.S. hospital centers

- Early results suggested higher adverse neurological events among HeartWare patients in ENDURANCE.
- FDA asked to see interim results as part of its review.
- Interim results indicated a higher rate of ischemic and hemorrhagic strokes for the HeartWare device (6.7% and 5.1% respectively) as compared with the control LVAD (rates of 4.3% and 0%, respectively).

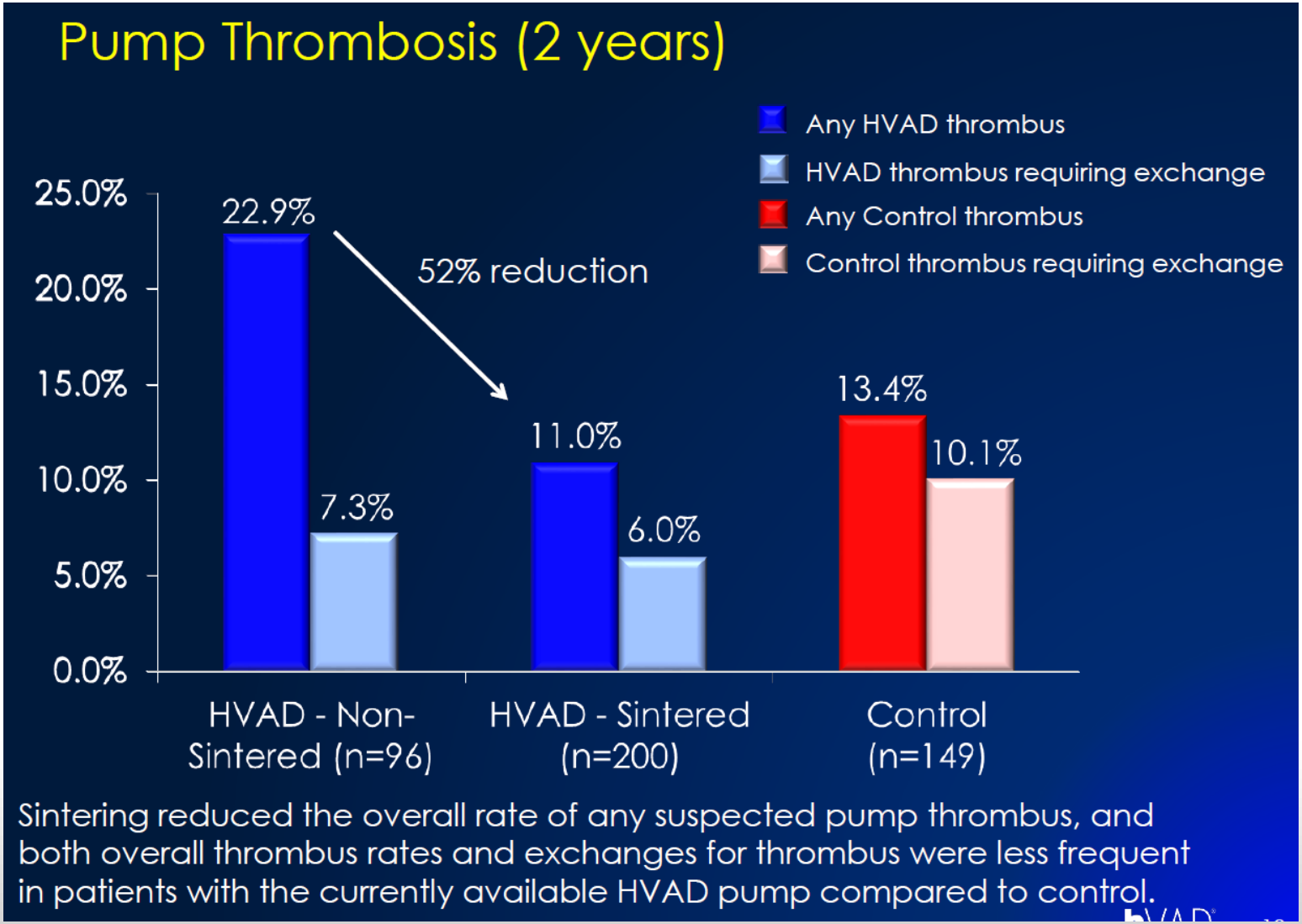
http://www.heartware.com/clinicians/clinical-trials

ENDURANCE Trial

- During the ENDURANCE Trial, changes were made to:
  - HVAD pump inflow cannula (sintering)
  - Apical coring tool
  - Anti-platelet/anticoagulation regimen (aspirin increased from 81mg to 325 mg and INR range to 2.0 – 3.0)

http://www.medscape.com/viewarticle/809661

ENDURANCE Trial



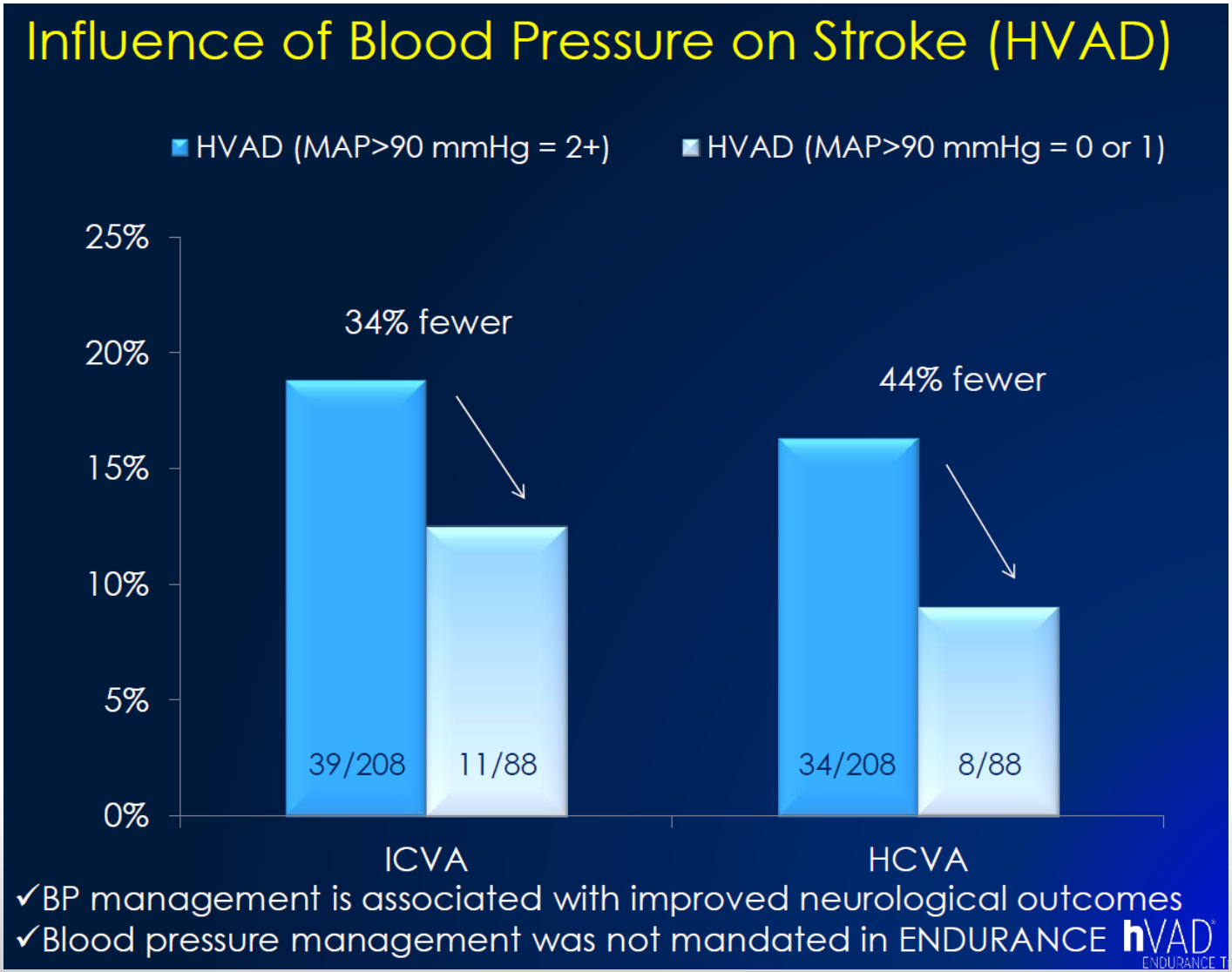
Pagani FD et al. Presented at the ISHLT 35th Annual Meeting and Scientific Sessions, April 15-18, 2015, Nice, France

ENDURANCE Trial

- One of the factors that may contribute to the interim results included high blood pressure
- Clinical centers involved in ENDURANCE that had done a better job monitoring and managing patients' blood pressure witnessed a notably lower incidence of neurologic events
- A supplemental cohort was set up: patients with the same inclusion/exclusion criteria at the same 50 ENDURANCE sites will be enrolled in the same way but subject to more rigorous blood-pressure management during the trial.

http://www.medscape.com/viewarticle/809661

ENDURANCE Trial



Pagani FD et al. Presented at the ISHLT 35th Annual Meeting and Scientific Sessions, April 15-18, 2015, Nice, France

ENDURANCE Trial Data

Key findings:

- Freedom from hemorrhagic stroke (93.9% vs 81.9%, p= 0.0016) and RHF (72.6% vs. 60.8%, p= 0.03) was significantly higher in the HMII cohort compared to HVAD

Assessment of the changes made mid-study:

- Analysis of the final third of enrollees (n= 96 HVAD, 49 HMII) demonstrated no significant difference in freedom from hemorrhagic stroke (94.5% vs. 85.4%, p= 0.172) or RHF (68.4% vs. 62.9%, p= 0.067) between HMII and HVAD

- Freedom from device exchange was not different in the complete cohort (89.7% vs 83.3%, p= 0.066) but was significantly less frequent in the HVAD cohort in the final third analysis (96.3% vs 85.0%, p= 0.0263)

Milano CA et al. JHLT 2015 Vol. 35, Issue 4, S9

ENDURANCE Trial Data

Conclusions:

- ENDURANCE demonstrated significant reductions in adverse events during trial conduct.
- Improvements related to enhanced patient selection and management and improvements in the device and implantation tools.
- No significant differences in adverse events between HVAD and HMII were observed in the final third of randomized patients, except for device exchange, that was statistically less frequent in patients receiving an HVAD.

Milano CA et al. JHLT 2015 Vol. 35, Issue 4, S9

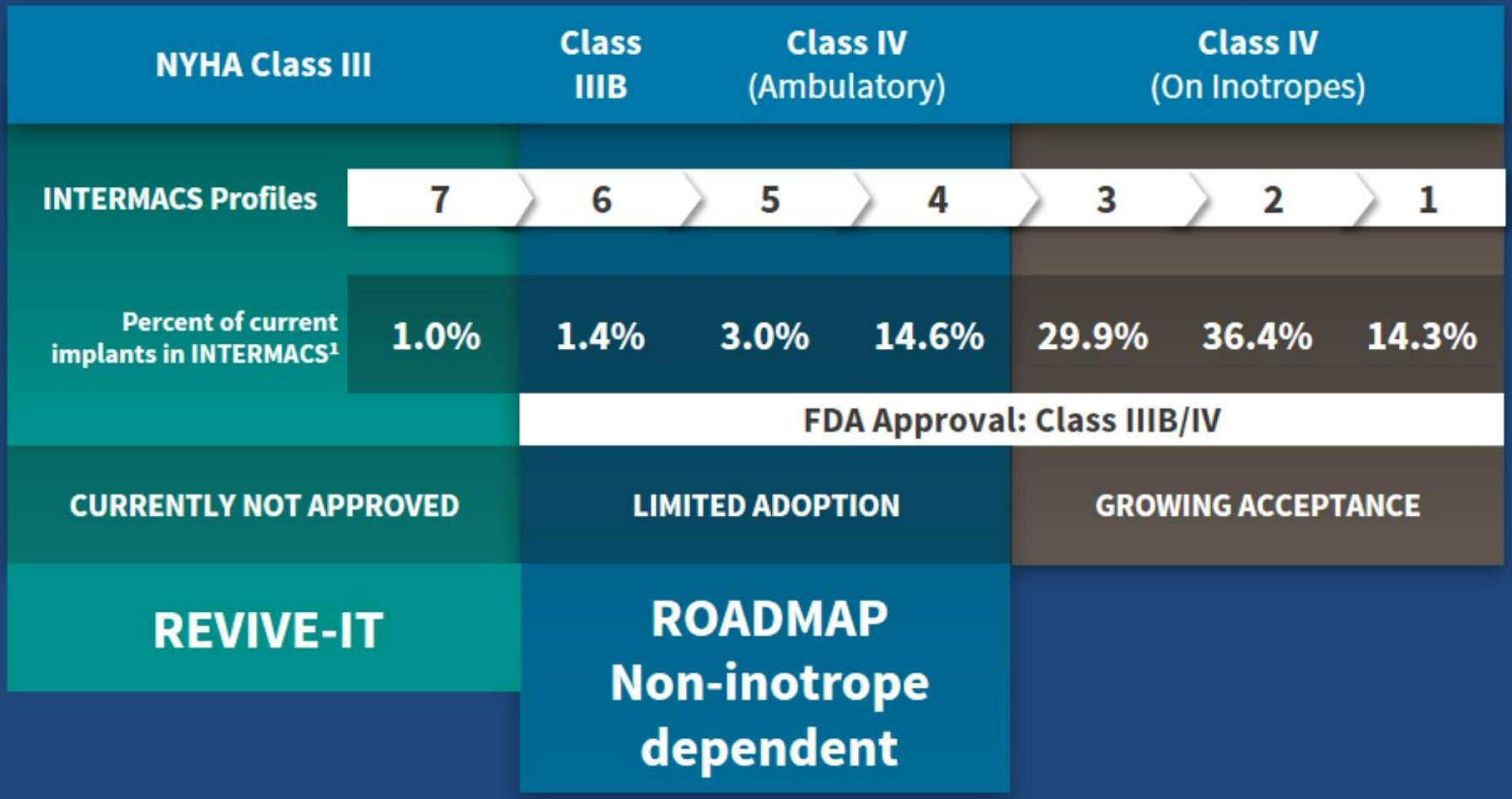
ROADMAP Trial

Evaluate and compare the effectiveness of the HM II vs OMM in ambulatory NYHA Class IIIB/IV HF patients who are not dependent on intravenous inotropic support and who meet the FDA approved indications for HMII as DT.

Prospective, multi-center, non-randomized, controlled, observational study

https://clinicaltrials.gov/ct2/show/NCT01452802

ROADMAP Patient Population



[1]Kirklin et al J Heart Lung Transplant 2014; 33:555-64
Rogers JG et al: ROADMAP Trial Design: Am Heart J. 2015 Feb;169(2):205-210

Jerry D. Estep, MD – Presented at ISHLT on April 17, 2015

ROADMAP Clinical Study

ROADMAP Trial

Primary Outcome

- Composite of survival with improvement in Six Minute Hallway Walk Test distance from baseline of ≥75m

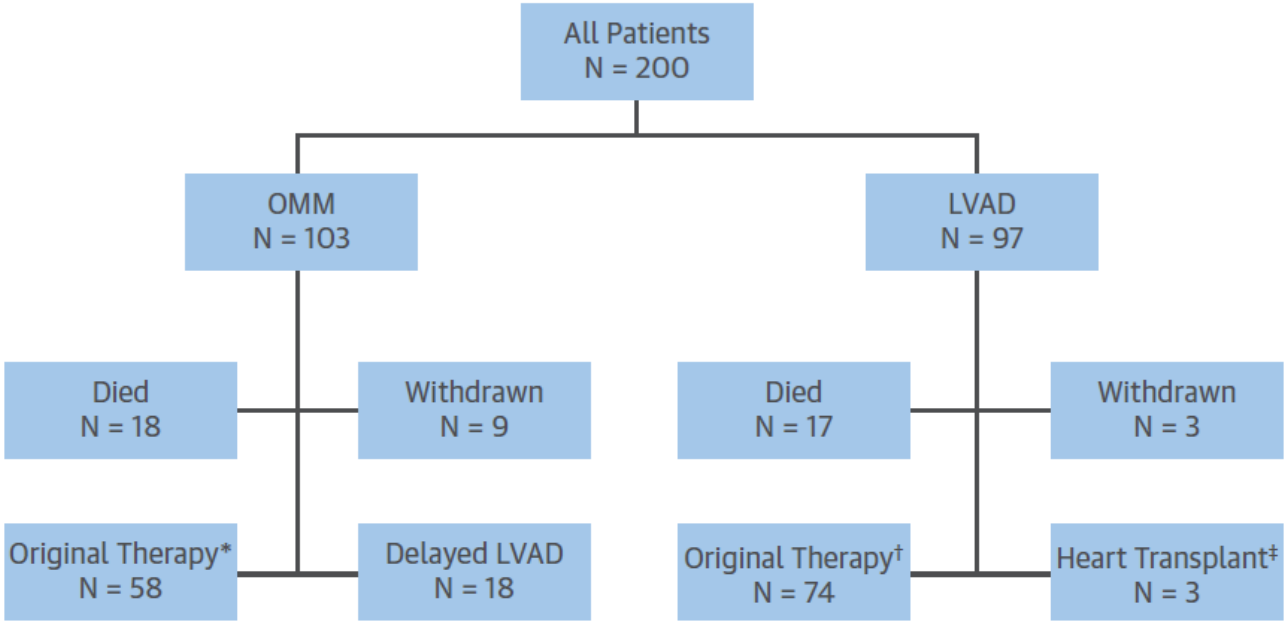
Secondary Outcomes

- Risk stratified subgroup analysis of the primary endpoint and temporal analysis of primary endpoint. [6, 12, 18, and 24 months]
- Accuracy of prognostic survival risk models including Seattle Heart Failure Model (SHFM) and HeartMate II Risk Score (HMRS) [Baseline and 6, 12, 18 and 24 months]
- Actuarial survival and survival free of stroke: a) intent-to-treat; and b) as treated. [24 months]
- Survival in LVAD group free of pump replacement. [24 months]
- Quality of Life using the EQ-5D-5L Health Utility Index. [Baseline and 6, 12, 18 and 24 months]
- Depression using Patient Health Questionnaire-9 (PHQ-9). [Baseline and 6, 12, 18 and 24 months]
- Questionnaire on patient decisions related to LVAD therapy versus OMM. [Baseline and 6, 12, 18 and 24 months]
- Functional status using 6MWT distance and NYHA Classification [Baseline and 6, 12, 18 and 24 months]
- Incidence of adverse events, rehospitalizations, days alive and not hospitalized. [3, 6, 9, 12, 15, 18, 21 and 24 months]

https://clinicaltrials.gov/ct2/show/NCT01452802

ROADMAP Trial

FIGURE 1 The ROADMAP Patients at 1 Year



Flow chart depicts outcomes and events within 12 months of enrollment in the ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device [LVAD] and Medical Management) trial. Patients who withdrew from the study or received an elective heart transplant within 1 year were excluded from the primary endpoint analysis. *12 optimal medical management (OMM) patients missing 6-min walk distance data were excluded from the primary endpoint analysis. †8 left ventricular assist device (LVAD) patients missing 6MWD data were excluded from the primary endpoint analysis. ‡Includes 1 elective and 2 urgent transplants.

Estep JD et al. J Am Coll Cardiol. 2015 Oct 20;66(16):1747-61.

ROADMAP Trial

TABLE 3 Patient and Physician Reasons Provided for LVAD or OMM

Patient reasons*: LVAD, n = 95	
It will improve chances to live longer	81 (85)
It will improve QoL	79 (83)
It will help improve HF symptoms	72 (76)
It will help me return to activities I enjoy	72 (76)
Patient reasons: OMM, n = 101	
Don't like the idea of major device implantation surgery	40 (40)
Don't want to depend on a machine	26 (26)
Don't feel sick enough	25 (25)
Worried about too many complications with a LVAD	21 (21)
Don't think an LVAD will improve QoL	13 (13)
Don't think an LVAD will improve chances to live longer	10 (10)
Physician reasons: OMM, n = 103	
Patient is not a good surgical candidate†	14 (14)
Patient is not sick enough	11 (11)
Other (e.g., substance abuse, financial, compliance concerns)	9 (9)

Values are n (%) of patients who completed questionnaire. *Patients may select >1 response. †Surgical reasons provided: history of anticardiolipin antibody and splenectomy (high risk of clotting); lack of social support and noncompliance; medical nonadherence; interstitial fibrosis; obesity; liver cirrhosis; severe chronic obstructive pulmonary disease; concern regarding post-operative recovery; large sacral decubitus ulcer; recent stroke.

Abbreviations as in Tables 1 and 2.

Estep JD et al. J Am Coll Cardiol. 2015 Oct 20;66(16):1747-61.

Baseline Data

Characteristic[1]		OMM (n=103)	LVAD (n=97)	P
Enrollment Age (yrs)[2]		66 [23-82]	64 [21-82]	0.269
Male sex (%)		71 (69%)	75 (77%)	0.204
Race	White (%)	60 (58%)	72 (74%)	0.061
	Black (%)	35 (34%)	21 (22%)	
	Other (%)	8 (8%)	4 (4%)	
Ischemic Etiology (%)		51 (50%)	58 (60%)	0.158
Duration of HF >1 yr (%)		95 (92%)	91 (94%)	0.784
CRT or CRT-D (%)		43 (42%)	44 (45%)	0.669
ICD or CRT-D (%)		66 (64%)	67 (69%)	0.549
ACE Inhibitors or ARB (%)		78 (76%)	66 (68%)	0.271
Beta Blockers (%)		99 (96%)	84 (87%)	0.021

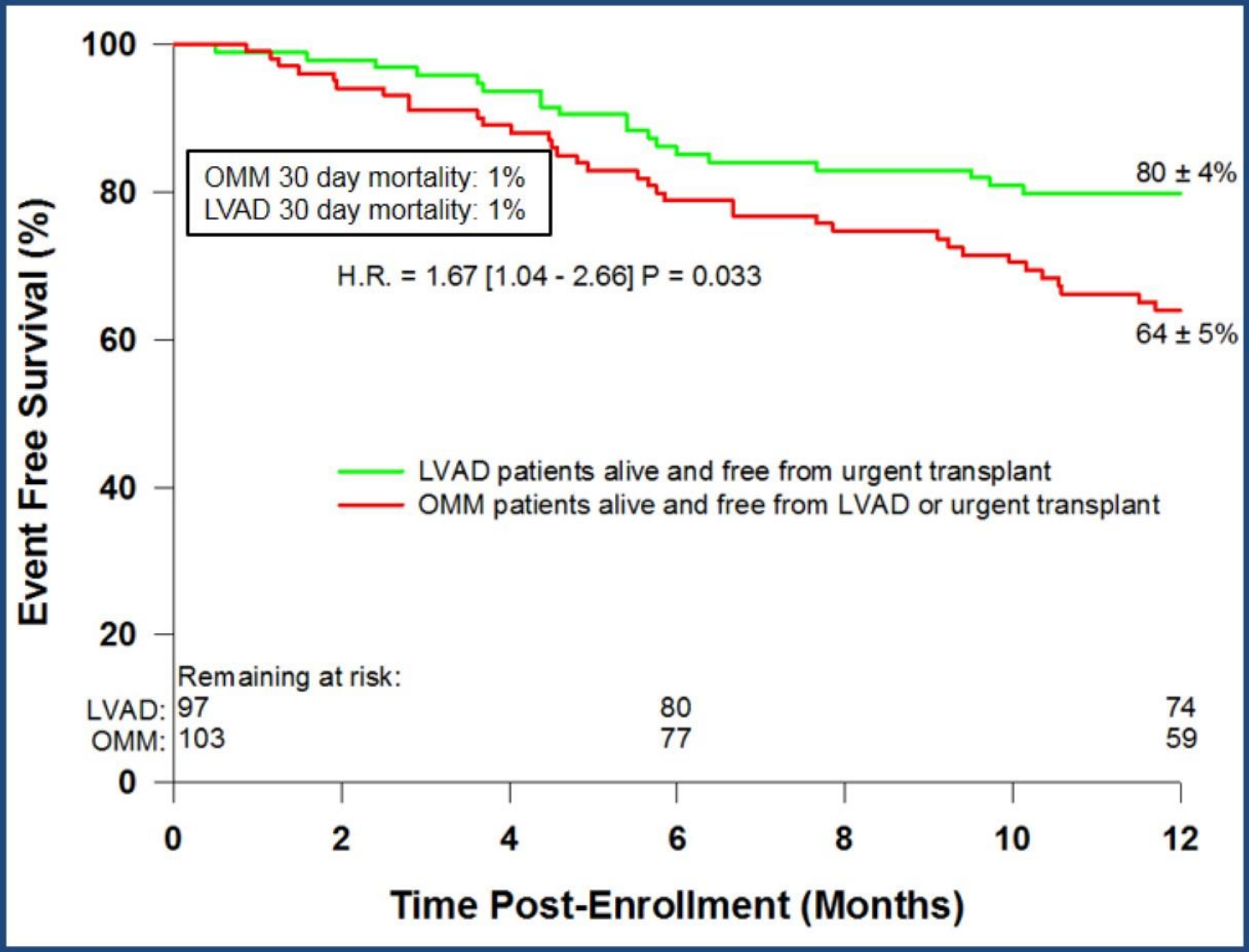
[1]200 subjects enrolled at 41 sites
[2]Median [range]

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

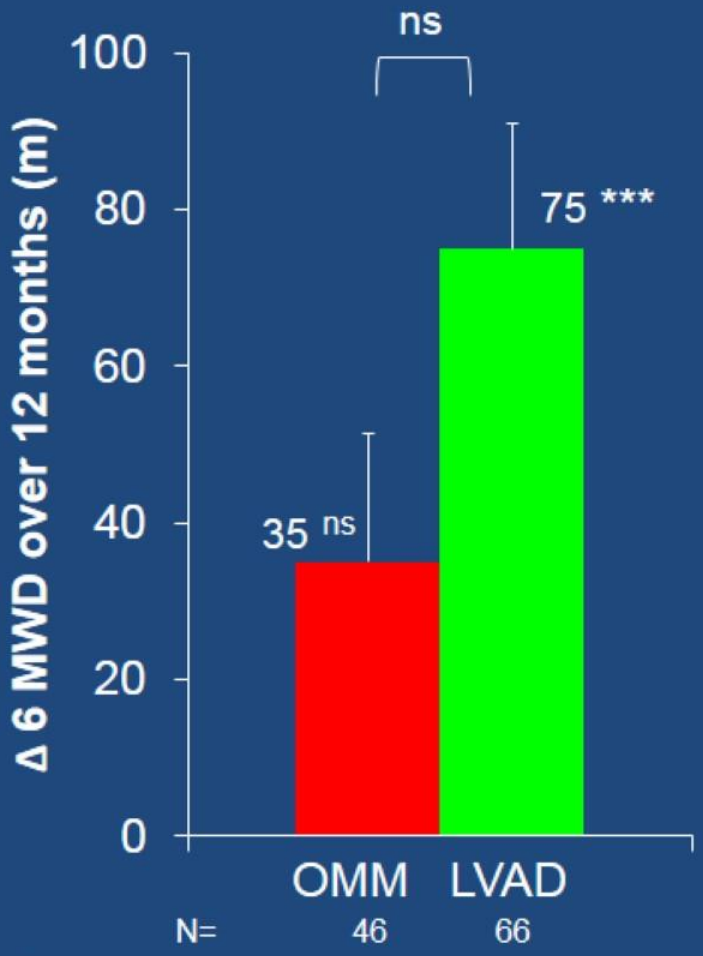
[1]Median [IQR]
[2]As determined at the site by an advanced practice practitioner other than principal investigator
[3]VAS score 0 -100 = worst to best health, 41 = mean VAS in DT post approval study (Jorde UP et al JACC 2014)
[4]PHQ-9 score 5-9 = mild depression, 10-14 = moderate depression

Survival As-Treated on Original Therapy



Changes in 6 Minute Walk Distance

1 Year Survivors on Original Therapy



*** P <0.001 paired change, baseline to 12 months
Mean ± std err

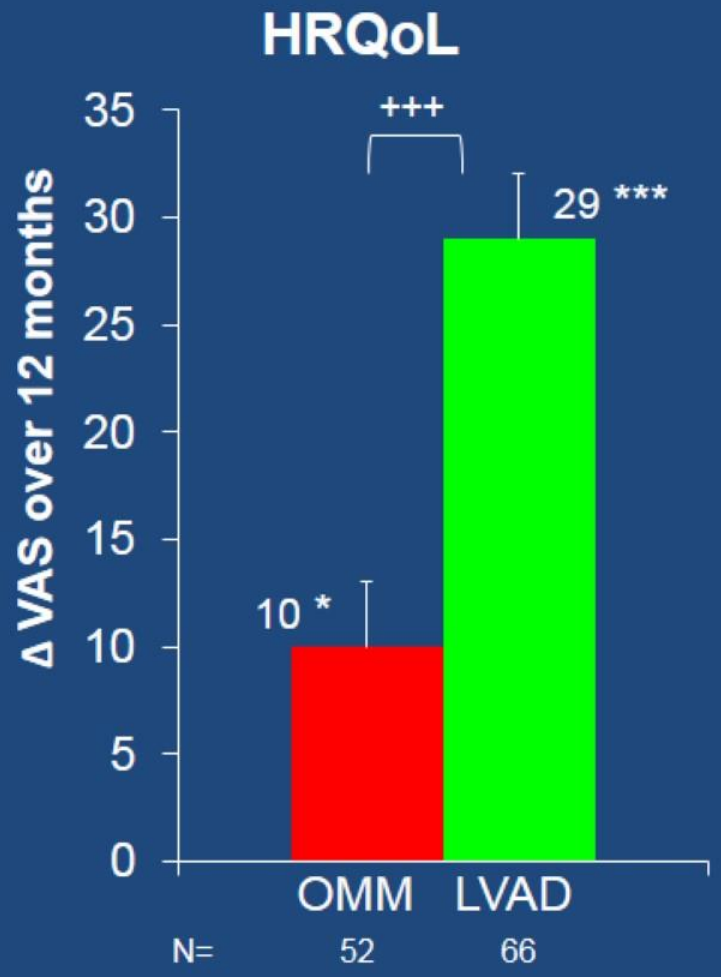
GL-HM2-04150215

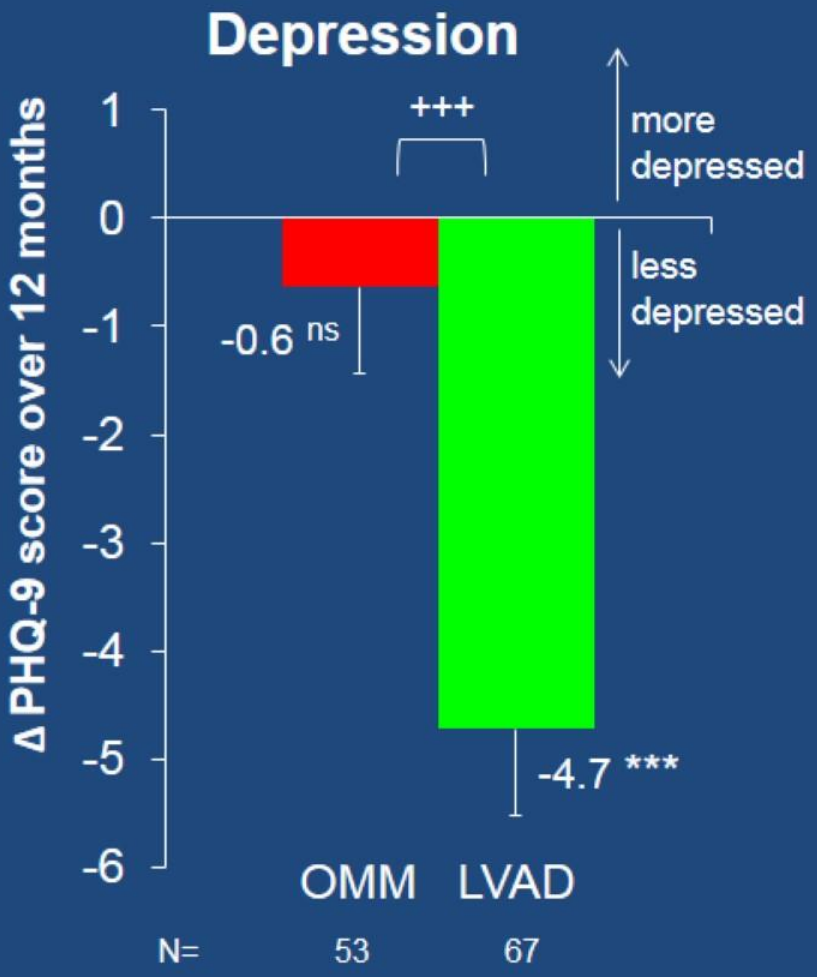
Jerry D. Estep, MD – Presented at ISHLT on April 17, 2015

ROADMAP Clinical Study

Changes in HRQoL and Depression

1 Year Survivors on Original Therapy





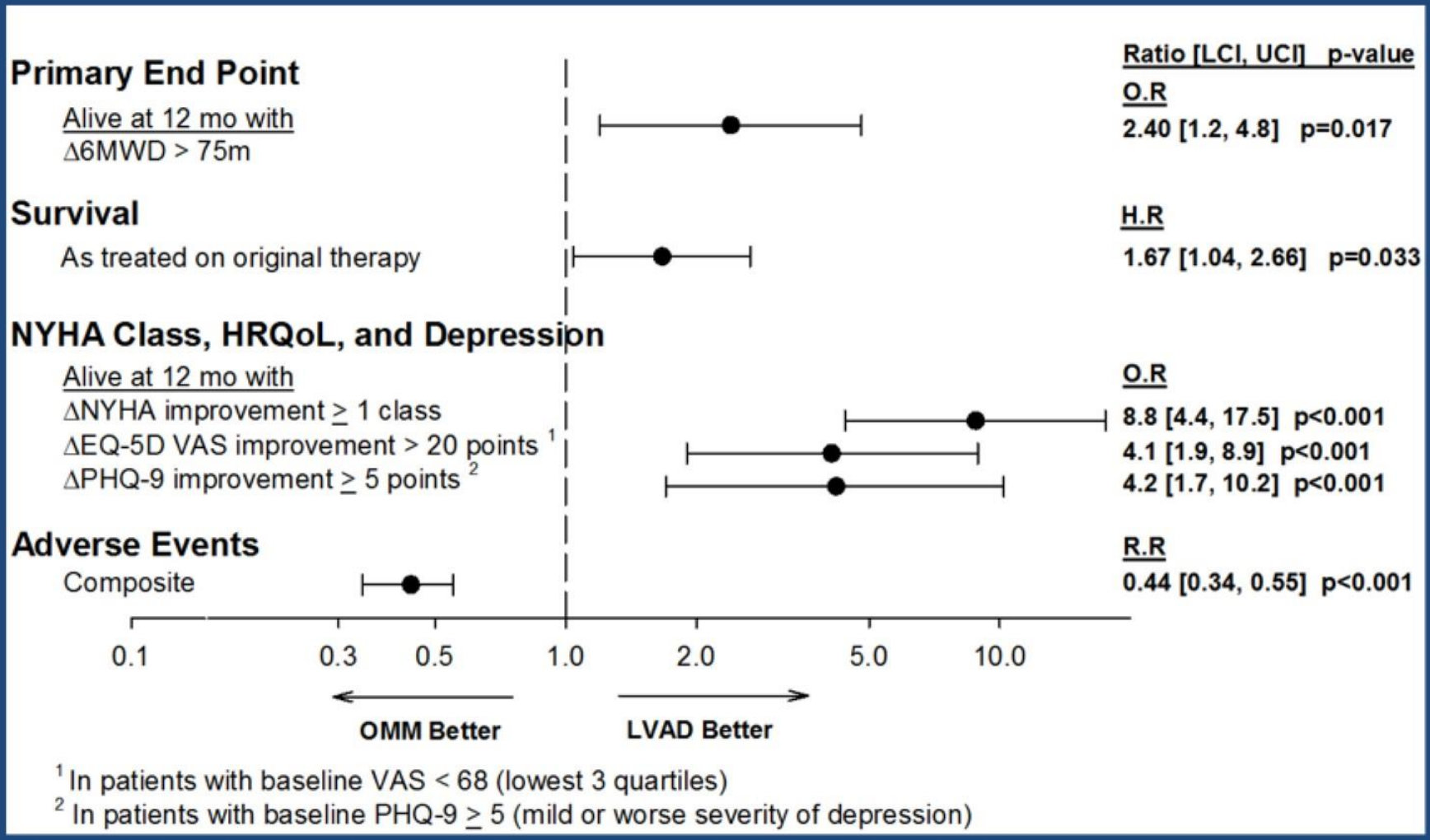
Mean ± stderr
* P<0.05, *** P<0.001 paired change, baseline to 12 months
+++ P<0.001 OMM vs LVAD

GL-HM2-04150215

Jerry D. Estep, MD – Presented at ISHLT on April 17, 2015

ROADMAP Clinical Study

Risk-Benefit Analysis



[1] In patients with baseline VAS < 68 (lowest 3 quartiles)
[2] In patients with baseline PHQ-9 ≥ 5 (mild or worse severity of depression)

Conclusions

- Survival with improved functional status was better with LVADs vs OMM
- Low LVAD operative mortality
- HRQoL and depression improved more with LVADs, even with more frequent adverse events

ROADMAP results support the use of HeartMate II® LVAD in functionally limited non-inotrope dependent heart failure patients.

MedaMACS

- Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS)

- MedaMACS will characterize patients who are not receiving LVAD currently for various reasons, including relative contra-indications, their own preferences, or their characterization as “less sick” either by perception or objective criteria.

- Serves as a parallel registry to INTERMACS of medically-managed ambulatory patients with advanced HF

- Cross-sectional, observational study of patients with ambulatory advanced HF being followed at 10 VAD/transplant centers in the US

Stewart GC et al. J Heart Lung Transplant. 2015 Dec;34(12):1630-3.
Stewart GC et al. Curr Cardiol Rep. 2013 Sep;15(9):394.

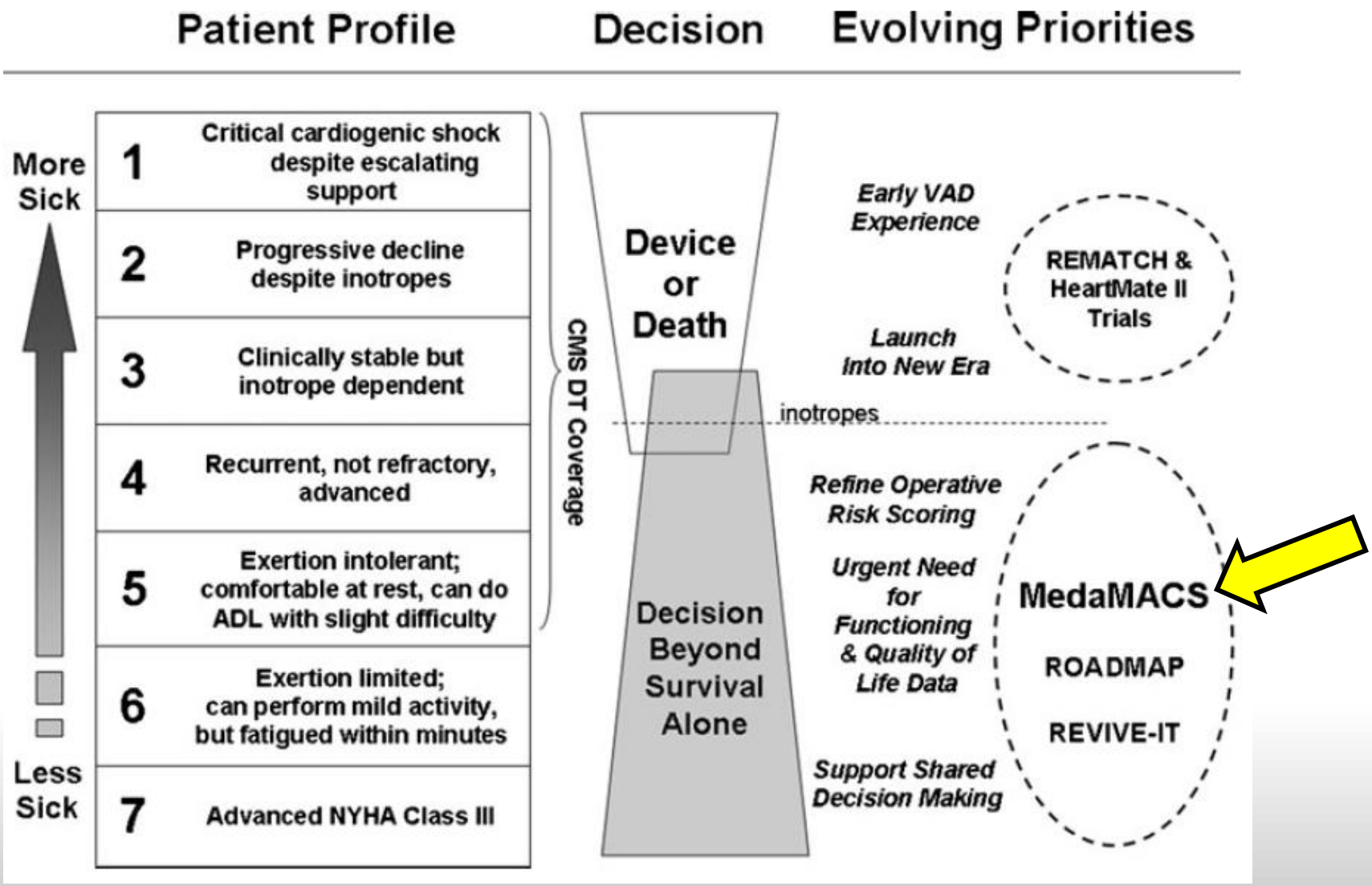
MedaMACS

Mission

- Map terrain of contemporary medical therapy for advanced heart failure
- Identify ambulatory patients for current MCS devices
- Support Institute of Medicine mandate for patient-centered care and shared decision making
- Design integrated endpoints that move beyond survival alone
- Define a broader context for next generation of MCS trials and future devices

Stewart GC et al. Curr Cardiol Rep. 2013 Sep;15(9):394.

MedaMACS



Stewart GC et al. Curr Cardiol Rep. 2013 Sep;15(9):394.

MedaMACS

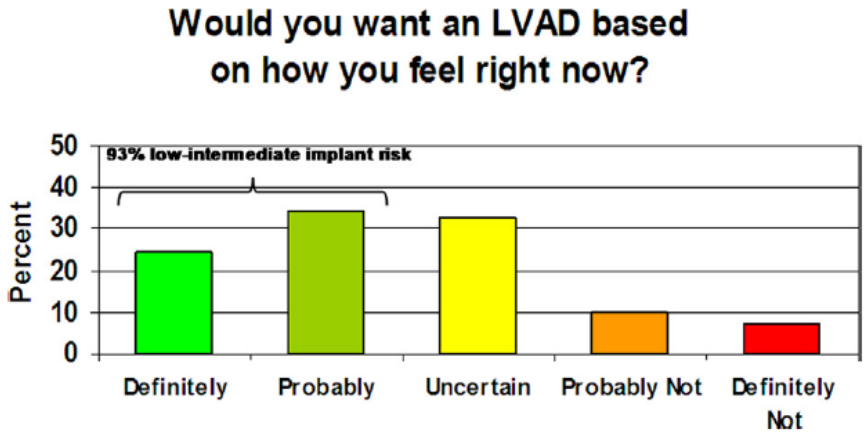


Figure 1 Advanced ambulatory HF patients express willingness to consider an LVAD at their current level of illness. In all, 56% of respondents said they would definitely or probably want an LVAD, with 93% at a low or intermediate implant risk based on the HeartMate II risk score.

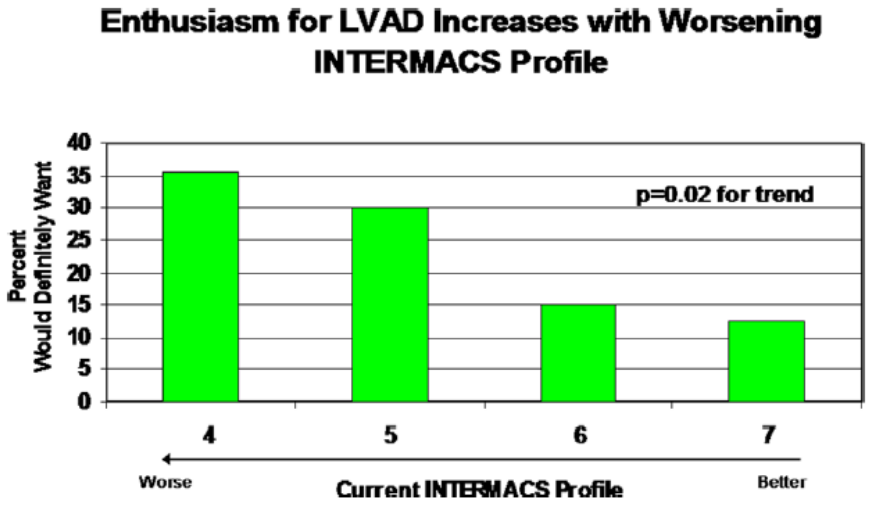


Figure 2 Enthusiasm for LVAD therapy increased with worsening severity of illness as assessed by INTERMACS profile ($p = 0.02$ for trend).

MedaMACS

Table 2 Concerns About Left Ventricular Assist Device Therapy

Overall rank[a]	Concern endorsed	"Definitely or probably" concerned (%)	Top-ranked concern (%)
1	Stroke risk	67	24
2	Pump durability	62	18
3	Infection risk	71	6
4	Effect on daily routine	62	8
5	Being dependent on a machine	58	10
6	Being a burden to family	56	16
7	Keeping batteries charged or pump plugged into a power source	53	4
8	Noise from device	36	7
9	Frequent doctor visits for check-ups	32	2
10	Effect on appearance	24	6
11	What family and friends will think	17	1

[a]Determined by a weighted rank order of the top 3 concerns elicited after considering each potential concern.

Stewart GC et al. J Heart Lung Transplant. 2015 Dec;34(12):1630-3.

MedaMACS

Inclusion Criteria

1. Age 18-80 years
2. NYHA class III-IV heart failure for 45 of the last 60 days
3. Left ventricular ejection fraction ≤ 35%
4. Heart failure diagnosis or typical symptoms for 12 months
5. Use of evidence based oral medications (beta-blockers, ACE-inhibitors/ARBs, aldosterone antagonist) for at least 3 months prior to enrollment or documented medication contraindication or intolerance.
6. Hospitalization for heart failure within the previous 12 months (other than for elective procedure)

In addition, they must have at least one of the following:

A. An additional unplanned hospitalization during the previous 12 months for a total of at least 2 inpatient hospitalizations lasting >24 hours with heart failure as the primary or secondary diagnosis within the previous 12 months

OR

B. (Any one of these)

1) Peak oxygen uptake (VO2) <55% of age- and sex-predicted (using Wasserman equation) OR a peak VO2 ≤16 ml/kg/min for men and ≤14 ml/kg/min for women in a test with an RER >1.08 on cardiopulmonary exercise testing.
2) 6-minute walk distance <300 meters without non-cardiac limitation.
3) Serum BNP > 1000 pg/ml (NT-proBNP > 4000 pg/ml) as outpatient or at hospital discharge.

OR

C. Seattle Heart Failure Model Score ≥ 1.5.

Ambardekar AV et al. J Heart Lung Transplant. 2016 Jan 18.

MedaMACS

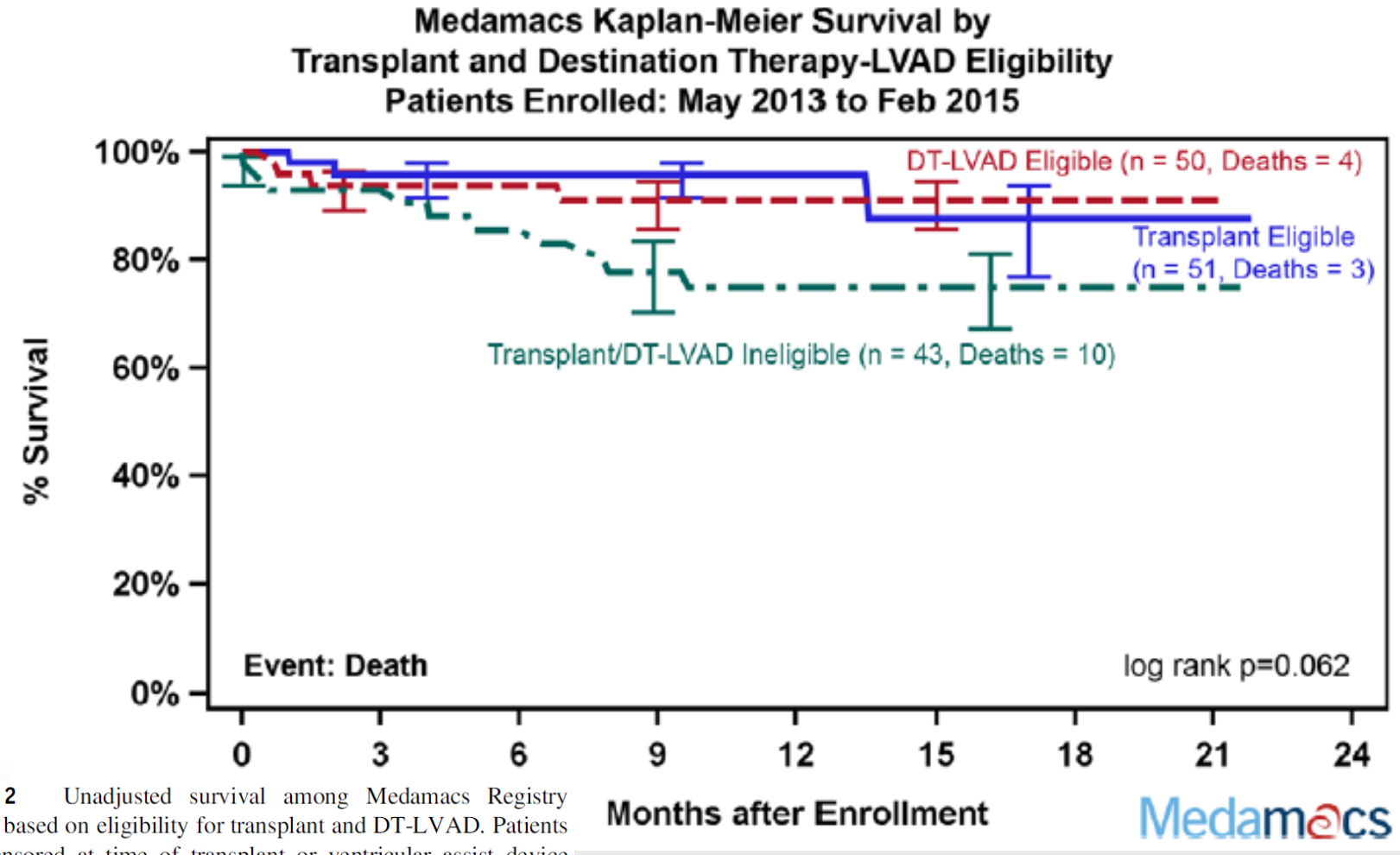


Figure 2 Unadjusted survival among Medamacs Registry patients based on eligibility for transplant and DT-LVAD. Patients were censored at time of transplant or ventricular assist device placement. Transplant/DT-LVAD ineligible patients had lower survival compared with the other cohorts. Error bars represent 70% confidence intervals.

Ambardekar AV et al. J Heart Lung Transplant. 2016 Jan 18.

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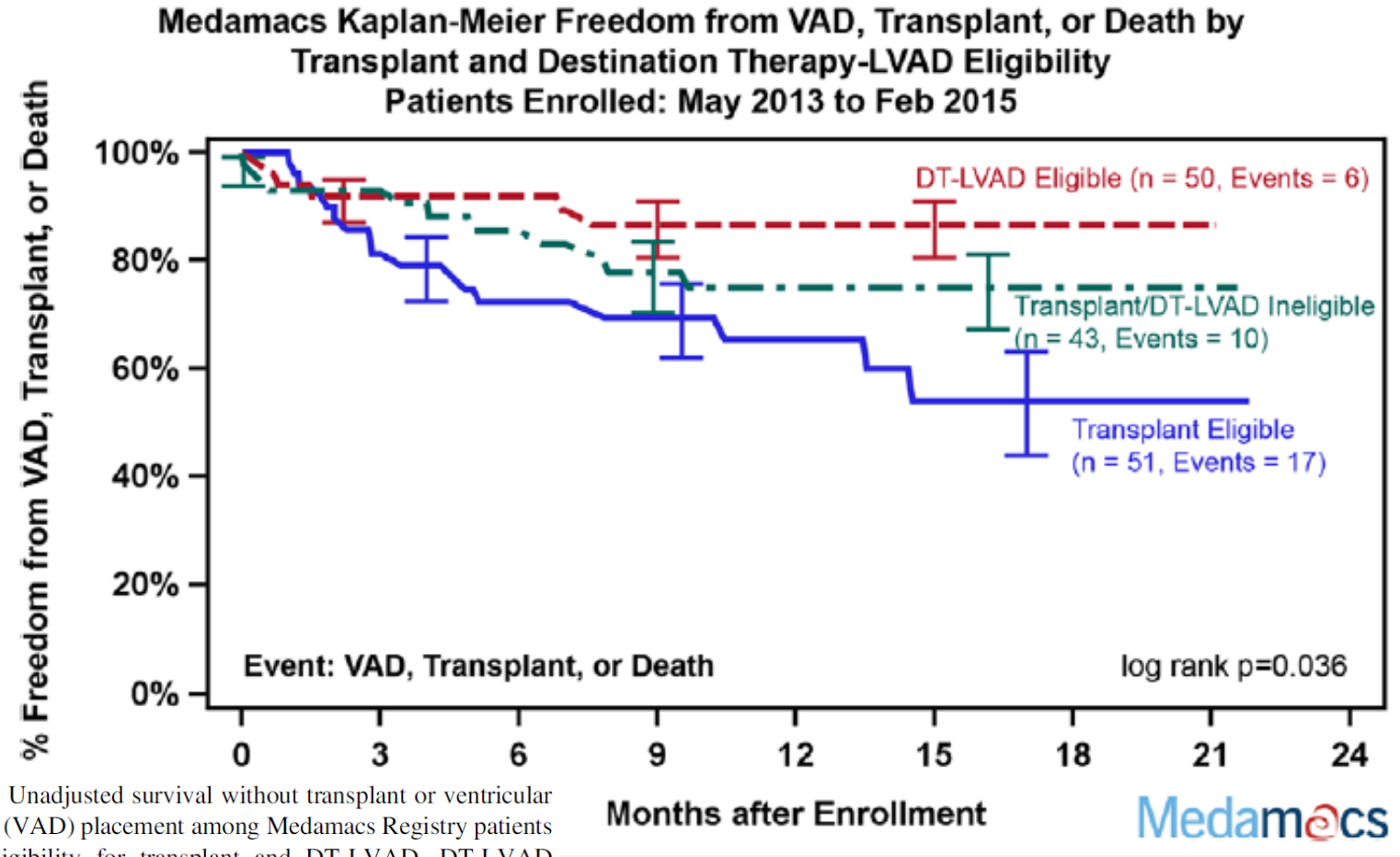


Figure 3 Unadjusted survival without transplant or ventricular assist device (VAD) placement among Medamacs Registry patients based on eligibility for transplant and DT-LVAD. DT-LVAD eligible patients had the best survival free from transplant or VAD, whereas transplant eligible patients had the lowest survival free from transplant or VAD. Error bars represent 70% confidence intervals.

Ambardekar AV et al. J Heart Lung Transplant. 2016 Jan 18.

MedaMACS

Table 4 Clinical outcomes based on the likely eligibility for transplant and/or LVAD

Clinical Outcome	Transplant Eligible	DT-LVAD Eligible	Transplant/DT-LVAD Ineligible	*p*-value
Survival outcomes				
Mortality	3 (6%)	4 (8%)	10 (23%)	0.02
Ventricular assist device received	8 (16%)	1 (2%)	0 (0%)	< 0.01
Transplant received	6 (12%)	1 (2%)	0 (0%)	0.02
Alive without LVAD or transplant	33 (65%)	43 (86%)	33 (77%)	0.04
Inotropes required	3 (6%)	3 (6%)	6 (14%)	0.31
At least 1 rehospitalization	9 (18%)	11 (22%)	14 (33%)	0.22
Total number of rehospitalizations	0.7 ± 1.2	0.7 ± 1.2	1.5 ± 2.0	0.09

DT-LVAD, destination therapy with left ventricular assist device; LVAD, left ventricular assist device.

Ambardekar AV et al. J Heart Lung Transplant. 2016 Jan 18.

MedaMACS

- Among ambulatory patients with advanced HF not dependent on inotropes, patients who were thought to be ineligible for transplant/DT-LVAD had markers of greater HF disease severity and had worse outcomes compared with patients thought to be transplant and DT-LVAD eligible.

- The mortality rate in ineligible patients after an average follow-up period of 10 months was 23.3%.

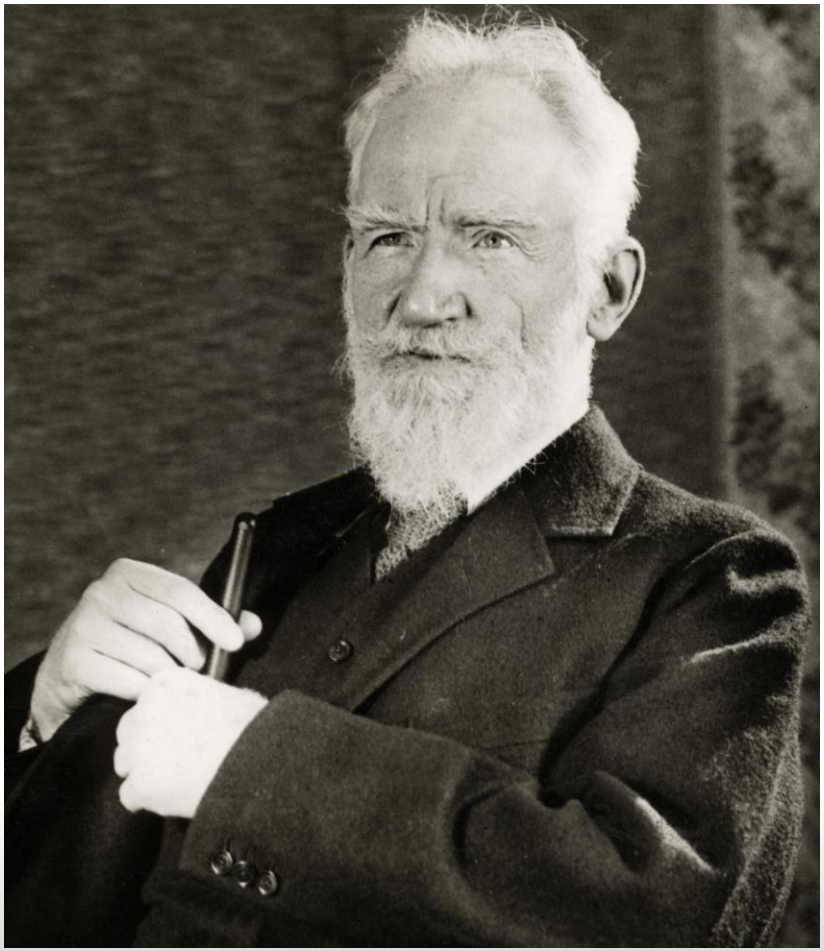
- Only 30% of patients in this group had undergone a formal evaluation for transplant and/or LVAD at the time of enrollment in MedaMACS.

- The overall survival rate without transplant or LVAD (after a follow-up period of <10 months) was ~75%.
  - HF patients with characteristics similar to those of patients enrolled in the Medamacs Registry are at particularly high risk for poor outcomes and warrant referral to centers for consideration of advanced HF therapies.

Ambardekar AV et al. J Heart Lung Transplant. 2016 Jan 18.

How to go forward?

George Bernard Shaw
1856-1950



"Science is always wrong. It never solves a problem without creating ten more."

What did we learn and how do we move forward?

1) VADs work and are beneficial in advanced heart failure
2) Adverse events/complications need honest assessment and rigorous multi-institutional clinical protocols to develop best practices and reduce center variation
3) INTERMACS levels do not provide clinically useful subsets of patients
   - 1 and 2 essentially the same
   - 3 thru 6 only slight clinical difference
4) INTERMACS levels need to be replaced with objective clinical criteria (size of LV, degree of MR, PAP, PCWP, RV function, renal function, etc)
5) Need to decide who gets a heart transplant
   - this will help determine role of long term VAD support

What did we learn and how do we move forward?

6) Patients need better education to participate in “decision making”

- fatal disease
- future options
- delaying decision may result in ineligibility
- role of palliative care

7) ***Thanks!!***