

Management of Heart Failure with the Use of Ventricular Assist Devices

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Conflict of Interest Disclosures

- Name: Keith Aaronson, MD, MS
- Occupation: Cardiologist
- Place of Work: University of Michigan Health System
- Speaking on behalf of: CMS

Financial Interests:

- I do not own stock or have another formal financial interest in any company that certifies/accredits healthcare entities or develops, manufactures, distributes or markets ventricular assist devices, artificial hearts or similar devices or is involved in oversight of their use
- I have received speaking fees and research grant support from HeartWare, Inc.
- I do not currently serve on, and have not previously served on any other advisory committees or panels that considered the topic before the MEDCAC today.

Talk Outline

- Review of Devices with ≥ 1 US Pivotal Study Completed
 - HeartMate II (Thoratec)
 - HVAD (HeartWare)
- Review of Planned Studies of Full Support Devices
 - Jarvik 2000 (Jarvik)
 - HeartMate III (Thoratec)
 - Pericardial MVAD (HeartWare)
 - Transapical VAD (HeartWare)
 - DuraHeart II (Terumo)
- Review of Planned Studies of Partial Support Device
 - Synergy (Circulite)
 - C-Pulse (Sunshine Heart)

Talk Outline

- Topics Highlighted
 - Survival
 - Adverse Outcomes
 - Quality of life
 - Exercise capacity
- Presentation of results limited to:
 - US pivotal trials and their continued access programs
 - Published data only (unless noted)
 - No INTERMACS data (except as noted)

VADs with FDA Approved Indication or Published Pivotal Trials

Device Name	Company	BTT	DT
HeartMate XVE*	Thoratec	Approved	Approved
HeartMate II	Thoratec	Approved	Approved
HVAD	HeartWare	FDA Advisory Panel rec. approval	Pivotal Trial in progress Conventional DT RCT vs. HM III, 450 pts 2:1 randomization Enrollment completed May '12. 2 year f/u

*No longer produced or sold

HeartMate II - BTT Survival

Reference	Study	Enrollment period	n	One-Year Survival
Miller, Pagani, Russell et al NEJM 357:885-896, 2007	HM II Pivotal Trial	3/05- 5/06	133	68%
Pagani, Miller, Russell et al JACC 54:312-321, 2009	HM II Pivotal Trial	3/05- 3/07	281	74%
Starling, Naka, Boyle et al JACC 57:1890-8; 2011	HM II Post Approval Study	4/08 – 8/08	169	85%
John, Naka, Smedira et al Ann Thor Surg 92:1406-13; 2011	HM II Commercial* vs. Trial	4/08 – 9/10	1469	85%

*Commercial results shown (as collected through INTERMACS)

HeartMate II BTT Studies

Baseline Demographics

Characteristic	HM II BTT Pivotal Trial Miller et al	HM II Commercial John et al
Patients Enrolled	133	1496
Age (yrs)	50.1 13.1	< 40y = 17% 40-59y = 53% ≥ 60y = 30%
Male sex (%)	105 (79%)	1154 (77%)
Ischemic Etiology (%)	49 (37%)	Not reported
NYHA Class IV (%)	133 (100%)	1465 (98%)
Body Surface Area (m ²)	2.0 0.3	2.1 0.3

HeartMate II BTT Studies

Baseline Hemodynamics / Lab Values

Characteristic	HM II BTT Pivotal Trial Miller et al		HM II Commercial John et al	
LVEF (%)	16.3	5.7	Not available	
Cardiac Index (L/min/m ²)	2.0	0.6	2.1	0.7
CVP (mmHg)	13.5	7.8	12.8	6.8
PCWP (mmHg)	26.1	7.9	24.5	8.6
PVR (W.U.)	3.0	1.5	2.8	2.2
Systolic BP (mmHg)	95.8	14.6	100.9	15.6
Diastolic BP (mmHg)	61.7	11.3	63.0	11.6
Creatinine (mg/dl)	1.4	0.5	1.39	0.76
BUN (mg/dl)	31.4	17.6	28.4	18.0
AST (U/L)	67	168	84	337
Total Bilirubin (mg/dl)	1.2	0.8	1.49	1.83
Serum Sodium (mmol/L)	132.9	5.1	134.5	5.1

HeartMate II BTT Studies

Baseline Concomitant Medications or Interventions

Characteristic	HM II BTT Pivotal Trial Miller et al	HM II Commercial John et al
CRT (%)	64 (48%)	Not reported
ICD (%)	98 (74%)	Not reported
Ventilator Support (%)	8 (6%)	138 (9%)
IABP (%)	55 (41%)	53 (19%)
ACE Inhibitors (%)	44 (33%)	Not reported
ARBs (%)	7 (5%)	Not reported
Beta-blocker (%)	51 (38%)	Not reported
Inotropes (%)	118 (89%)	1203 (80%)

HeartMate II - Destination Therapy Survival

Reference	Study	Enrollment period	n	One-Year Survival	Two-Year Survival
Slaughter, Rogers, Milano et al NEJM 2009;361:2241-51	HM II Pivotal Trial Primary Data Cohort	3/05- 5/07	134	68%	58%
Park, Milano, Tatroles et al Circ HF 2012; 5:241-248	HM II Pivotal Trial Continued Access Protocol (CAP)	5/07- 3/09	281	73%	63%

HeartMate II DT Pivotal Trial

Baseline Demographics

Characteristic	Early Trial <i>Primary data cohort</i>		Mid Trial <i>Continued access protocol</i>		P
Patients Enrolled	133		281		-
Age (yrs)	62.5	11.5	63.3	12.6	0.282
Male sex (%)	107 (80%)		221 (79%)		0.699
Ischemic Etiology (%)	88 (66%)		163 (58%)		0.132
NYHA Class IV (%)	95 (71%)		178 (63%)		0.105
History of Prior Stroke (%)	22 (17%)		39 (14%)		0.765
Body Surface Area (m ²)	2.03	0.26	1.96	0.26	<u>0.018</u>
Weight (kg)	86	20	81	19	<u>0.011</u>

HeartMate II DT Pivotal Trial

Baseline Hemodynamics / Lab Values

Characteristic	Early Trial <i>Primary Data Cohort</i>		Mid Trial <i>CAP</i>		P
LVEF (%)	17	6	17	6	0.387
Cardiac Index (L/min/m ²)	2.06	0.57	2.03	0.62	0.567
CVP (mmHg)	12.8	6.2	13.0	6.6	0.776
PCWP (mmHg)	24.1	8.4	24.4	7.9	0.699
PVR (W.U.)	3.29	1.63	3.57	1.83	0.273
Systolic BP (mmHg)	103	15	103	15	0.492
Diastolic BP (mmHg)	60	13	63	12	0.080
Creatinine (mg/dl)	1.59	0.58	1.53	0.58	0.214
BUN (mg/dl)	38	25	34	19	0.589
ALT (U/L)	39	37	42	66	0.343
AST (U/L)	36	47	40	62	0.132
Total Bilirubin (mg/dl)	1.21	0.76	1.21	0.86	0.957
Serum Sodium (mmol/L)	134.8	4.3	135.0	4.5	0.510

HeartMate II DT Pivotal Trial

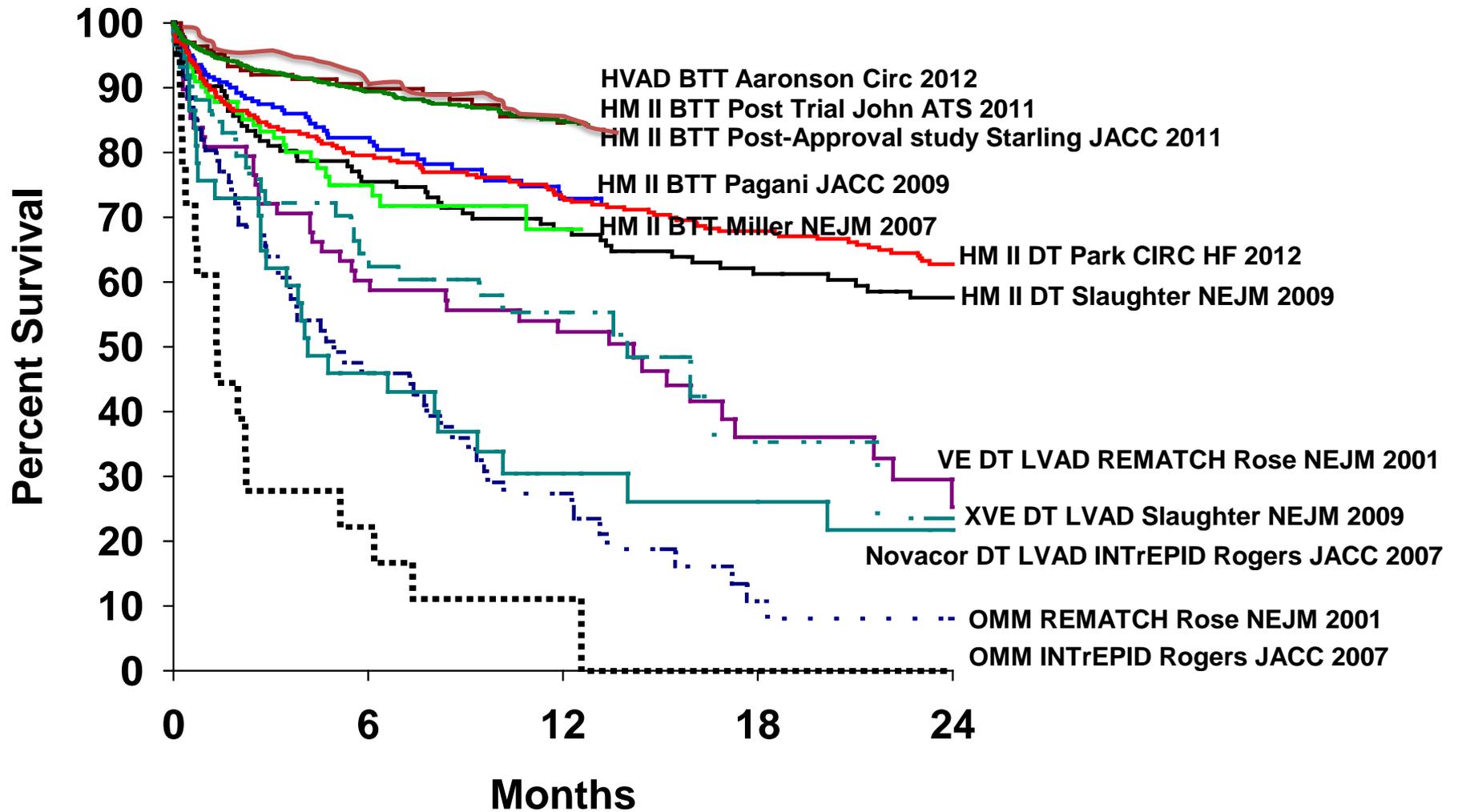
Baseline Concomitant Medications or Interventions

Characteristic	Early Trial <i>Primary Data</i> Cohort	Mid Trial <i>CAP</i> Cohort	P
CRT (%)	85 (64%)	166 (59%)	0.389
ICD (%)	109 (82%)	233 (83%)	0.890
Ventilator Support (%)	9 (7%)	10 (4%)	0.206
IABP (%)	30 (23%)	53 (19%)	0.430
Ace Inhibitors (%)	44 (33%)	79 (28%)	0.303
Beta-blocker (%)	72 (54%)	134 (48%)	0.247
Inotropes (%)	102 (77%)	220 (78%)	0.706

HVAD - BTT Survival

Reference	Study	Enrollment period	n	One-Year Survival
Aaronson, Slaughter, Miller, et al Circ 2012;125:3191-3200	ADVANCE Pivotal Trial Primary Cohort	8/08 - 2/10	140	86%
HeartWare, data on file	ADVANCE Pivotal Trial Primary + CAP	8/08 - 12/11	332	84%

Improving Survival in LVAD Trials



INTERMACS Patient Profiles in LVAD Clinical Trials

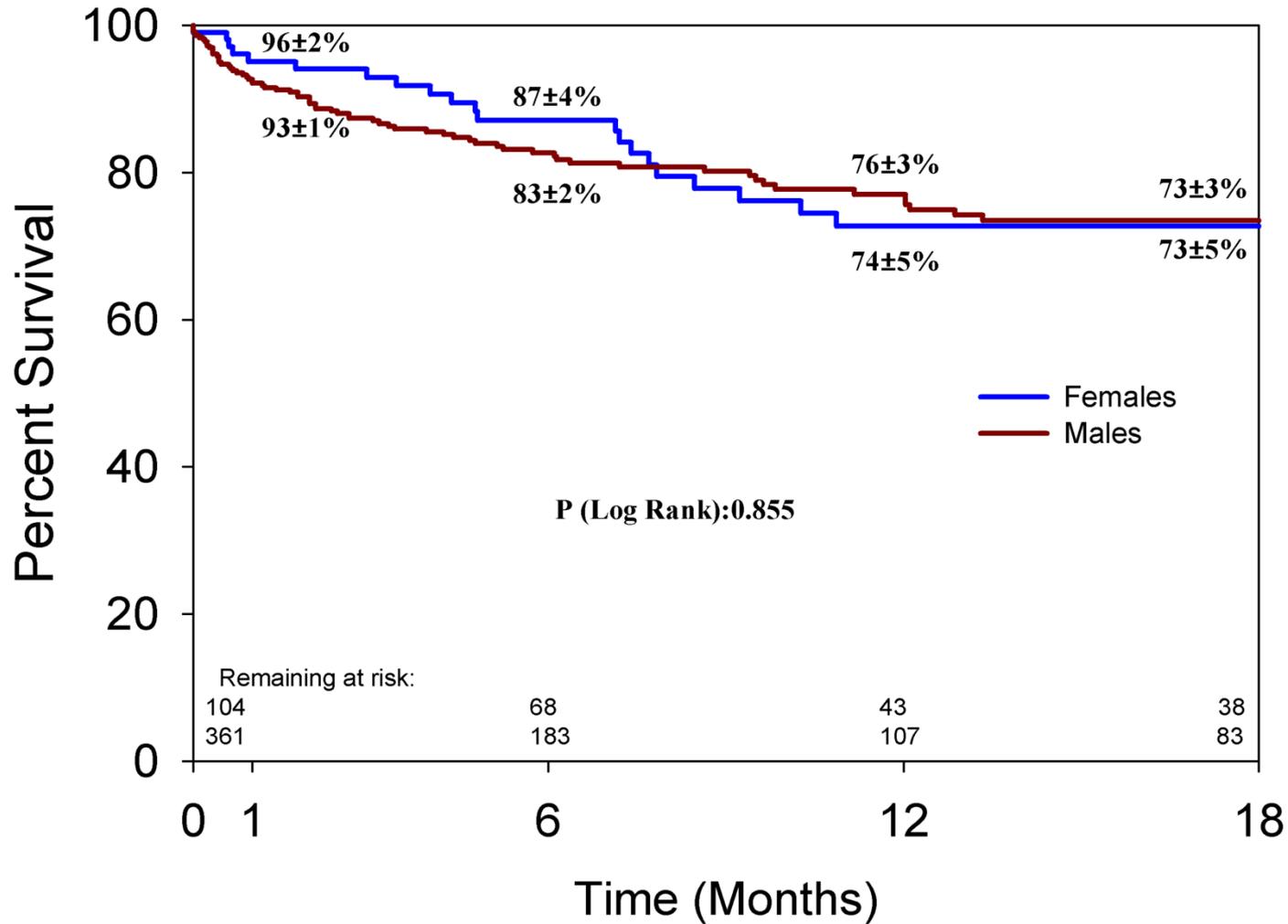
Trend Away from Profiles 1 and 2

INTERMACS Patient Profile	HM II BTT Post-Approval 2008*	HM II DT Commercial 2008-2010*	HVAD BTT Pivotal 2008-2010*
1	24%	17%	5%
2	37%	45%	24%
3	20%	20%	52%
4	12%	12%	9%
5-7	7%	7%	9%

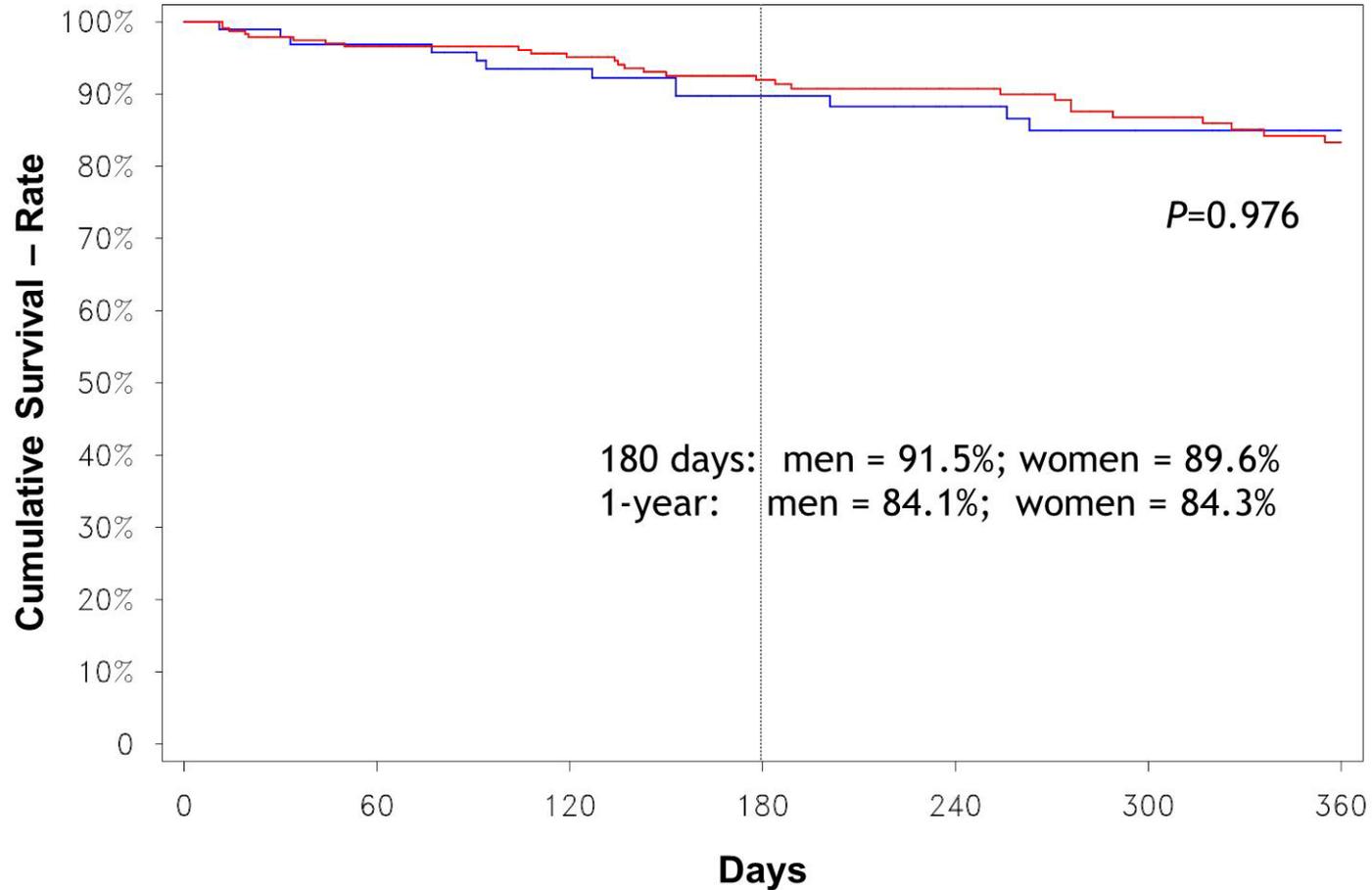
* Year of enrollment

Effect of Gender on Survival

HM II BTT Survival is Similar for Women and Men



HVAD BTT Survival is Similar for Men and Women



Patient and Center Characteristics Influencing Survival

The HeartMate II Risk Score: Predicting Survival in Candidates for Left Ventricular Assist Device Support

**Jennifer Cowger¹, Kartik Sundareswaran², Joseph Rogers³, Soon Park⁴,
Francis Pagani¹, Geetha Bhat⁵, Brian Jaski⁶, David Farrar² and Mark
Slaughter⁷**

For the HeartMate II Clinical Investigators

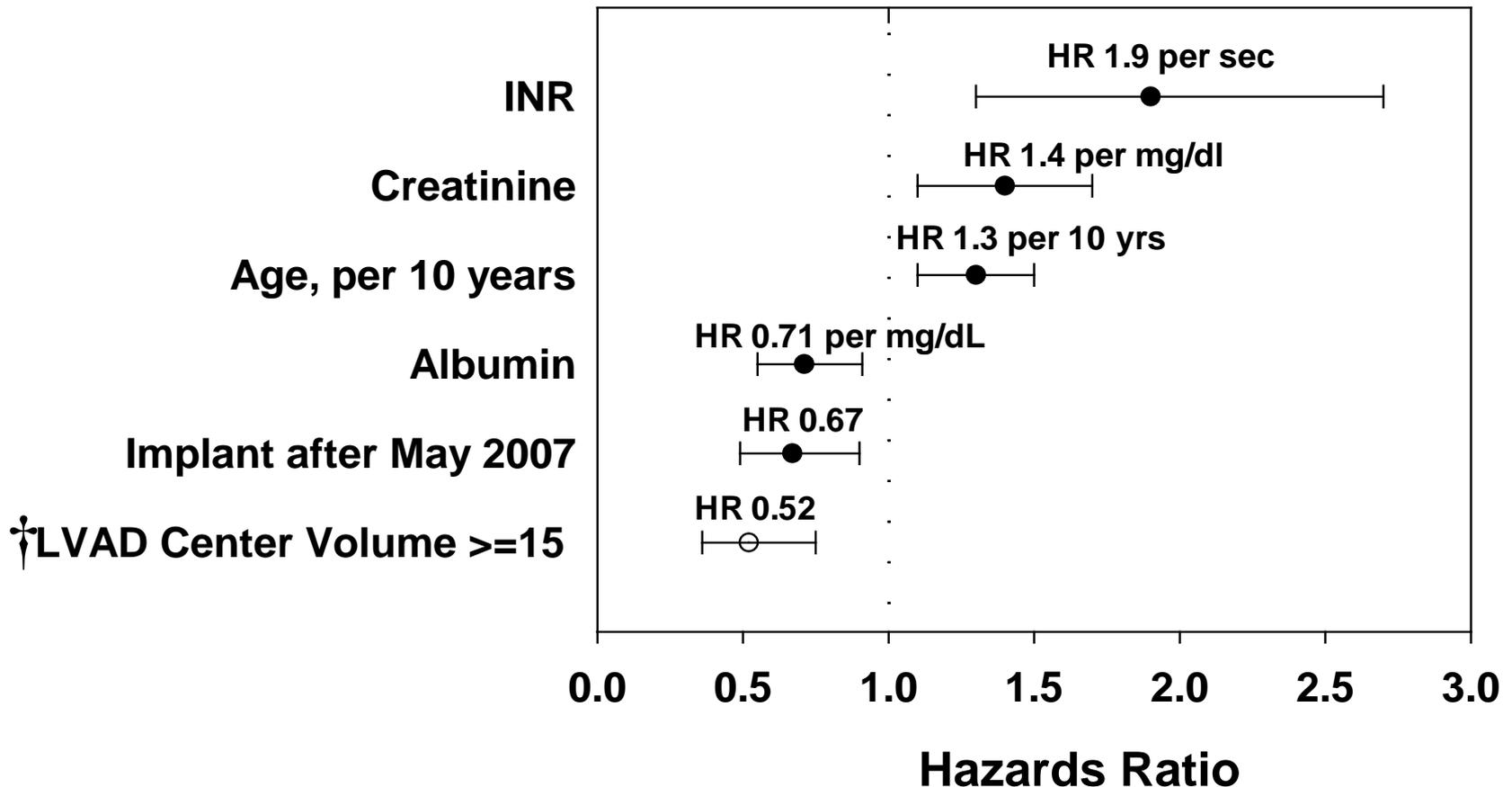
¹University of Michigan Health System, Ann Arbor, MI; ²Thoratec Corporation, Pleasanton, CA; ³Duke University Medical Center, Durham, NC; ⁴Mayo Clinic, Rochester, MN; ⁵Advocate Christ Medical Center, Oaklawn, IL; ⁶Sharp Memorial Hospital, San Diego, CA; ⁷University of Louisville, Louisville, KY, United States.

The HeartMate II Risk Score

- Goals
 - Derive and validate a risk model for predicting short and longer term survival following continuous flow LVAD implantation.
- Patients - HeartMate II Clinical Trial
 - Bridge to Transplant (N=489)^{1,2}
 - Destination Therapy (N=633)³
 - Total N=1122
- Cohorts
 - Patients were prospectively and randomly assigned to either the derivation cohort or to the validation cohort.
- Analyses
 - Multivariable analyses were performed to identify risk factors of death following LVAD implantation.

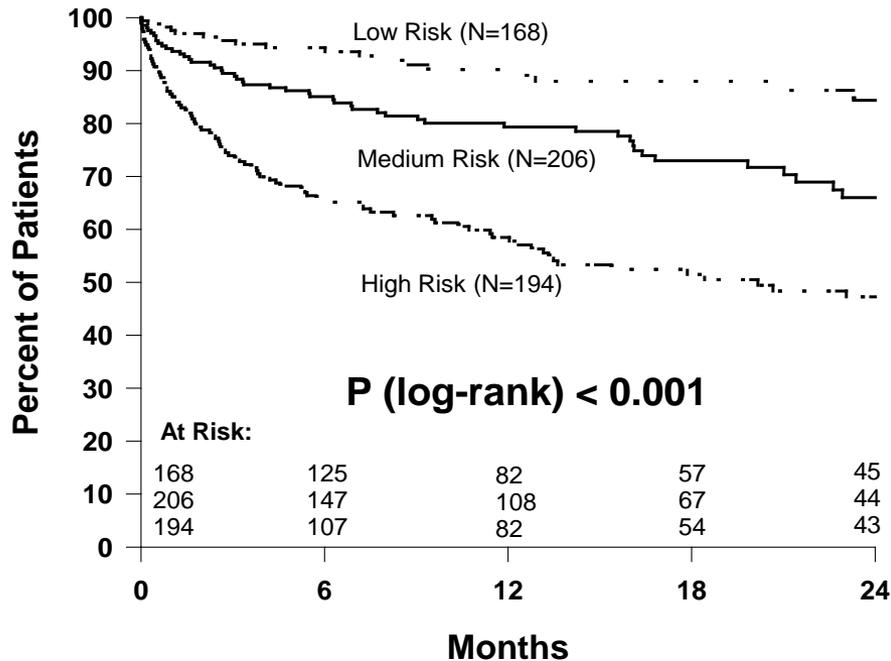
HeartMate II Risk Score

Multivariable Risk Factors for Death After Implant

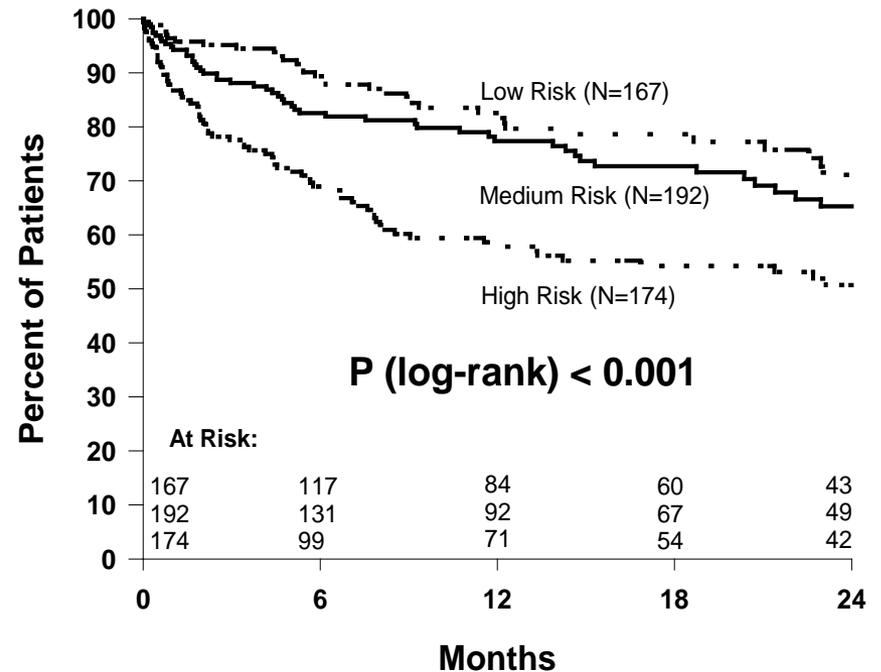


HeartMate II Risk Score Derivation vs. Validation Cohorts

Derivation Cohort

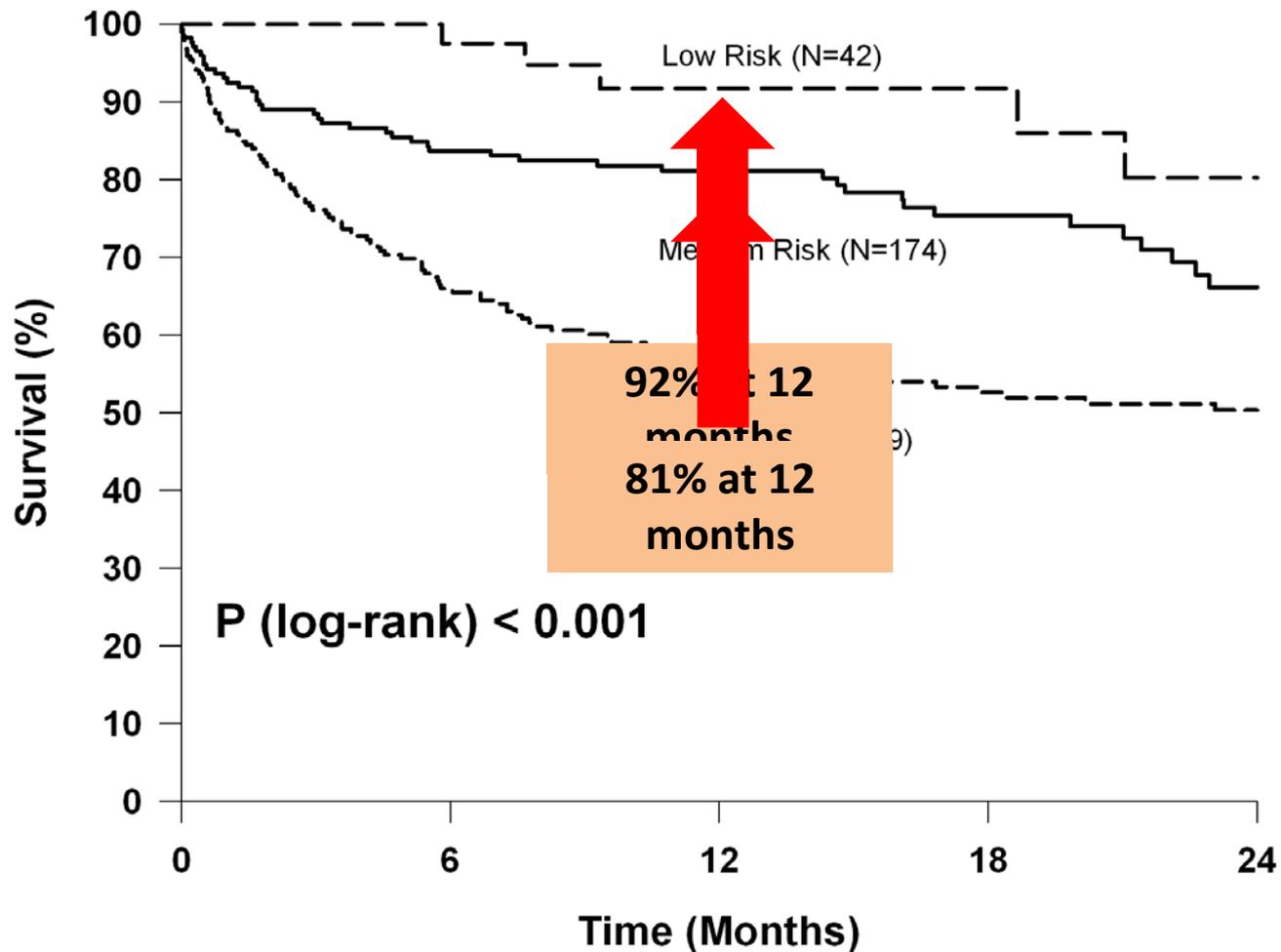


Validation Cohort



HM II Risk Score

Stratification in Patients Over 65 Years of Age



Quality of Life and Functional Capacity

HeartMate II DT Trial

HeartMate II DT Trial

HeartMate II DT Trial

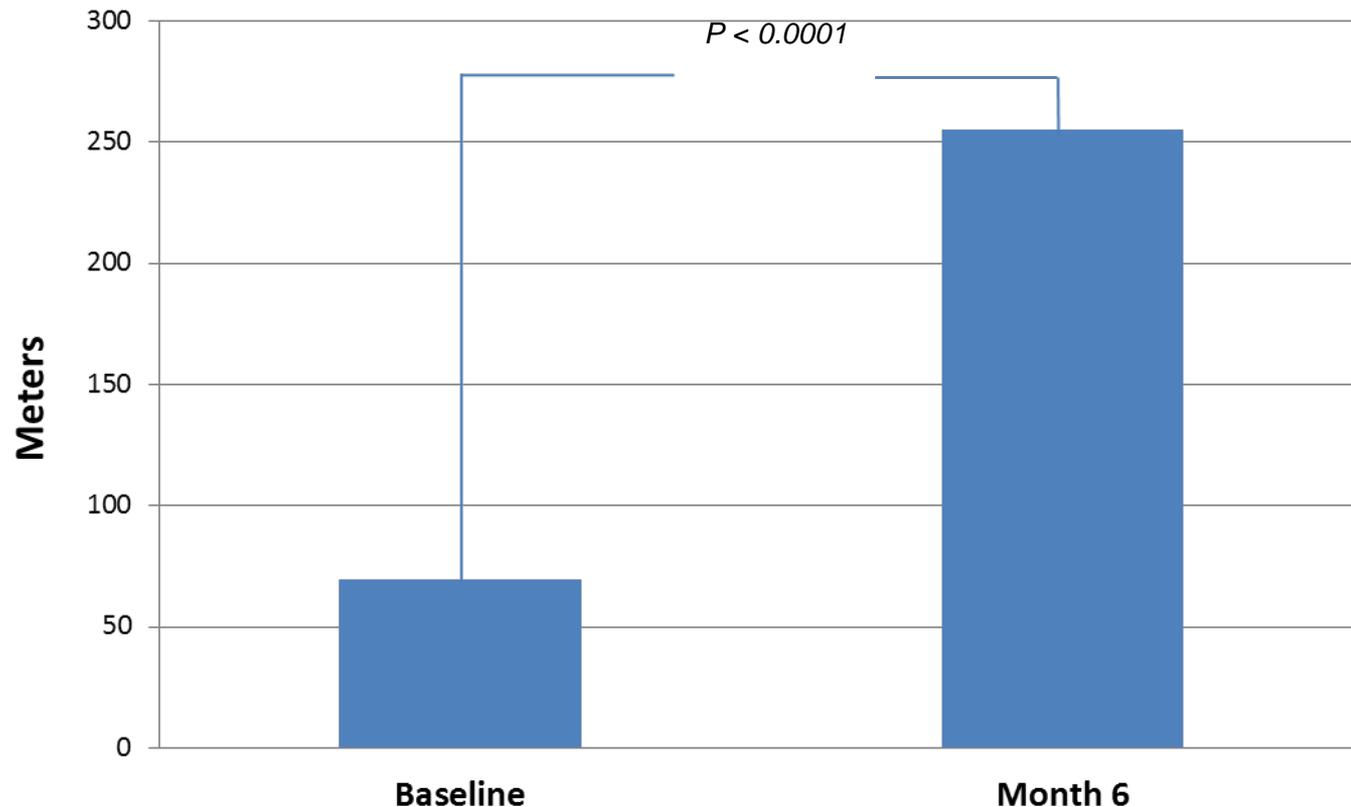
HVAD BTT + CAP

Quality of Life Improvements

QOL or Functional Status	Day	N	Mean*	SD*	Change	P-value
EQ-5D: Visual Analog Scale	0	178	44.3	25.3		
EQ-5D: Visual Analog Scale	180		71.7	18.9	27.5	<0.001
KCCQ: Overall Summary	0	169	36.6	21.9		
KCCQ: Overall Summary	180		67.5	18.9	30.8	<0.001
SD = standard deviation * Value represents points						

HVAD BTT + CAP

Improvement in 6-Minute Walk



Paired data at baseline and 6 months post HVAD for 209 patients. Patients unable to complete the assessment for any reason other than incomplete follow-up visit were given an imputed value of zero. At 6 months, 6 MWT distance improved by 185.4 meters

Adverse Events

Adverse Events in LVAD Clinical Trials

Adverse Event	HM II BTT Pivotal Primary+CAP ¹	HVAD BTT Pivotal Primary + CAP ²	HM II DT Pivotal Primary ³	HM II DT Pivotal CAP ³
	N=281, 182 py	N=332, 306 py	N=133, 211 py	N=281, 498 py
Pump replacement	0.07	0.10	0.06	0.04
Ischemic stroke	0.09	0.09	0.06	0.05
Hemorrhagic stroke	0.05	0.09	0.07	0.03
Hemolysis	0.06	0.06	0.02	0.03
LVAD related infections	0.34	0.25	0.47	0.27
Sepsis	0.35	0.23	0.38	0.27
Bleeding requiring surgery	0.45	0.19	0.23	0.14
Right heart failure	0.29	0.29	0.16	0.13

Other important adverse events include gastrointestinal bleeding and aortic insufficiency

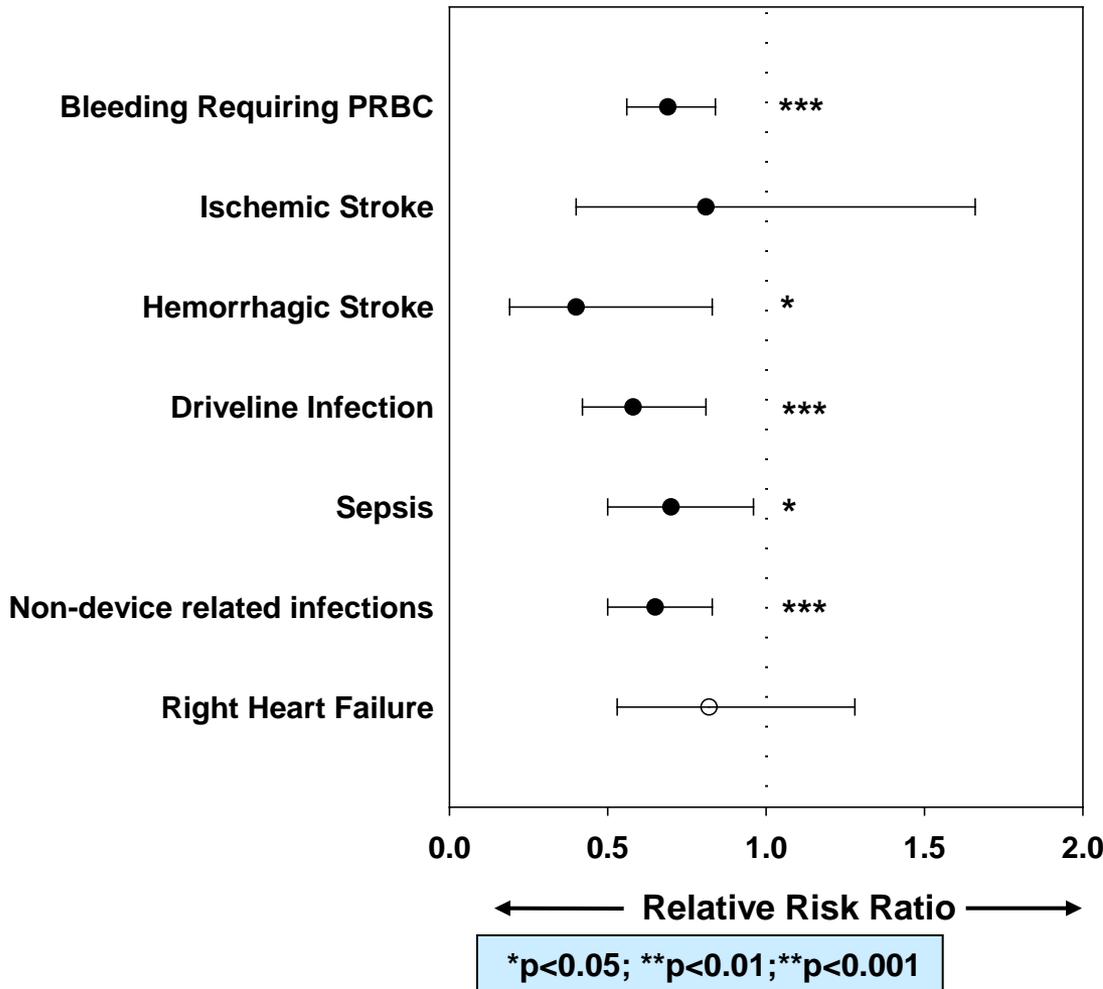
¹Pagani, *JACC* 2009

²HeartWare, data on file

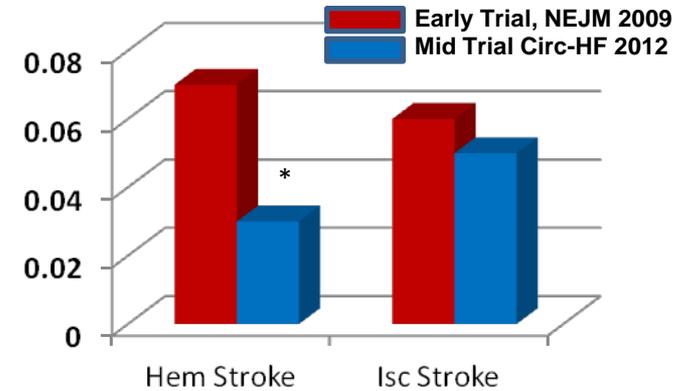
³Park, *Circulation Heart Failure* 2012

DT Trial CAP: Adverse Event Summary

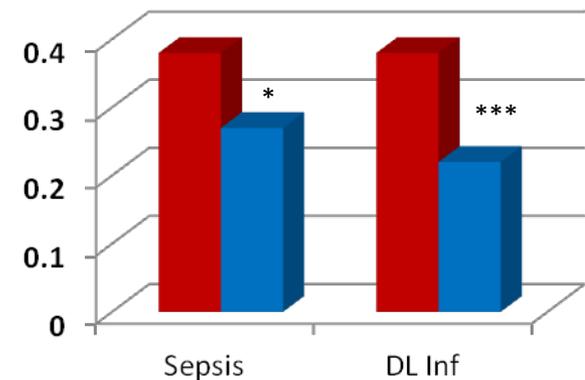
Improvements in Adverse Event Rates: Early to Mid Trial



Stroke (events per pt-year)



Infection (events per pt-year)



RV Failure post LVAD

- Preimplant diagnosis is challenging and there is a lack of consensus regarding diagnostic criteria
- RV failure after LVAD support can be acute (more common) or chronic
- RVF leads to:
 - High mortality (38% for acute RVF)¹
 - High morbidity: increased risk renal failure (3.4 higher odds),² cardiac cirrhosis, lower extremity venous stasis → poor mobility.
 - Prolonged length of stay
- Predictive tools helpful but much room for improvement

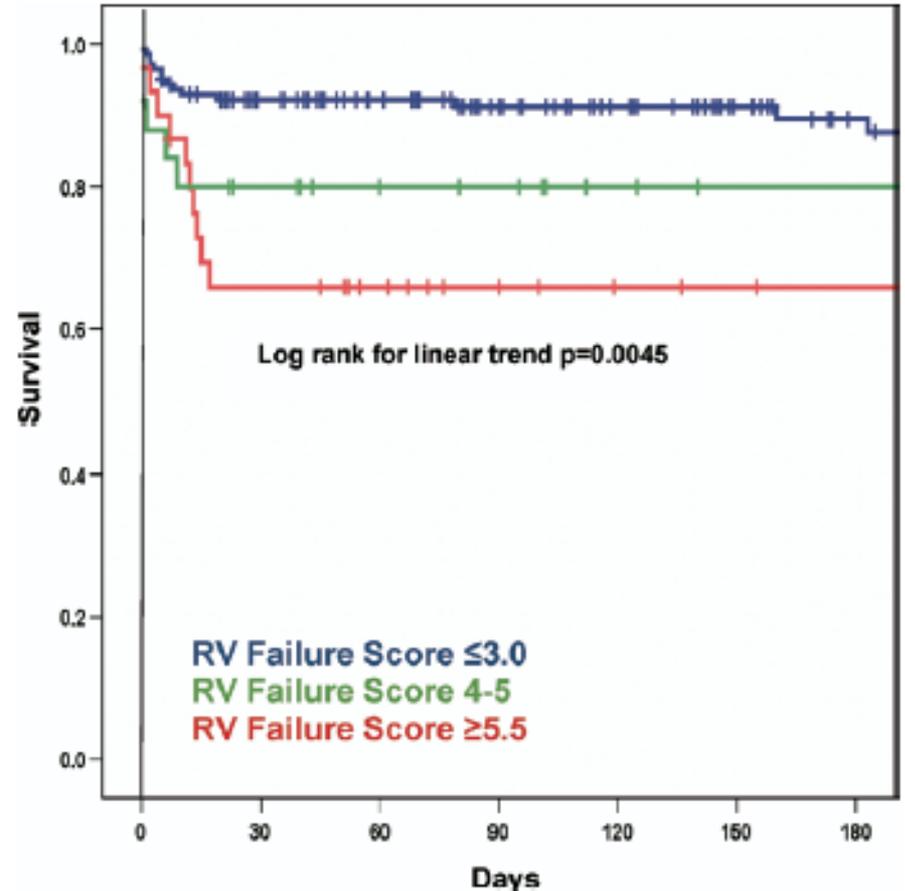
1. Cowger Matthews *J Am Coll Cardiol* 2008;51:2163.

2. Cowger Matthews *Circulation* 2010;121:214.

RV Failure Risk Score

Vasopressor Requirement	3.9 (1.5-9.8)	4
AST \geq 80 IU/L	2.1 (0.96-4.5)	2
Bilirubin \geq 2.0 mg/dL	2.4 (1.1-5.2)	2.5
Cr \geq 2.3 mg/dL	2.9 (1.1-7.7)	3

RVFRS	n	RVF (n)	No RVF (n)	LR RVF [95% CI]
\leq 2.5	142	29	113	0.49 [0.37-0.64]
3.0-4.0	25	15	10	2.8 [1.4-5.9]
\geq 5.5	30	24	6	7.6 [3.4-17.1]



Bleeding following LVAD

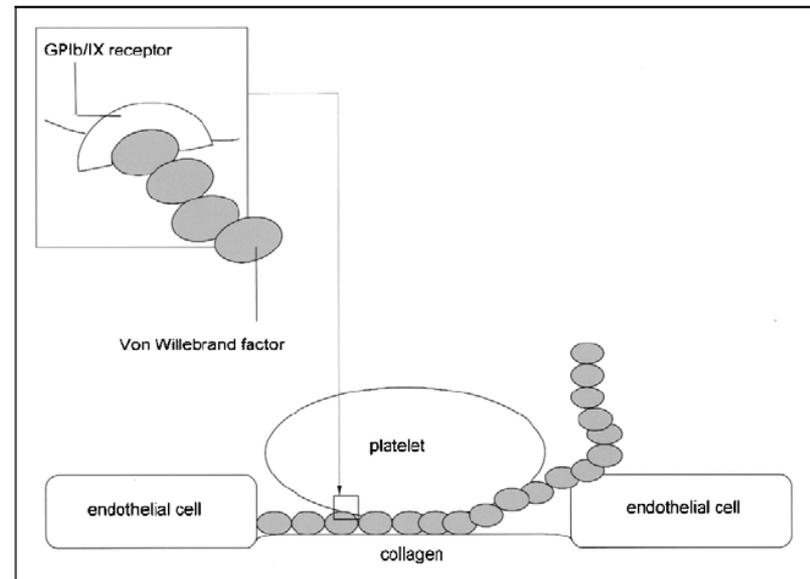
- Incidence of nonsurgical bleeding post-LVAD is 30-44%.^{1,2,3}
 - most common manifestation by far is GI bleeding (69% of bleeds)¹
 - 50% of GI bleeds occur within 2-4 months of LVAD implant^{1,3}
 - Bleeding diathesis *appears* greater with continuous flow devices (HM-II) than pulsatile (HM-XVE)¹.

1. Uriel. *J Am Coll Cardiol* 2010;56: epub. 3. UM Registry

2. Stern *J Card surg* 2010;25:352:epub

Bleeding following LVAD

- Causes for increased bleeding:
 - Medication: antiplatelets and anticoag
 - Acquired bleeding diathesis (vWF) during LVAD support¹⁻³
 - Heyde's syndrome

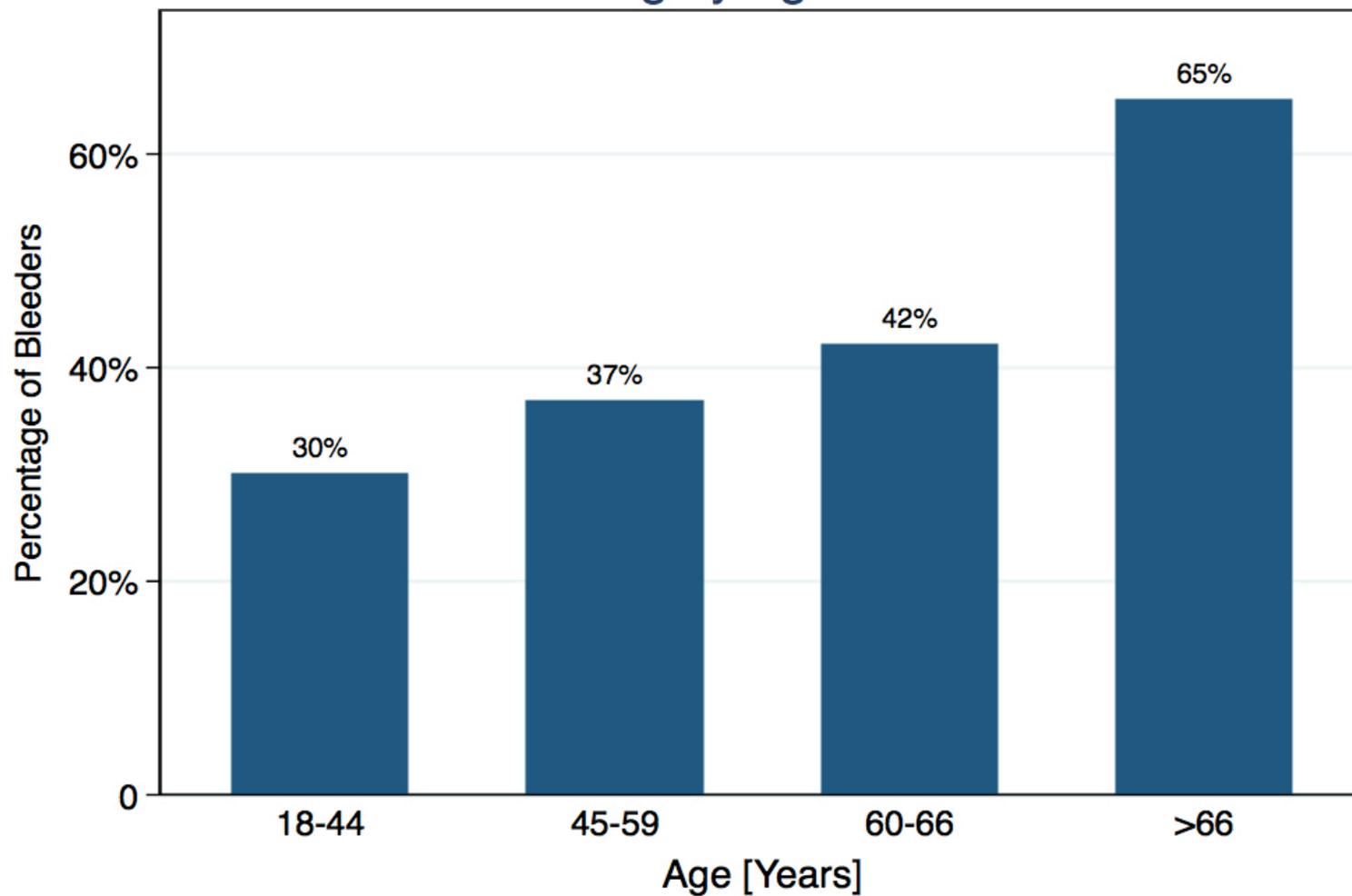


1 Geisen. *E J Cardio Thoracic Surg.* 2008;33:679

2 Crow. *ASAIO J.* 2010 Jul 6; epub

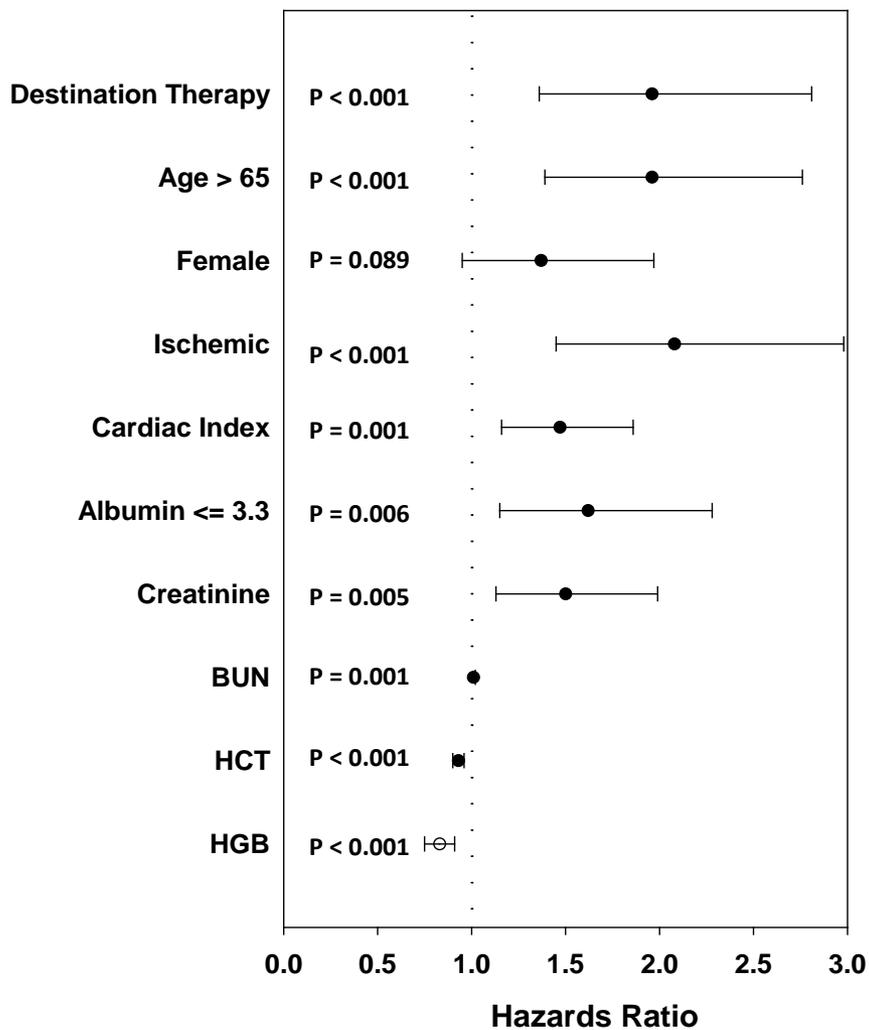
3 Uriel. *J Am Coll Cardiol* 2010.

Bleeding by Age Quartiles

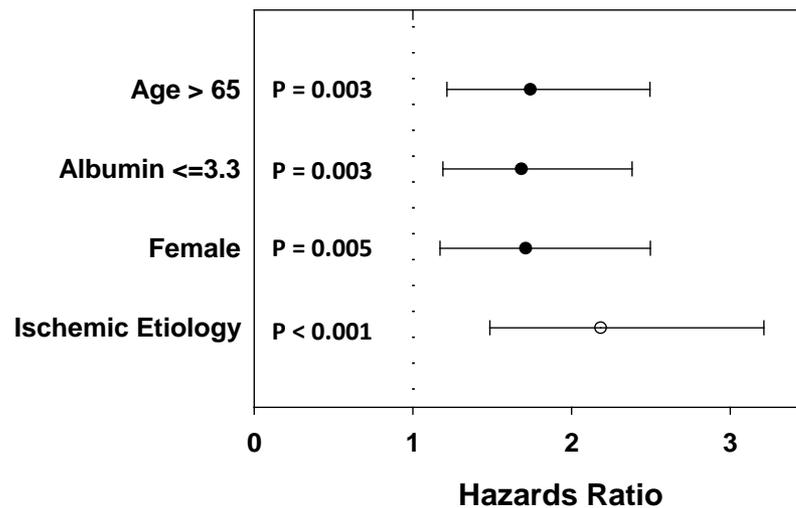


Preoperative Predictors of GI-Bleeding

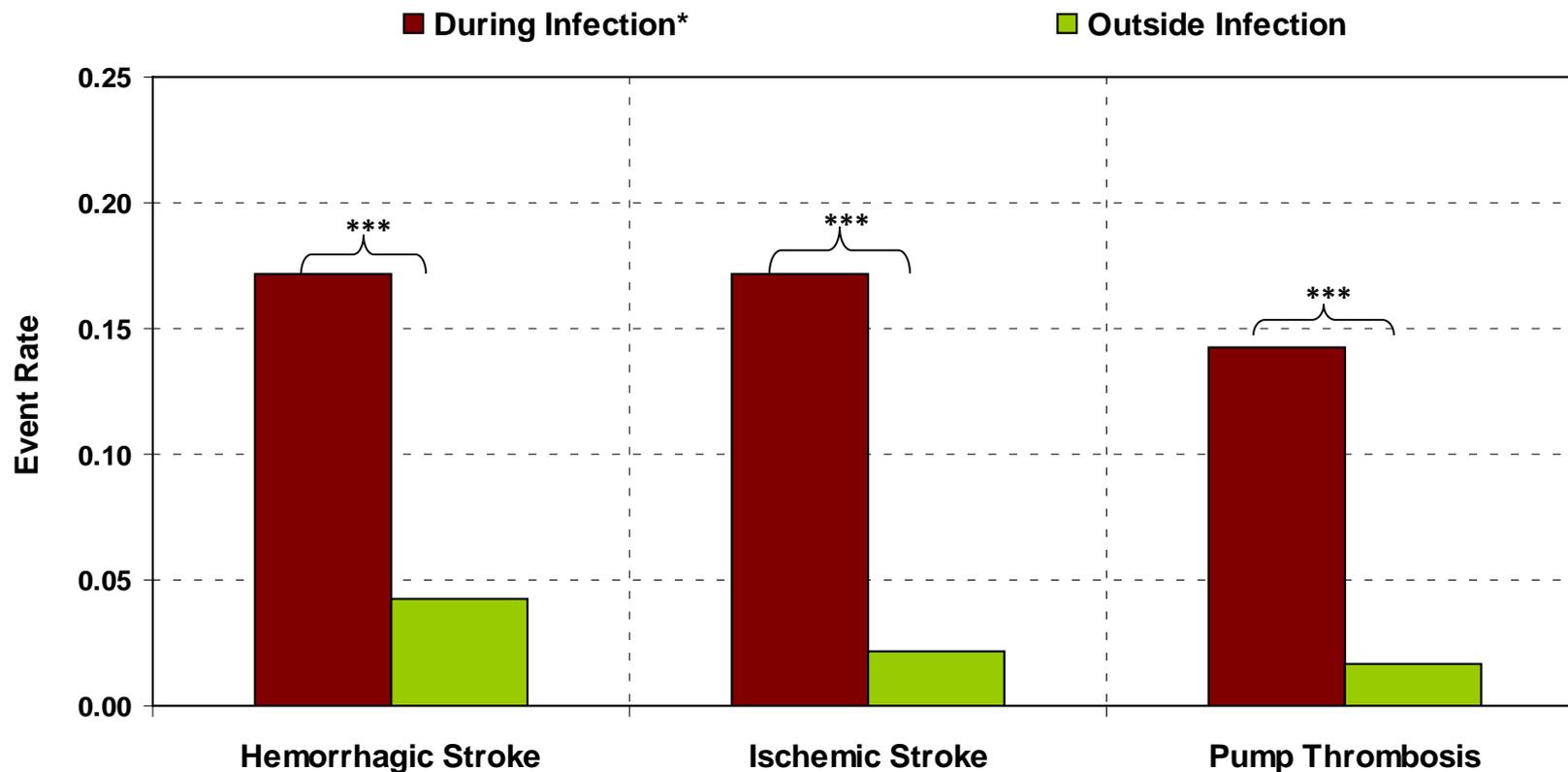
Univariable Correlates



Multivariable Predictors



Infection Increases Risks of Stroke and Pump Thrombus

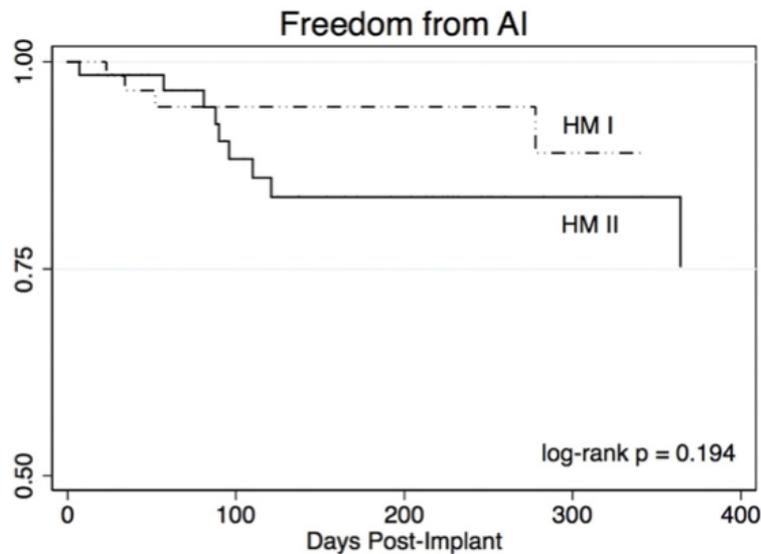


During a 14 day window around an infection event patients were:

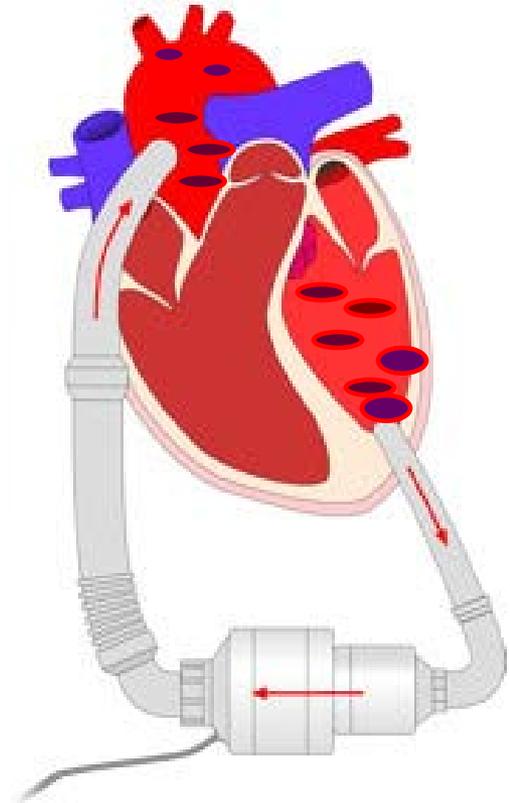
- 4 times likely to experience a hemorrhagic stroke event
- 8 times likely to experience an ischemic stroke event
- 9 times likely to experience a pump thrombus event

Aortic Insufficiency During LVAD Support

- Aortic insufficiency (AI) can lead to ineffective LVAD output via recirculation



Number at risk	0	100	200	300	400
HM I	67	39	22	14	7
HM II	63	40	29	15	9



Planned Studies of Full Support VADs

Device Name	Company	BTT	DT
Jarvik 2000	Jarvik	Pivotal Study in progress (Prospective, single-arm) 150 patient primary sample completed f/u May '12	Pivotal Trial planned, Conventional DT RCT vs. HM II, 309 pts IDE approved Sept '12
HeartMate III	Thoratec	CE Mark Trial 2012 IDE Pivotal Trial 2013	IDE Pivotal Trial 2013
Pericardial MVAD	HeartWare	International I BTT/DT combined, 50 patients 2012/2013 US BTT/DT Pivotal concurrent, 2013	
Transapical VAD (Longhorn)	HeartWare	International: 50 pt feasibility, pivotal BTT/ Conventional DT combo 2014 US: BTT/DT Pivotal concurrent, 2015	
DuraHeart II	Terumo	BTT/DT Pivotal trial planned for 2013	

Planned Studies of Partial Support VADs

Device Name	Company	BTT	DT
Synergy	Circulite	Feasibility study to include BTT, BTD and DT subjects ----->	Feasibility study planned for Q1 2013 Single arm 20 patients @ 7 sites
C-Pulse	Sunshine Heart	Pivotal trial to include BTT, BTD and DT subjects ----->	Pivotal Trial planned, NYHA III/ambulatory IV, RCT v OMM, 350-400 pts Conditional IDE Sept '12

Ongoing or Planned DT Studies for Less Advanced Heart Failure

Study Name	Device	Sponsor	Design	Target Population
ROADMAP	HeartMate II	Thoratec	Observational	NYHA class IIIB or IV (w/o iv inotrope)
REVIVE-IT	TBD	NHLBI & Industry (TBD)	RCT (vs. OMM*)	NYHA III (selected using Seattle Heart Failure Model and exercise capacity)

* Optimal Medical Management

ROADMAP Study

Risk Assessment and Comparative
Effectiveness Of Left Ventricular Assist
Device and Medical Management in
Ambulatory Heart Failure Patients

ROADMAP STUDY DESIGN AND STATUS

- Prospective, multi-center, industry-sponsored (Thoratec) non-randomized, controlled, observational study
- Primary Objective:
 - Evaluate the effectiveness of HM II support vs. Optimal Medical Therapy
 - Ambulatory NYHA Class IIIB/IV HF patients
 - Not dependent on intravenous inotropic support
 - Must meet the FDA approved indications for HM II destination therapy
- Centers: 40 LVAD centers, 12 community referring centers
- Target enrollment: 200
- Enrollment status: 57 patients enrolled at 25 sites as of 10/16/12

RE♥IVE IT

Randomized Evaluation of VAD InterVEntion before Inotropic Therapy

REVIVE-IT STUDY DESIGN

- Pilot, open-label, RCT testing a *strategy* of earlier LVAD vs. OMM in pts not txp eligible
 - Ambulatory, systolic heart failure (LVEF \leq 35%)
 - NYHA 3 months on optimal med Rx, no inotropes
 - Model-based estimated 1-yr mortality \geq 17%
 - 1:1 randomization, 50 patients per group
 - OMM patients may receive LVAD if meet standard contemporary DT criteria
 - Intention-to-treat analysis
- Screen failures entered into REVIVE-IT Registry
 - \approx 2500 patients
 - Evaluation of prognostic information (including biomarkers) in larger, more heterogeneous group

REVIVE-IT PRIMARY STUDY ENDPOINT

- The Primary Study Outcome for REVIVE-IT will be evaluated at 2 years and include the composite outcome of:
 - Survival
 - Freedom from disabling stroke (defined as Modified Rankin Scale (MRS) ≥ 3)
 - Improvement of 6 minute walk test distance by ≥ 75 meters from prerandomization baseline

SUMMARY

- Durable, implanted left ventricular assist devices have very high survival to transplant for the BTT indication
- Survival when used for DT is improving, likely as a result of better patient selection and management
- Major adverse events include stroke, bleeding, infection, right heart failure, pump thrombus and aortic insufficiency.
- Very large improvements in QOL and functional capacity despite AE profile
- Studies planned in patients with less advanced heart failure with existing full flow device and with partial flow devices.