

Evaluation of the HeartWare HVAD Left Ventricular Assist System for the Treatment of Advanced Heart Failure: Results of the ADVANCE Bridge to Transplant Trial

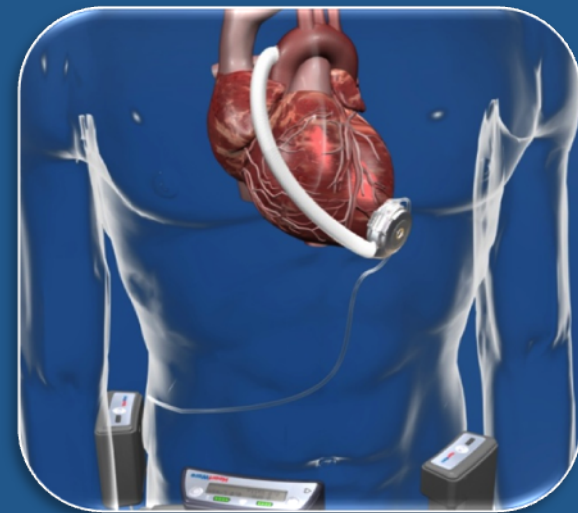
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Presenter Disclosure Information

- Keith Aaronson, MD, MS
- FINANCIAL DISCLOSURE
 - Research Support: HeartWare*, Thoratec*, Terumo
 - Clinical Steering Committee: HeartWare
 - Personal remuneration: none
 - * My activities with HeartWare and Thoratec have been reviewed and approved by the University of Michigan Medical School Conflict of Interest Board and a management plan is in place.
- UNLABELED/UNAPPROVED USES DISCLOSURE
 - I will discuss investigational use of the HeartWare HVAD

HeartWare Ventricular Assist System

- HVAD miniaturized implantable blood pump
 - Pericardial placement – no pump pocket
 - Provides up to 10 L/min of flow
 - Centrifugal design, continuous flow
 - Hybrid magnetic / hydrodynamic impeller suspension
 - Optimizes flow, pump surface washing, and hemocompatibility
- Thin (4.2 mm), flexible driveline with fatigue resistant cables



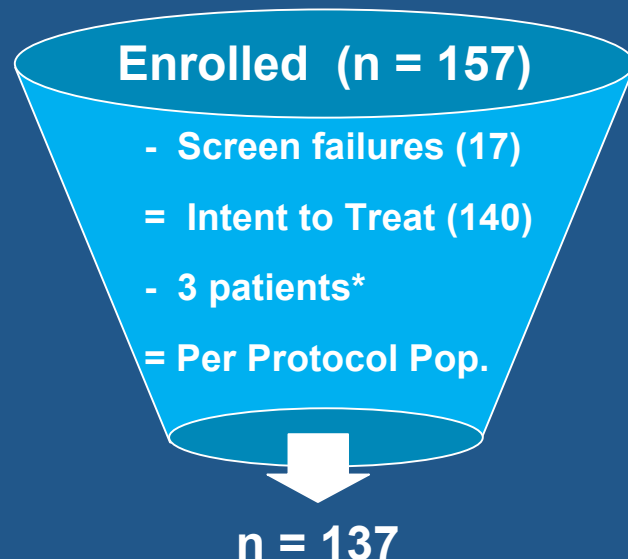
ADVANCE Trial Design

- Multi-site (30), prospective trial to evaluate the HeartWare HVAD as a bridge-to-transplant in the US
- Enrollment period was August 2008 to February 2010
- All patients were followed for ≥ 180 days following implant or until earlier cardiac transplantation, device explant for recovery or death
- Treatment group was compared to a contemporaneous control group consisting of patients enrolled in the *Interagency Registry for Mechanically Assisted Circulatory Support* (INTERMACS) who received a commercially-available, durable, left ventricular assist device as a BTT

Derivation of Treatment & Control Populations

Treatment Group (n=137)

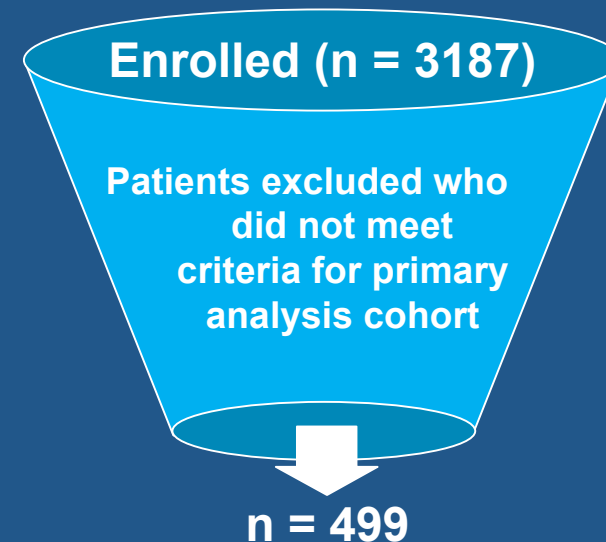
- **Inclusion Criteria:** age >18 years, BSA >1.2m², NYHA Class IV, listed UNOS Status 1A or 1B
- Standard LVAD/transplant exclusion criteria
- IABP only allowable preop circulatory support



INTERMACS Control (n=499)

Adult patients who received a primary LVAD as a BTT during the enrollment period

- Listed for transplant at time of implant
- BSA ≥ 1.2m²
- Serum creatinine ≤ 5 without dialysis
- Not on ventilator
- First VAD
- IABP only allowable preop circulatory support



* 2 excluded for liver enzymes >3x normal, 1 excluded for participation in another trial

ADVANCE Trial: Analyses

- Primary Outcome
 - Success*, defined as survival on the originally implanted device, transplant or explant for ventricular recovery (must survive 60 days post-explant) at 180 days
 - Analysis adjusted by propensity score
 - Predictors: age, gender, BUN, creatinine, BSA, right atrial pressure, prior sternotomy, INTERMACS profile
- Secondary Outcomes
 - Comparison of survival between treatment and control groups
 - Functional and QoL outcomes and AEs in the treatment group
 - Functional status changes, measured by 6-min walk test
 - QoL changes, measured by KCCQ and EuroQoL EQ-5D
 - Incidence of SAEs

* Per Protocol cohort

ADVANCE Trial: Baseline Characteristics

	Treatment (n=140)	Control (n=499)	P value
Age (years)	53.3 ± 10.3	52.2 ± 12.2	0.19
Female Gender, n (%)	39 (28%)	120 (24%)	0.36
BSA (m ²)	2.06 ± 0.28	2.07 ± 0.3	0.59
BUN (mg/deciliter)	25.3±13.5	28.9 ± 20.9	0.94
Right atrial pressure (mmHg)	10.8 ± 3.3	11.5 ± 5.0	0.53
Serum creatinine (mg/dL)	1.3 ± 0.4	1.4 ± 0.6	0.89
Etiology - % Ischemic	41%		
LVEF (%)	17.8 ± 7.1		
CI (L/min/m ²)	2 ± 0.5		
PCWP (mmHg)	23 ± 9		
Mean arterial blood pressure (mmHg)	77 ± 13		
Intravenous inotropic agents, n (%)			
Any inotrope	115 (82%)		
Two or more inotropes	16 (11%)		
IABP	35 (25%)		

INTERMACS & Propensity Score

		Treatment *	Control	P value
INTERMACS Patient Profile	INTERMACS 1	7 (5.0%)	39 (7.8%)	<.002
	INTERMACS 2	39 (27.9%)	259 (51.9%)	
	INTERMACS 3	62 (44.3%)	103 (20.6%)	
	INTERMACS 4 -7	32 (22.9%)	98 (19.7%)	
Propensity Score	Quartile 1	12 (8.8%)	145 (29.2%)	<.0001
	Quartile 2	28 (20.4%)	131 (26.4%)	
	Quartile 3	51 (37.2%)	107 (21.5%)	
	Quartile 4	46 (33.6%)	114 (22.9%)	

* Safety Population (N=140) for INTERMACS Patient Profile;
Per Protocol Population (N=137) for Propensity Score

ADVANCE Trial Primary Outcome: Success

Control Group Success:	90.1%
Treatment Group Success:	92.0%
Difference:	-1.9%
95% Upper Confidence Limit (UCL) on difference	0.9%

Principal Analysis: Noninferiority

The UCL, 0.9%, is less than the prespecified 15% noninferiority margin. Treatment group success is noninferior to control (p<0.001)

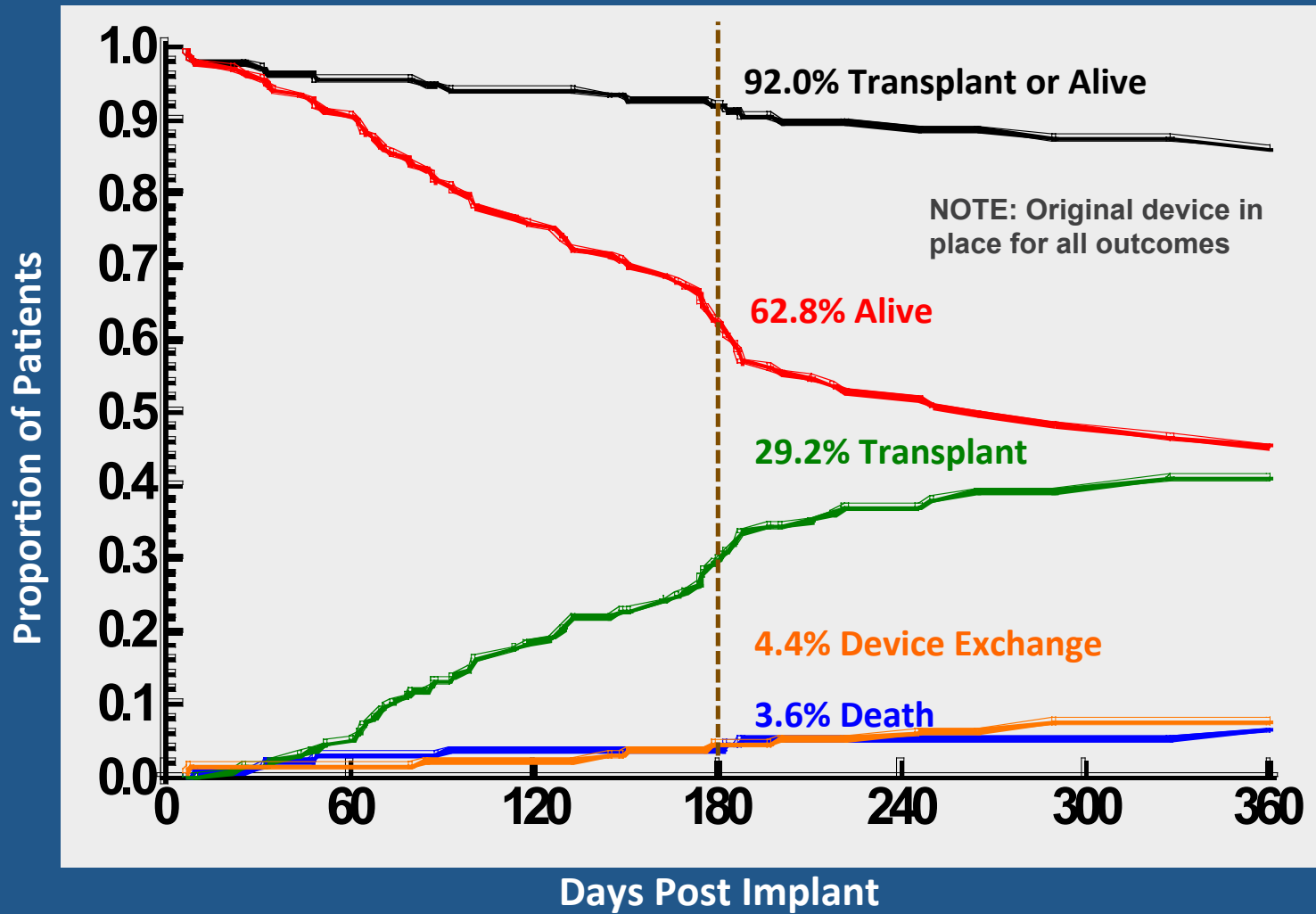
Secondary Analysis: Superiority

Unadjusted:	Difference = -1.9%, p = 0.62
Propensity score adjusted:	Difference = -3.1%, p = 0.20

All results are from the Per Protocol cohort.

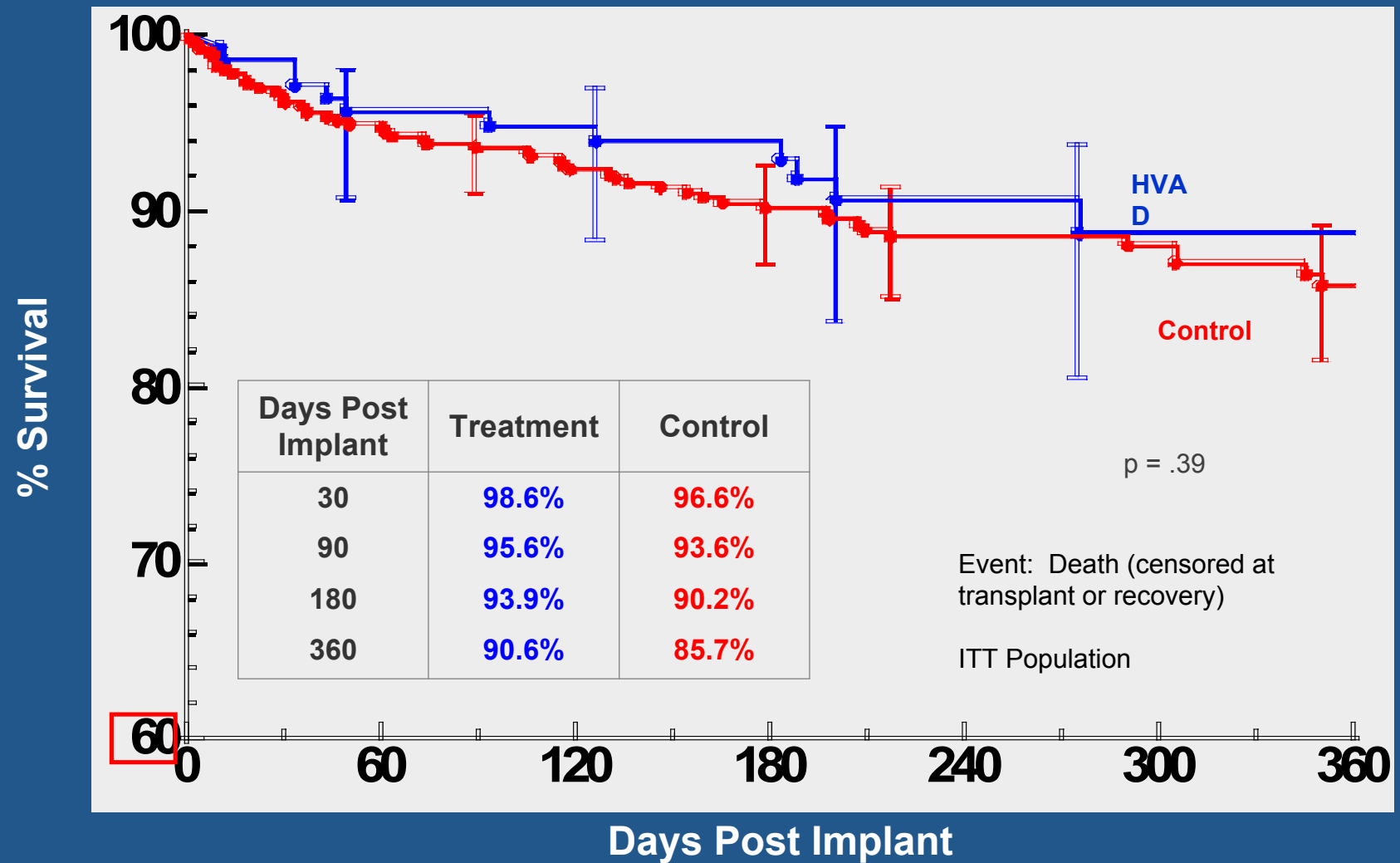
For noninferiority analysis, p value one-sided; for superiority analysis, p values two-sided

ADVANCE Trial Treatment Group Outcomes (Per Protocol Population)



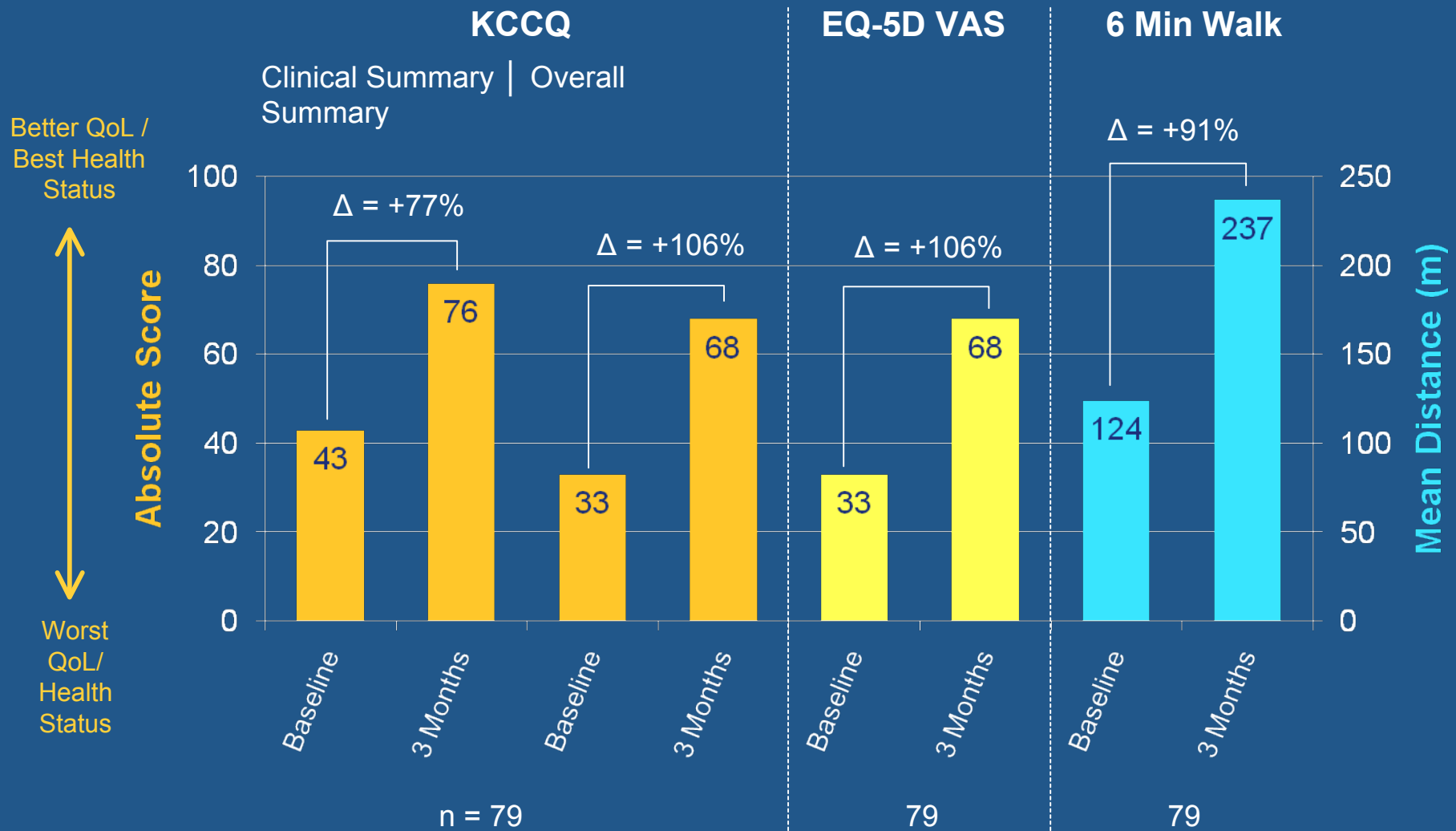
Patients at Risk 137 125 104 86 58 31 22

ADVANCE Trial Secondary Outcome: Survival



Patients at Risk	Treatment	140	128	108	92	63	36	26
	Control	499	440	370	305	228	176	127

Quality of Life and Functional Capacity



All paired differences $p < 0.001$

Adverse Events in Treatment Group (n = 140)

	Patients with Event	# Events	Event Rate PPY [†]	Pagani, et al. Event Rate PPY ^{††}
Bleeding				
Requiring surgery	21 (15.0%)	24	0.27	0.45
GI bleeding	13 (9.3%)	22	0.25	Not reported
Infection				
Localized non-device	34 (24.3%)	34	0.39	0.85
Driveline exit	15 (10.7%)	18	0.21	0.31
Sepsis	9 (6.4%)	10	0.11	0.35
Pump Pocket	0 (0.0%)	0	0.0	0.03
Stroke				
Ischemic ^{2,3}	10 (7.1%)	10	0.11	0.09
Hemorrhagic	4 (2.9%)	4	0.05	0.05
TIA	7 (5.0%)	7	0.08	0.04

² Five of 10 (50%) ischemic strokes occurred in first 48 hours following HVAD implant

³ Eight of 10 (80%) of ischemic stroke patients recovered to Modified Rankin Scores ≤ 3

[†]87.47 Patient-Years

^{††}Pagani, et al. JACC 54: 312-321, 2009; 181.8 Patient-Years

Adverse Events in Treatment Group (n = 140)

	Patients with Event	# Events	Event Rate PPY [†]	Pagani, et al. Event Rate PPY ^{††}
Ventricular Arrhythmias	11 (7.9%)	11	0.13	0.40
Right Heart Failure				
RVAD requirement	4 (2.9%)	4	0.05	0.09
Inotropic support	27 (19.3%)	28	0.32	0.20
Peripheral TE	9 (6.4%)	9	0.10	0.14
Hemolysis	2 (1.4%)	2	0.02	0.06
Hepatic dysfunction	4 (2.9%)	4	0.05	0.04
Respiratory Failure	27 (19.3%)	34	0.39	0.48
Renal Failure	13 (9.3%)	14	0.16	0.17
Device Replacement				
Low INR thrombosis	3 (2.1%)	3	0.03	
Surgery related	3 (2.1%)	3	0.03	
<u>Exchange for BiVAD</u>	<u>1 (0.7%)</u>	<u>1</u>	<u>0.01</u>	
TOTAL	7 (4.9%)	7	0.07	0.07

[†]87.47 Patient-Years

^{††}Pagani, et al. JACC 54: 312-321, 2009; 181.8 Patient-Years

ADVANCE Trial: Study Limitations

- Treatment assignment was not randomized and therefore relevant baseline characteristics may differ between groups
- Difficult to compare clinical trial outcomes to those of a national registry due to differences in data collection and adjudication
- Serial assessment of functional capacity and quality of life were limited by inability to collect data on some critically ill patients, possibly leading to underestimations of the true benefits of investigational device therapy

ADVANCE Trial: Conclusions

- Implantation of the small, continuous-flow HVAD pump contained in the pericardial space was associated with a high probability of success (92%) at 180 days
- HVAD pump demonstrated noninferiority to contemporaneously implanted, commercially available ventricular assist devices
 - 1.4% 30-day mortality
 - 94% survival at 180 days, 91% survival at 360 days
- Favorable adverse event profile when used as a BTT
- Marked improvement in functional capacity and quality of life improvements similar to those obtained with cardiac transplantation