HeartWare HVAD for the Treatment of Patients with Advanced Heart Failure Ineligible for Cardiac Transplantation: Results of the ENDURANCE Destination Therapy Trial

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hVAD® ENDURANCE Trial

On behalf of all ENDURANCE investigators

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Relevant Financial Relationship Disclosure Statement

Investigational use of the

HeartWare® Ventricular Assist Device will be discussed.

FD Pagani: HeartWare research contract managed by the University of Michigan.

Study Timelines

CAP initiated

FDA Approval, November 2012

ADVANCE (BTT+CAP)

BTT enrollment complete

Favorable FDA panel recommendation

2008 2009 2010 2011 2012 2013 2014 2015

DT enrollment begins

DT enrollment complete

Primary Endpoint complete

ENDURANCE (DT)

Improved Pump Sintering/Coring Tool

ENDURANCE Supplemental

Enrollment begins (protocol BP management)

ENDURANCE Trial Design

A prospective and randomized trial to compare the safety and effectiveness of the HeartWare® HVAD System to a FDA-approved LVAD in patients with end-stage heart failure who do not qualify for heart transplantation.

Primary endpoint:

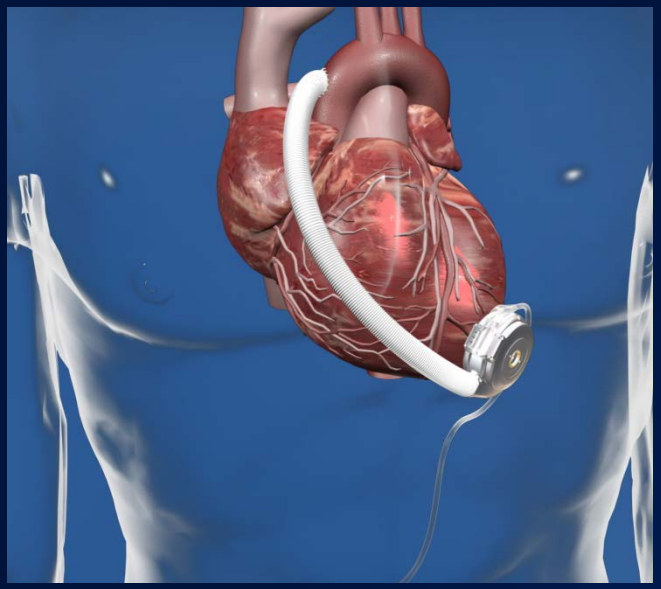
- Survival at two years free from disabling stroke (Modified Rankin Score ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery

Secondary endpoints:

- Adverse events per INTERMACS definition (version 2.3)
- KCCQ and EuroQol EQ-5D Health Status
- NYHA functional class and 6-minute walk distance

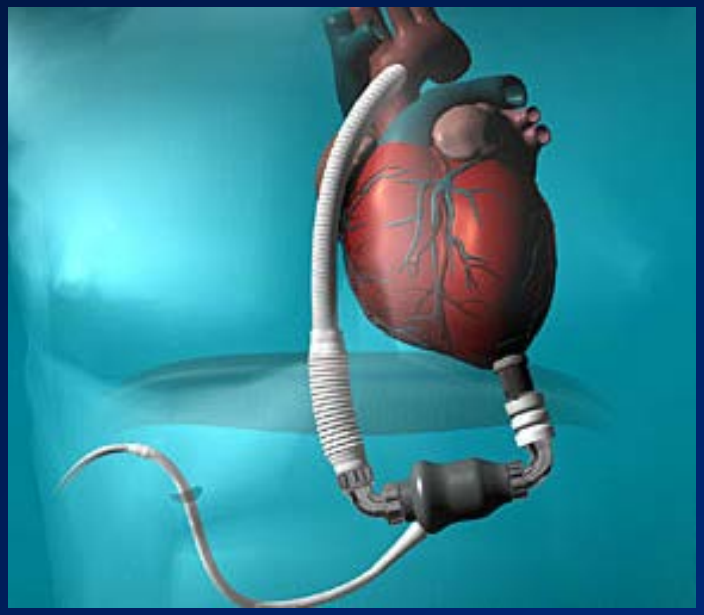
ENDURANCE Study Devices

Treatment Device:



- Continuous flow centrifugal HVAD® Pump
- Pericardial placement
- FDA approved for BTT in 2012

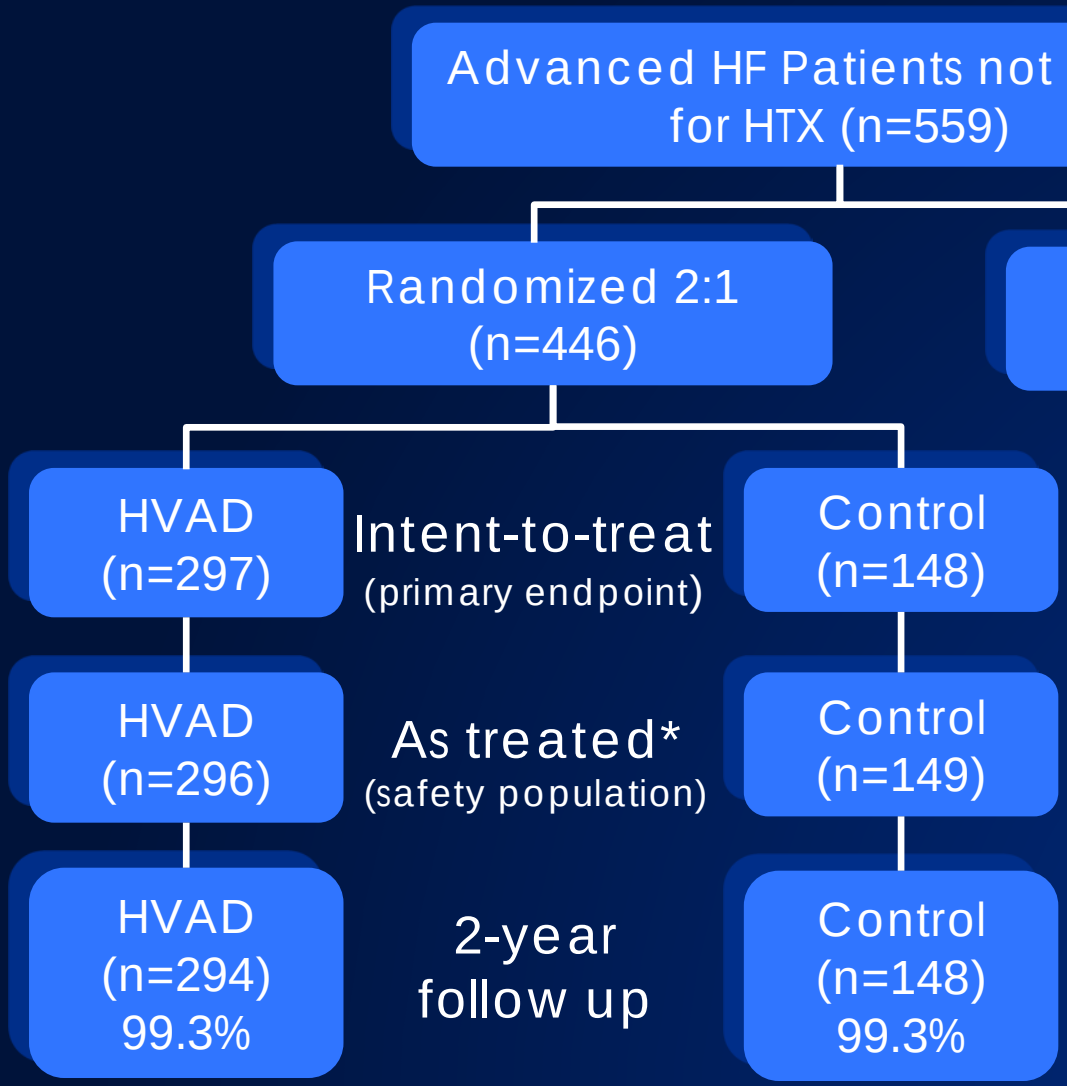
Control Device:



- Continuous flow axial pump
- Sub-diaphragmatic placement
- FDA approved for BTT in 2008, DT in 2010

ENDURANCE Trial Design

Patients randomized from 04 August 2010 through 08 May 2012



Top 3 reasons for Screen Failure:

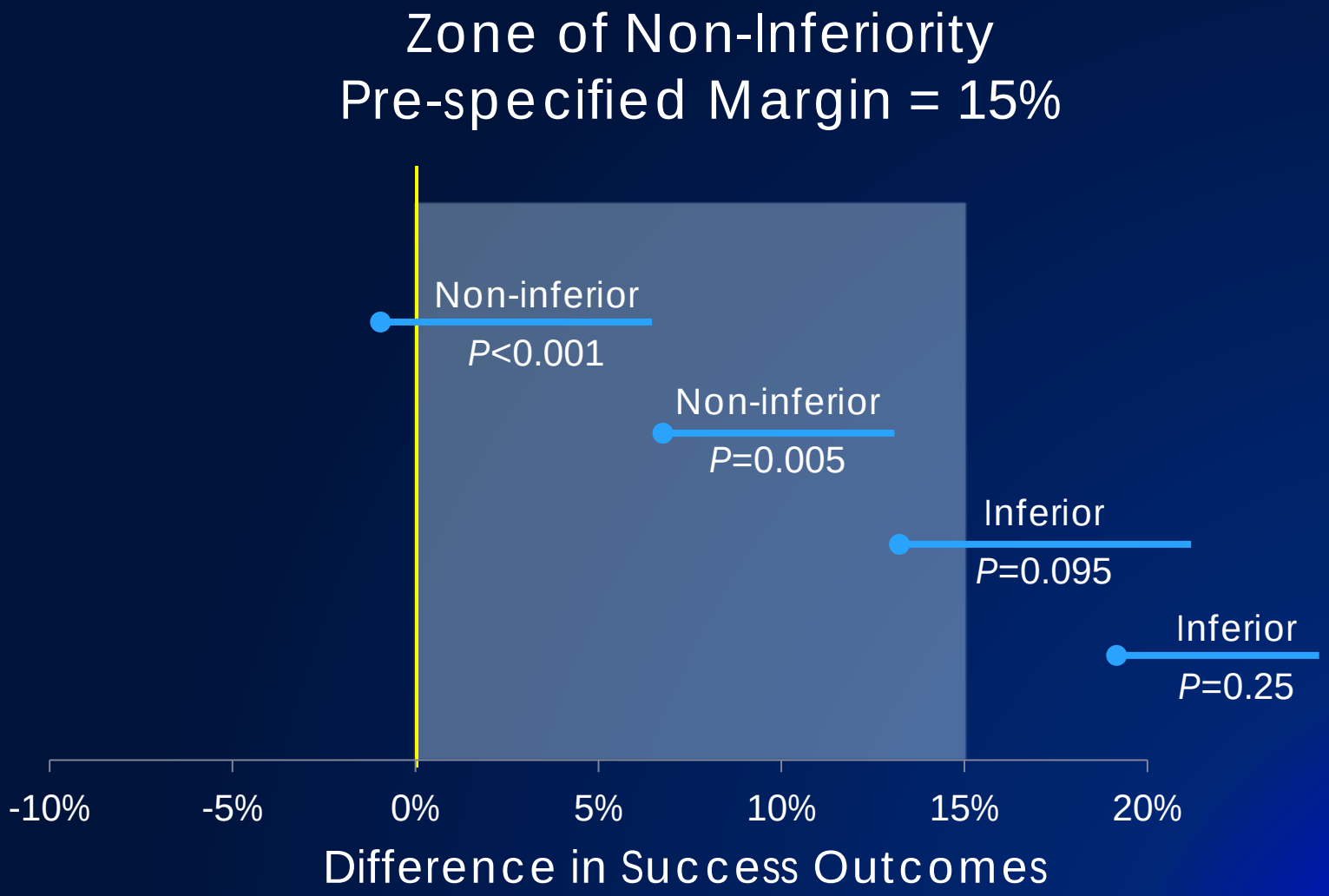
- Body habitus
- Unwillingness to comply with study requirements
- LVEF

*Crossovers: HVAD to control (N=4); control to HVAD (N=3)

Patient Characteristics and Demographics

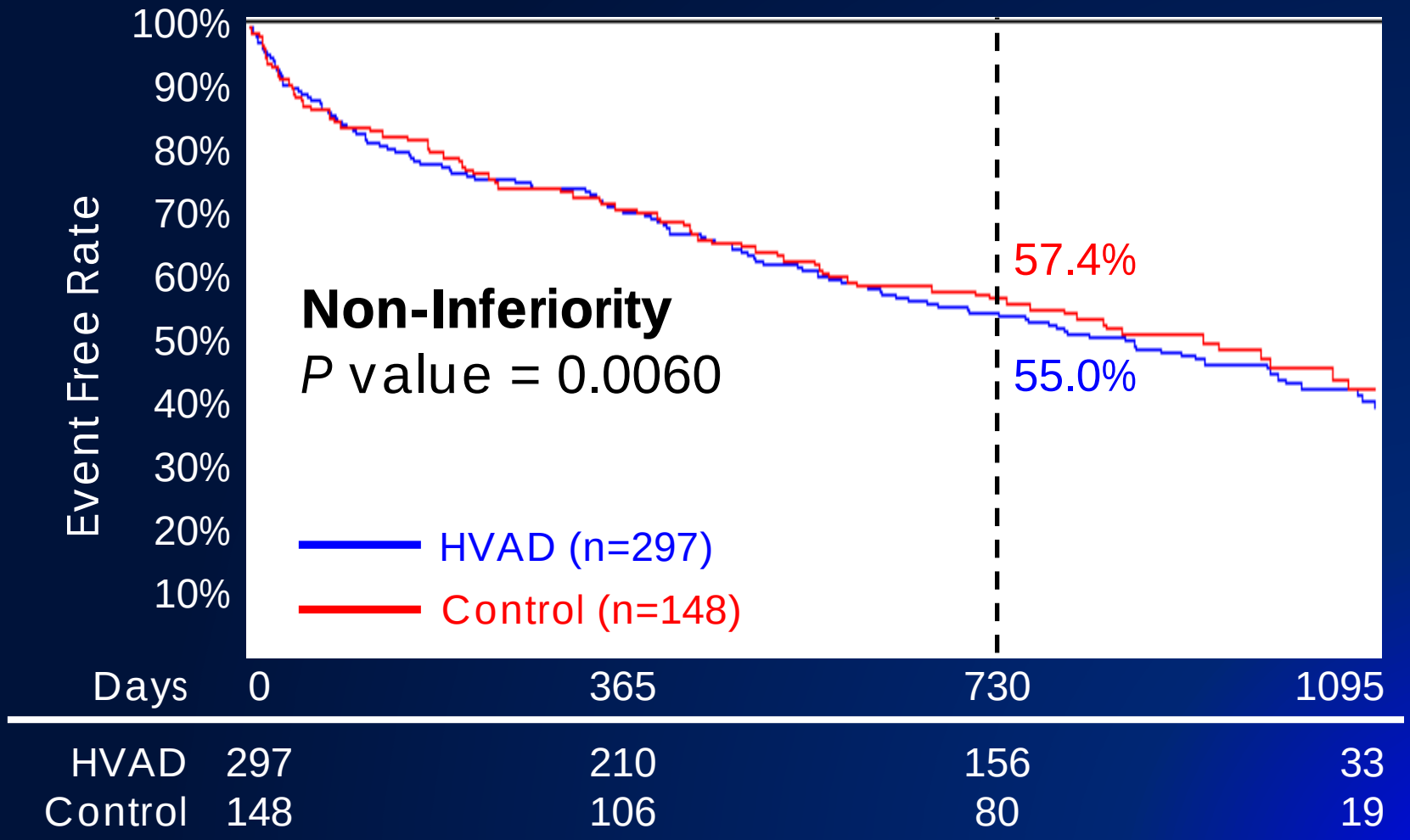
Baseline Characteristics	HVAD (n=297)	Control (n=148)	*P* value
Age (years)	**63.9**	**66.2**	**0.04**
Gender: Male Female	76.4% 23.6%	82.4% 17.6%	0.18
Height (cm)	173.8	175.5	0.07
Body Surface Area (m^2)	2.0	2.0	0.62
INTERMACS Profile 1 2 3 4 5 6 7	 3.4% 29.0% 40.4% 19.9% 4.0% 1.3% 2.0%	 3.4% 31.1% 40.5% 18.2% 3.4% 0.0% 3.4%	0.85
Ischemic Etiology of Heart Failure	57.9%	60.1%	0.68
Smoker	68.0%	62.2%	0.24
Stroke/TIA	19.2%	16.2%	0.51
Arrhythmia	78.1%	83.1%	0.26
Severe Tricuspid Insufficiency	**11.8%**	**5.4%**	**0.04**
Inotropes (pre-implant)	71.3%	71.1%	>0.99
Hypertension requiring medication	65.3%	70.9%	0.24

Non-inferiority Margins

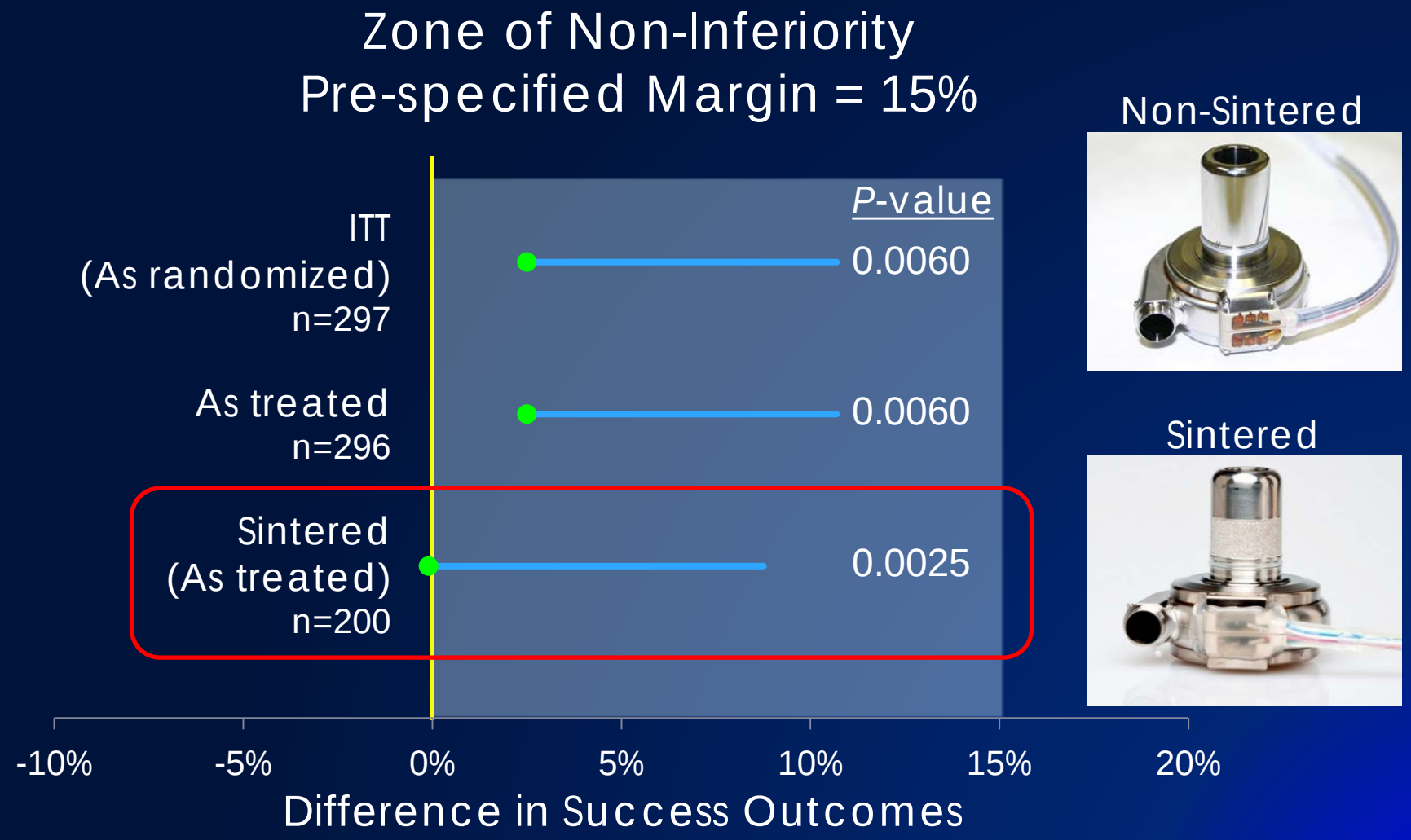


Primary Endpoint - Achieved

Survival at two years free from disabling stroke (MRS ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery



Primary Endpoint Non-inferiority Margins



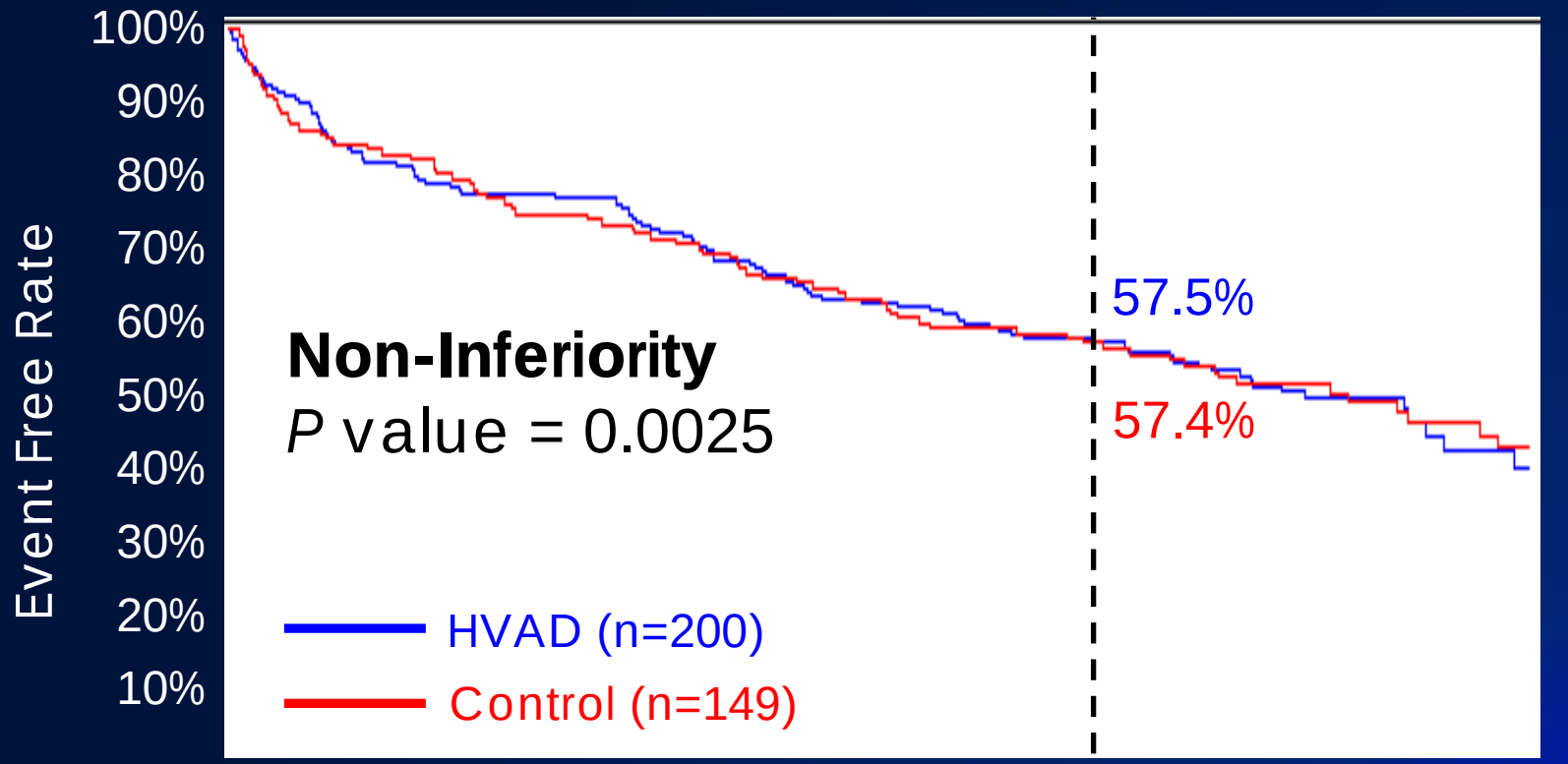
Non-Sintered

Sintered

Sintered HVAD Pump = currently available pump

Primary Endpoint - Sintered HVAD vs. Control

Survival at two years free from disabling stroke (MRS ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery



Days	0	365	730	1095
HVAD	200	145	109	8
Control	149	106	80	19

Sintered HVAD Pump = currently available pump

Binary Summary of Primary Efficacy Endpoint

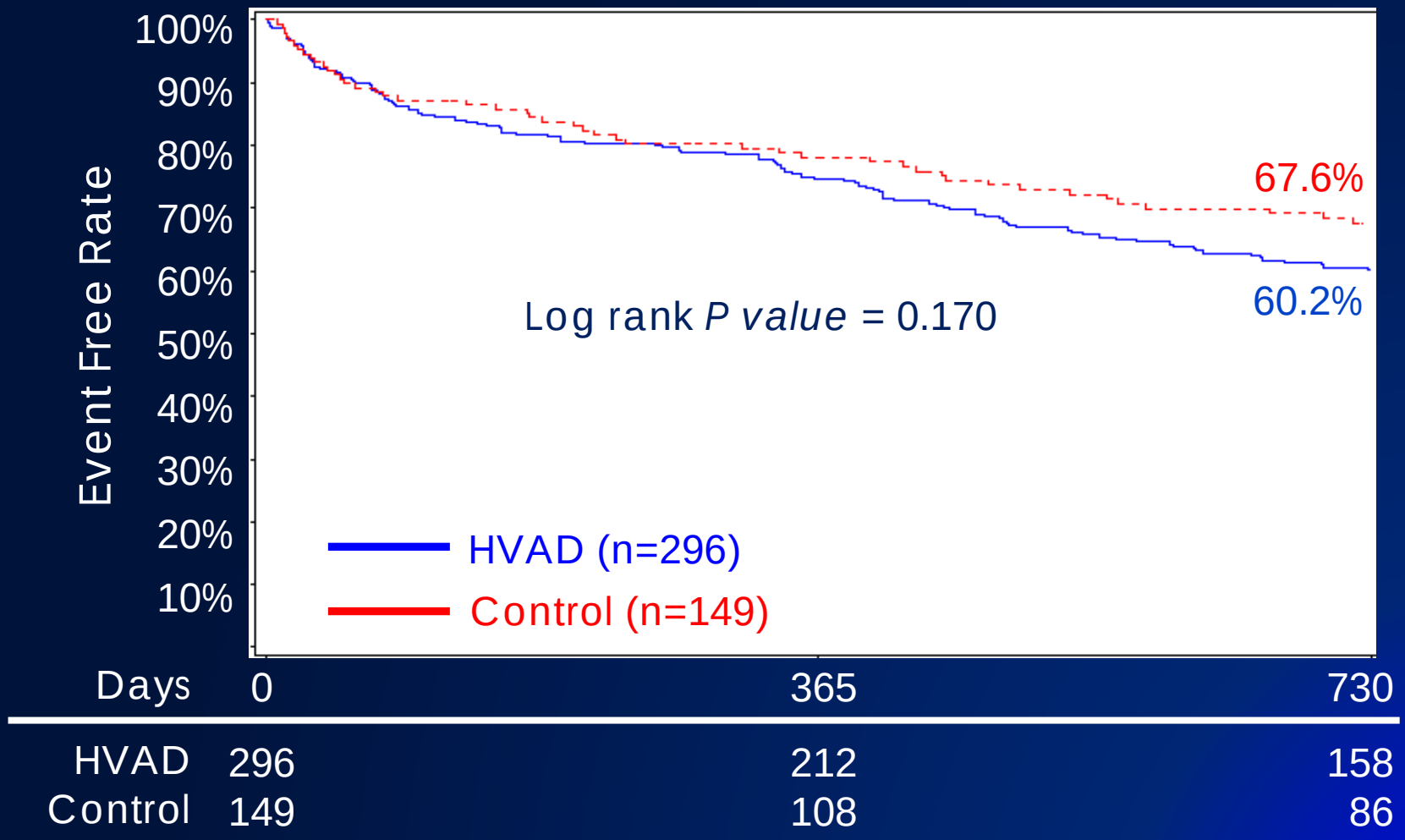
Stroke Free Survival at 2 years	HeartWare (n=297)	Control (n=148)	*P* value
Success	**164 (55.2%)**	**85 (57.4%)**	**0.69**
Failure	133 (44.8%)	63 (42.6%)	0.69

Reasons for Failure			
Patient dies	103 (34.7%)	39 (26.4%)	0.08
Device malfunction, failure requiring exchange, urgent transplant, explant	26 (8.8%)	24 (16.2%)	0.025
Subject has disabling stroke (MRS $\geq$4 at 24 weeks)	3 (1.0%)	0 (0.0%)	0.55
Imputed failure*	1 (0.3%)	0 (0.0%)	>0.99

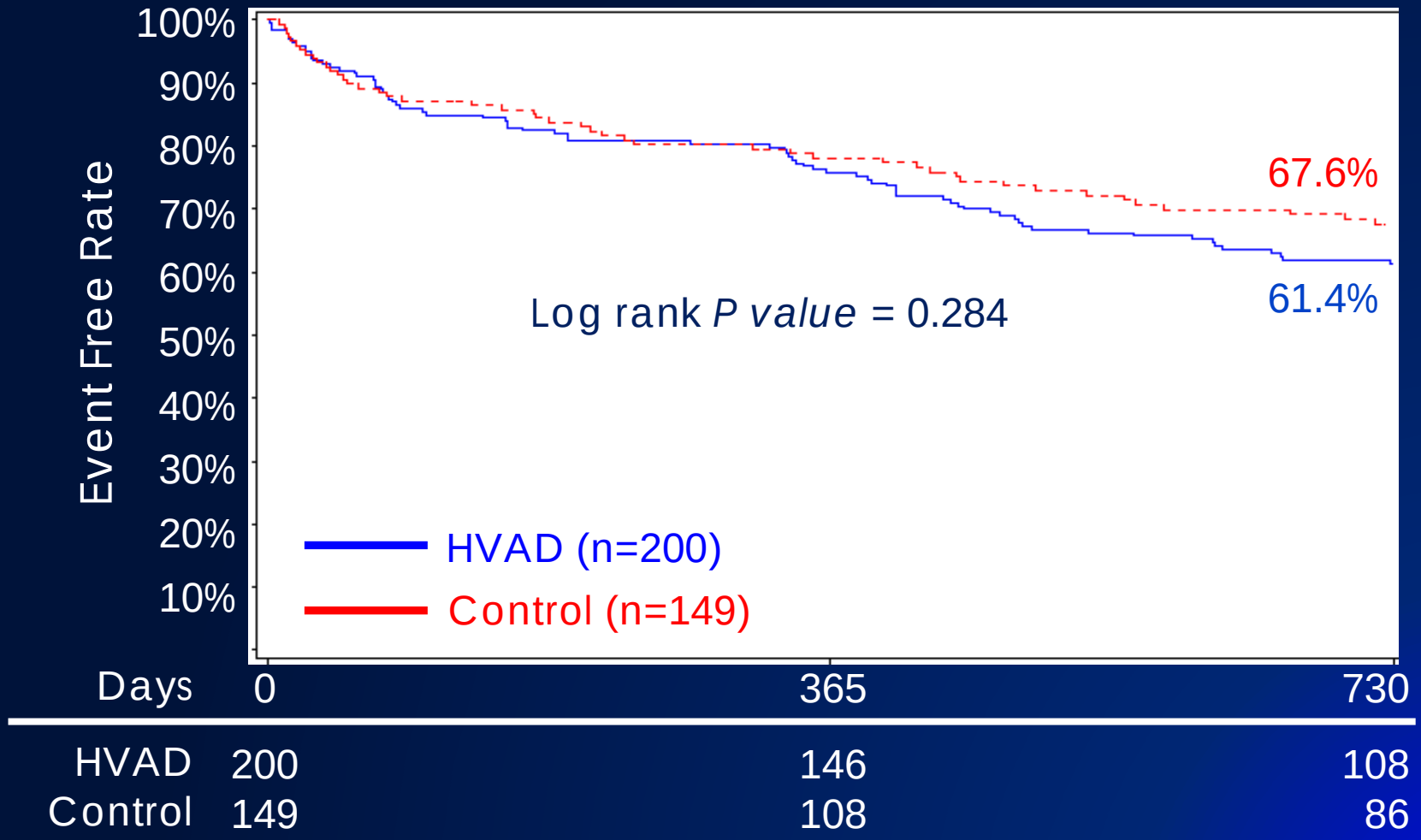
* Patient experienced a stroke prior to their 2 year endpoint, and died beyond the 2 year endpoint, but before the 24 week MRS assessment.

Note: ENDURANCE defined each component hierarchically – e.g., if a patient has a disabling stroke and dies, they are counted as a death.

Kaplan-Meier Survival
Overall HVAD Compared to Control



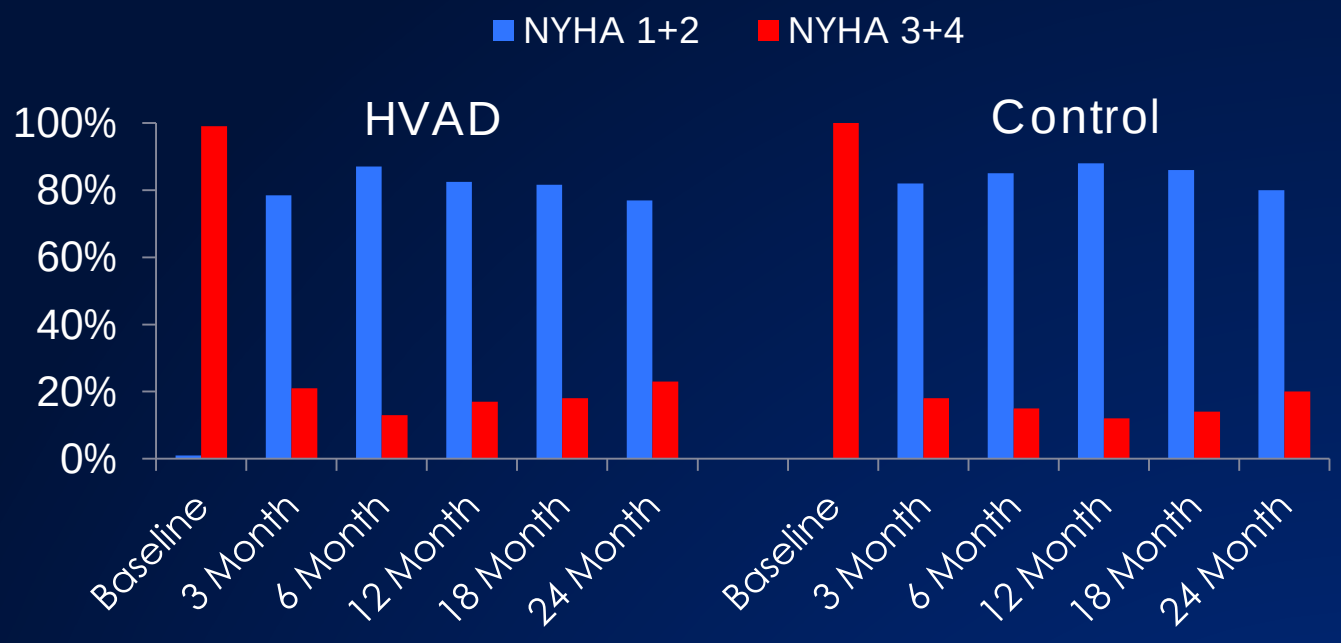
Kaplan-Meier Survival
Sintered HVAD Compared to Control

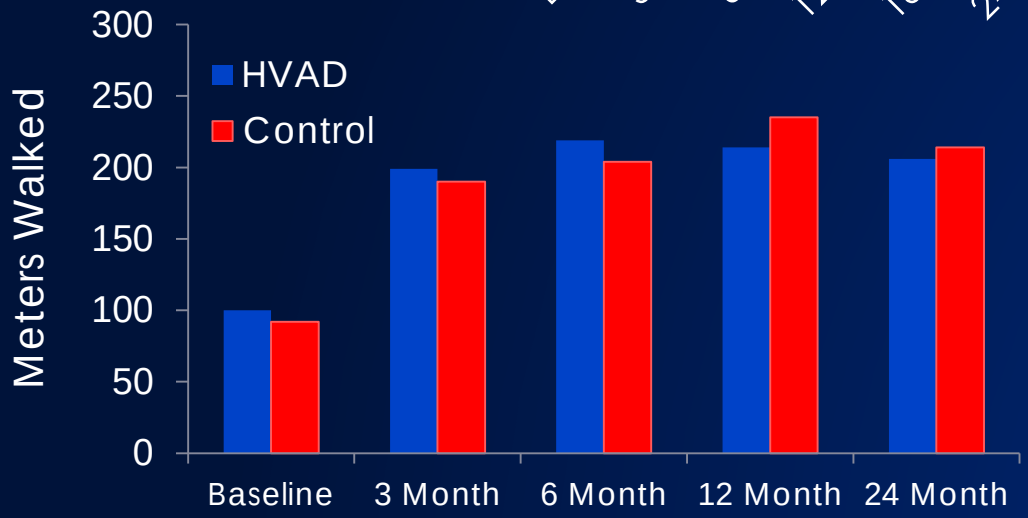


Sintered HVAD Pump = currently available pump

NYHA Classification and 6 Minute Walk

Sustained improvements in patients' NYHA Classification*



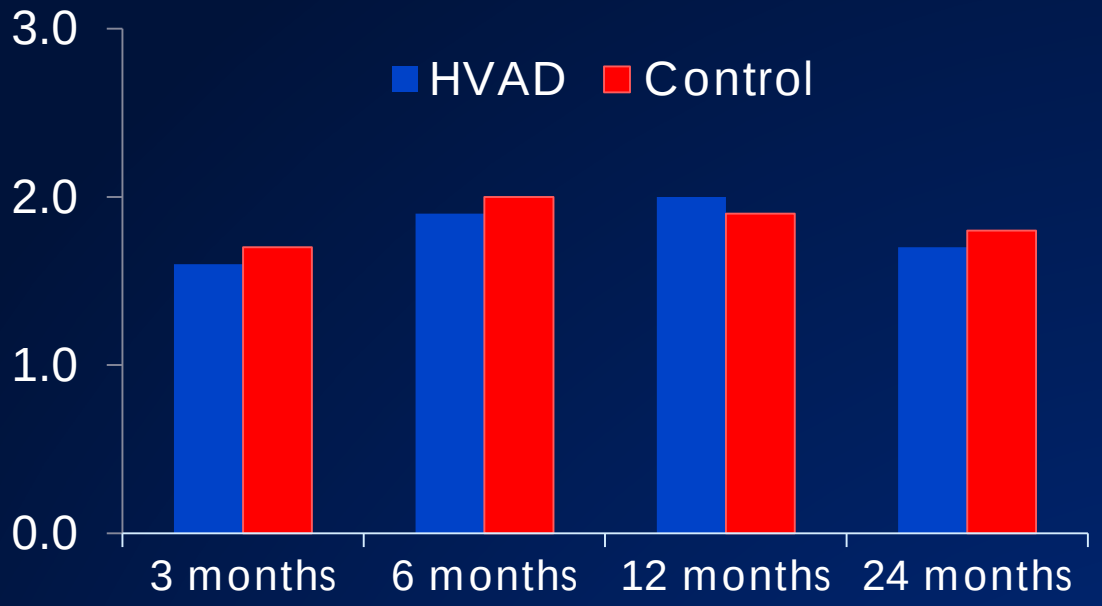


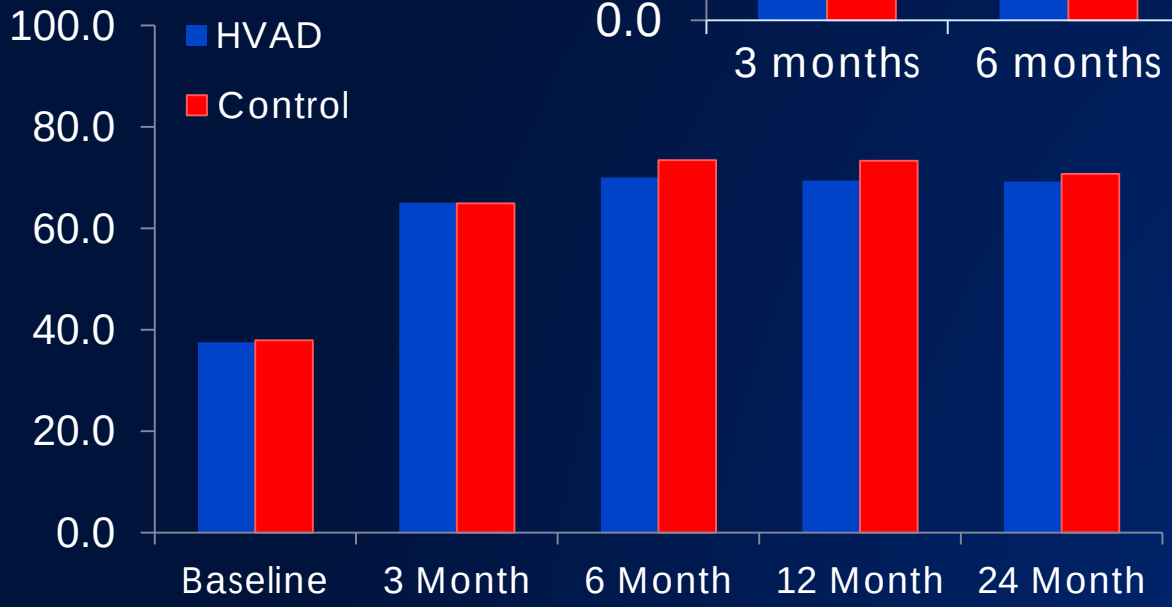
Sustained and significant increase in total distance walked in both cohorts.*

*P=NS for all HVAD vs. Control comparisons

EQ-5D VAS and Overall KCCQ

Statistically significant improvements compared to baseline in EuroQol-5D Visual Analog Scores in both cohorts*





Sustained and significant improvements in Kansas City Cardiomyopathy Questionnaire overall summary scores in both cohorts*

*P=NS for all HVAD vs. Control comparisons

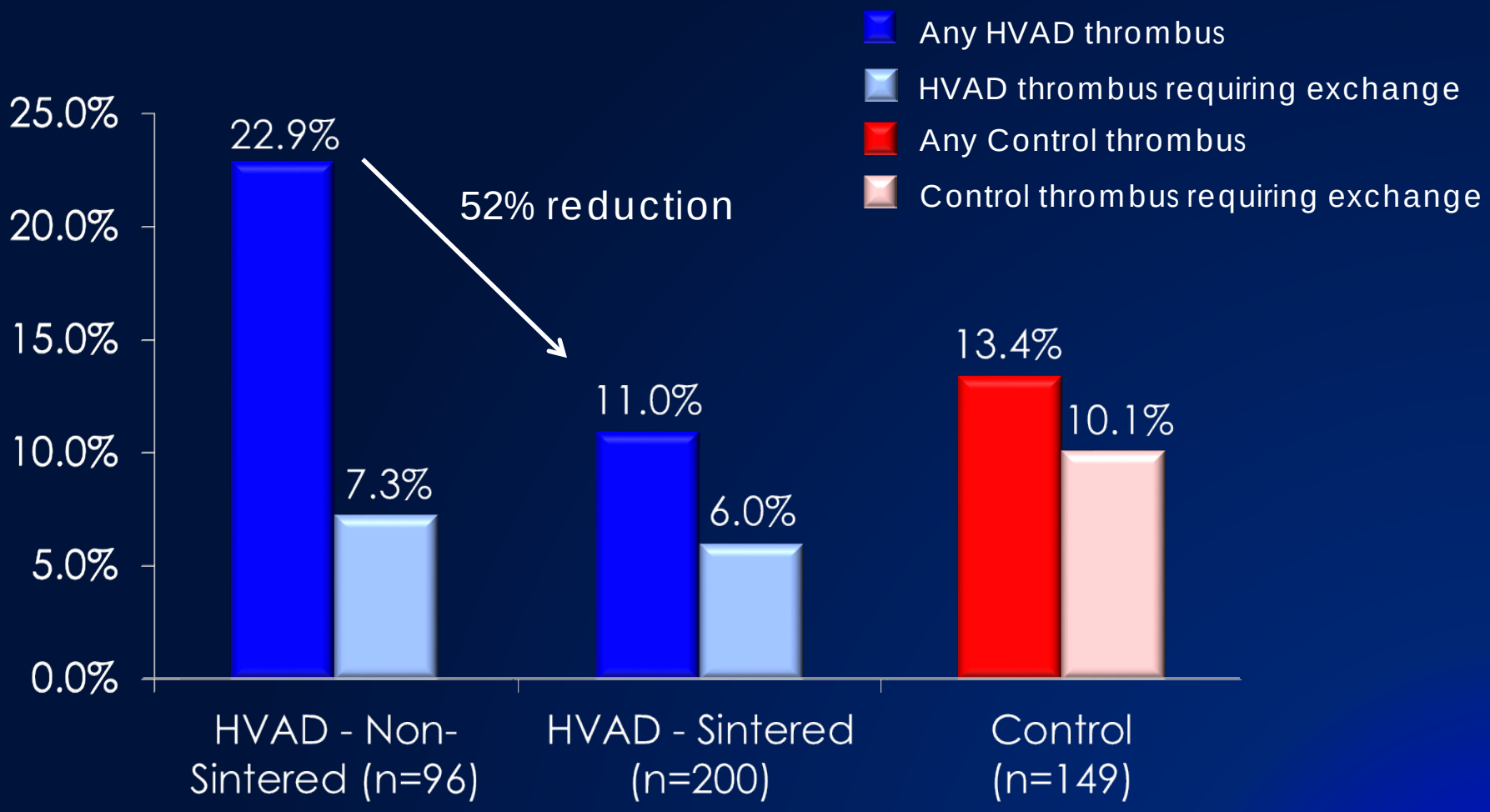
Overall CEC Adjudicated Adverse Events

INTERMACS defined events through 2 years

	HVAD (n=296)			Control (n=149)			
Adverse Event	No. of Patients	No. of events	EPPY (410.02PY)	No. of Patients	No. of events	EPPY (203.89PY)	*P* value
Bleeding	176 (59.5%)	400	0.98	90 (60.4%)	196	0.96	0.92
GI Bleed	103 (34.8%)	225	0.55	51 (34.2%)	90	0.44	0.92
Cardiac Arrhythmia	111 (37.5%)	175	0.43	61 (40.9%)	82	0.40	0.54
Infection	201 (67.9%)	452	1.10	92 (61.7%)	182	0.89	0.21
Driveline Infection	56 (18.9%)	72	0.18	21 (14.1%)	25	0.12	0.23
Stroke	85 (28.7%)	110	0.27	18 (12.1%)	19	0.09	<0.001
Ischemic CVA	50 (16.9%)	65	0.16	13 (8.7%)	13	0.06	0.021
Hemorrhagic CVA	42 (14.2%)	45	0.11	6 (4.0%)	6	0.03	0.001
TIA	24 (8.1%)	27	0.07	7 (4.7%)	7	0.03	0.24
Renal Dysfunction	43 (14.5%)	54	0.13	19 (12.8%)	22	0.11	0.67
Right Heart Failure*	110 (37.2%)	129	0.31	39 (26.2%)	45	0.22	0.025*
Pump Exchange	23 (7.8%)	27	0.06	20 (13.4%)	23	0.10	0.06

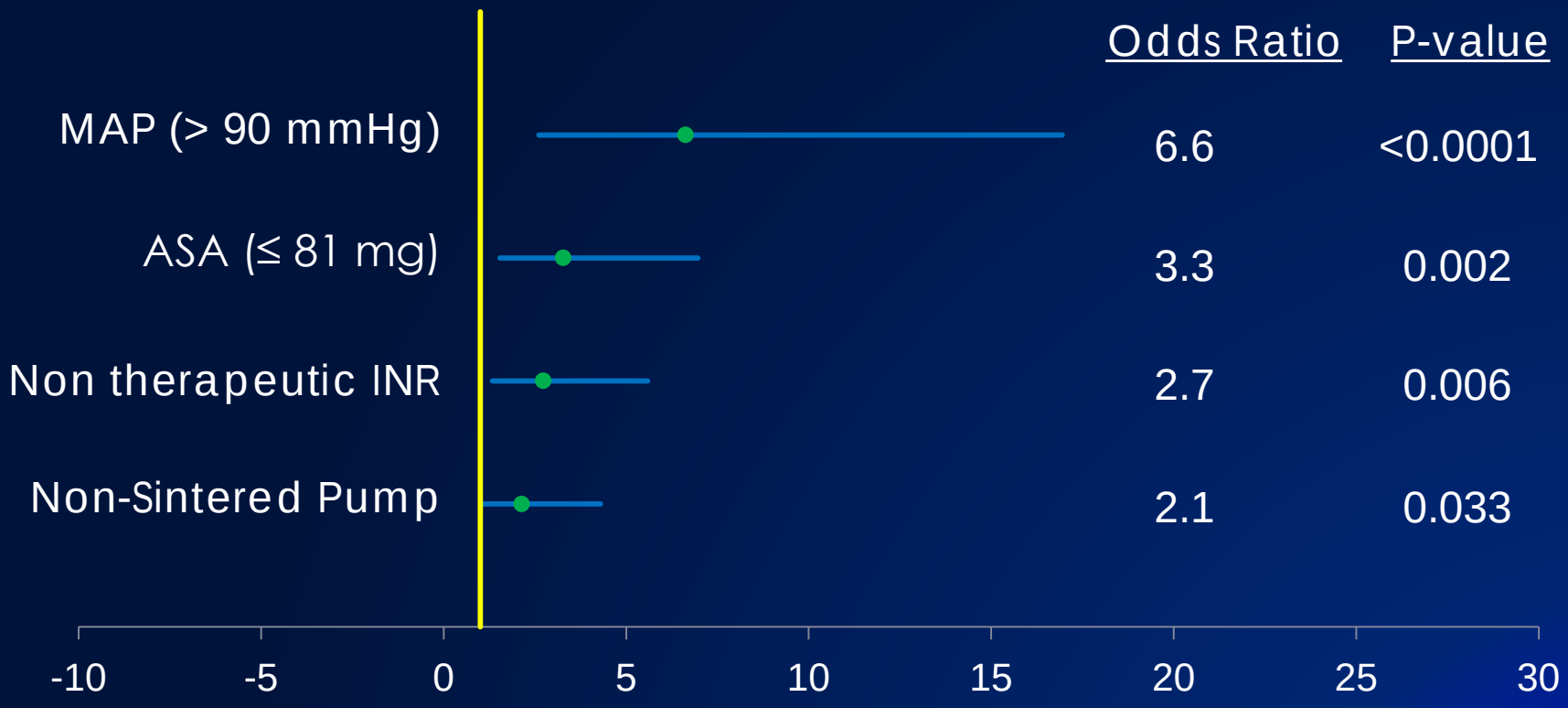
* There was no statistical difference in the rate of RHF in the sintered cohort vs . Control.

Pump Thrombosis (2 years)



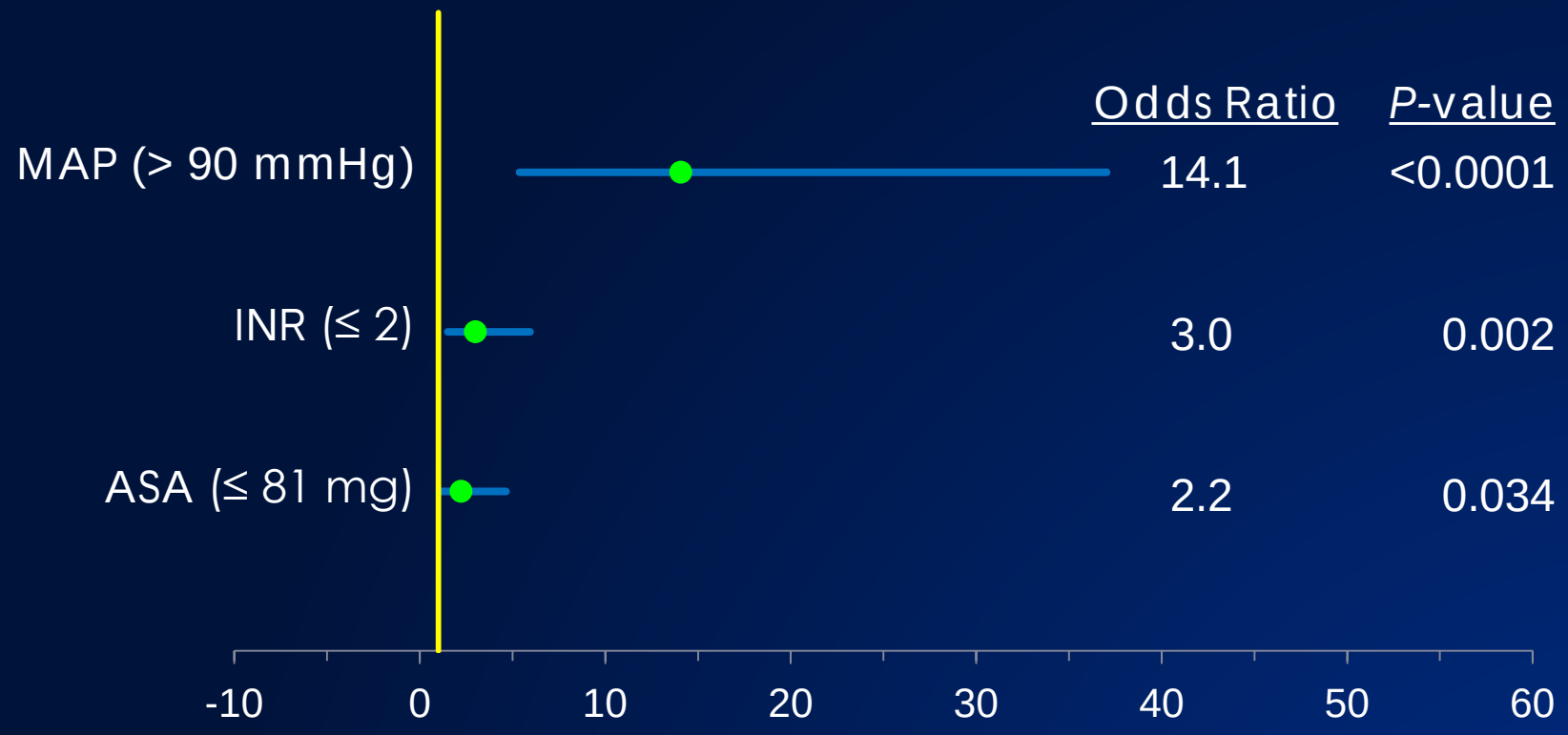
Sintering reduced the overall rate of any suspected pump thrombus, and both overall thrombus rates and exchanges for thrombus were less frequent in patients with the currently available HVAD pump compared to control.

HVAD Thrombus Risk Factor Multivariable Analysis



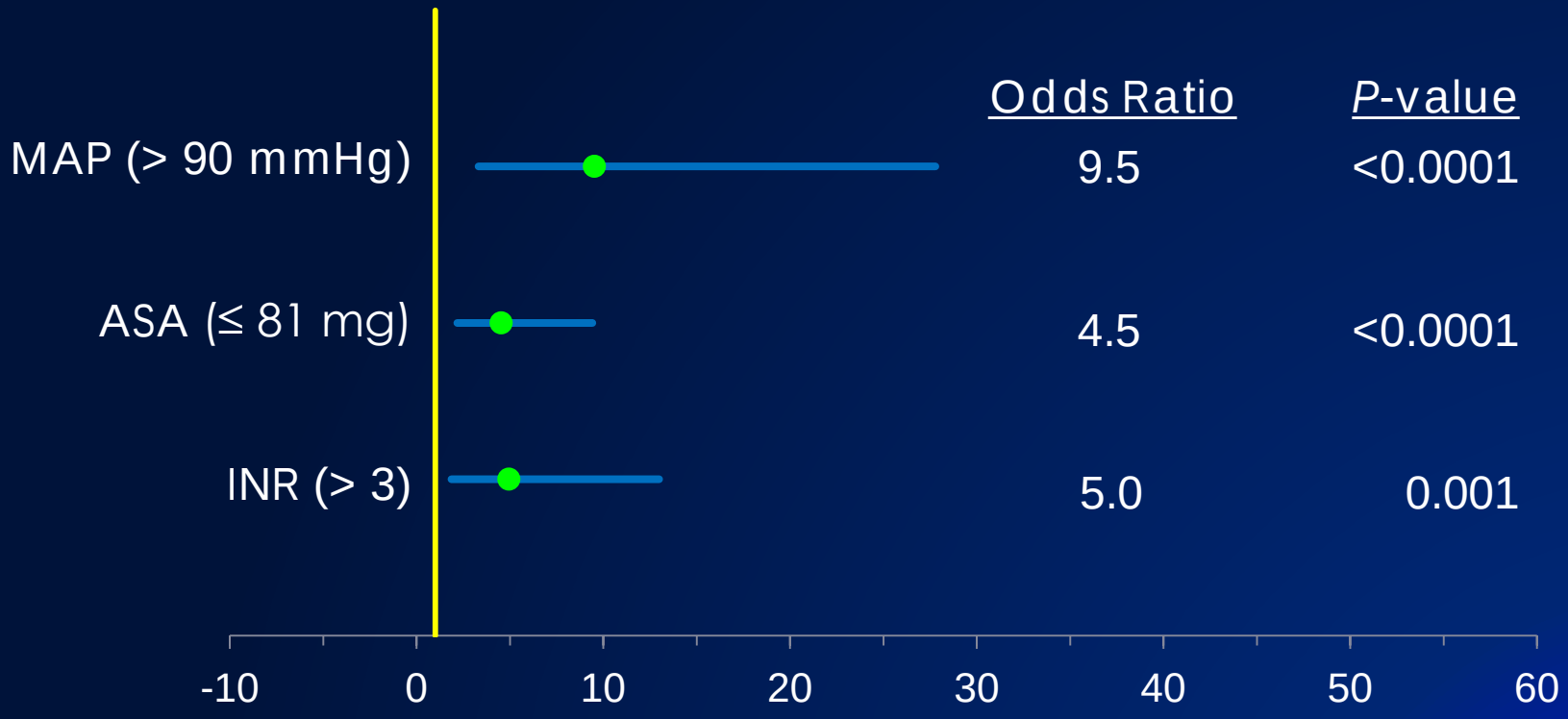
- ✓ Statistically significantly more HVAD patients (7.3%, 0.07 EPPY) had a sub-therapeutic INR <2.0 compared to control patients (2.2%, 0.02 EPPY), *P*=0.04.

ICVA Risk Factor Multivariable Analysis (HVAD)

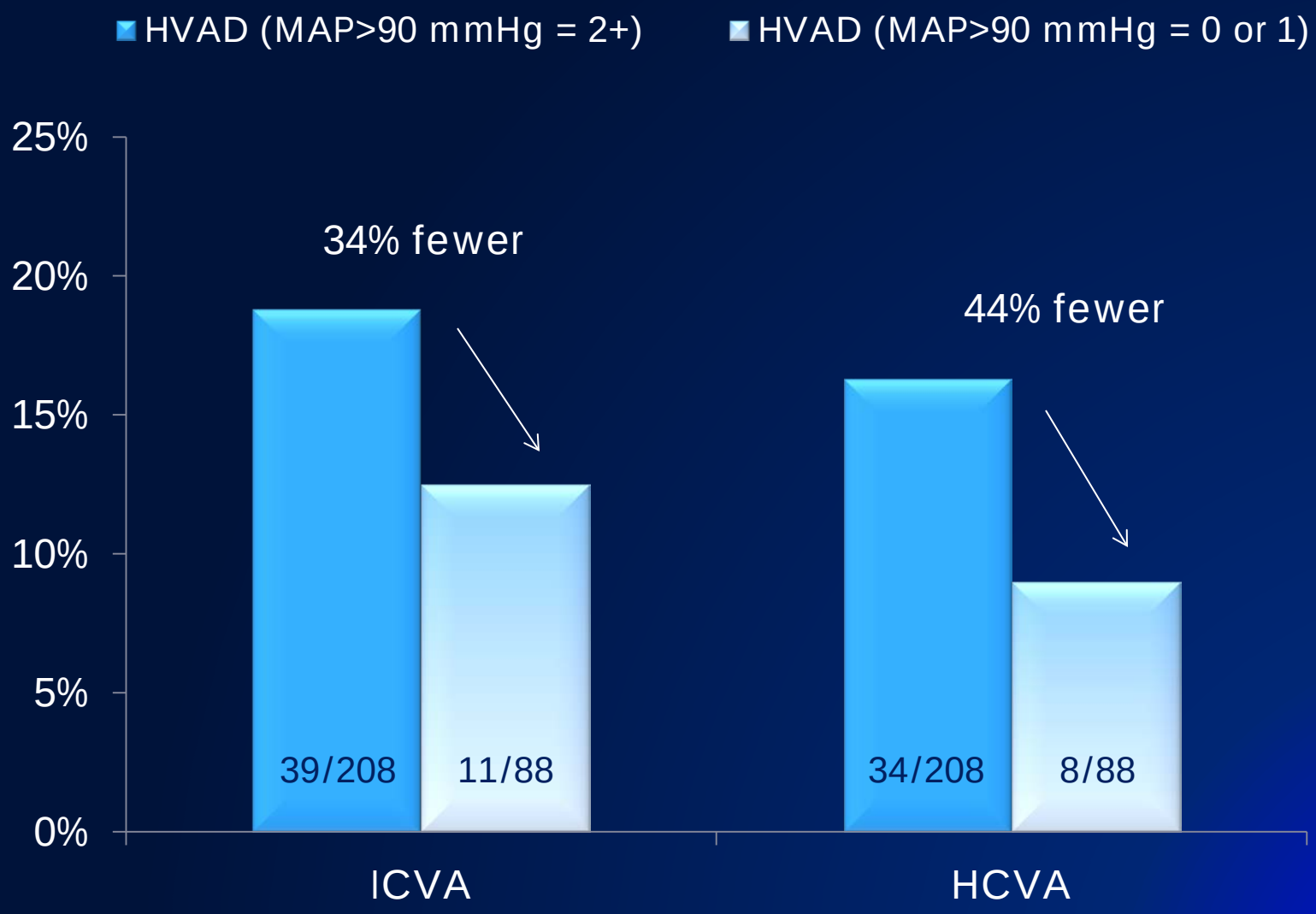


- ✓ Statistically significantly more HVAD patients (7.3%, 0.07 EPPY) had a sub-therapeutic INR <2.0 compared to control patients (2.2%, 0.02 EPPY), *P*=0.04.

HCVA Risk Factor Multivariable Analysis (HVAD)



Influence of Blood Pressure on Stroke (HVAD)



✓BP management is associated with improved neurological outcomes

✓Blood pressure management was not mandated in ENDURANCE

hVAD® ENDURANCE Trial

Limitations

- Randomization was not stratified by site
- Changes to the study device and implant tools introduced mid-study may have impacted adverse events and/or outcomes
- Blood pressure management was not mandated in the protocol and varied among sites during follow-up
- Treatment arm had a higher rate of sub-therapeutic anticoagulation during follow-up

Summary

- Primary Endpoint achieved
- Patients had significant and sustained improvements in functional and quality of life measures
- Device malfunctions leading to exchange or urgent transplant were more frequent in the control group, whereas strokes occurred more frequently in the HVAD group
- Device and design improvements, including sintering of the inflow cannula, resulted in a reduction in pump thrombosis
- Elevated MAP was the strongest predictor of stroke by multivariable analysis. HVAD patients with well-managed blood pressure had fewer strokes

Conclusion

- There was **no difference between HVAD and control** in survival at two years free from disabling stroke (Modified Rankin Score ≥4 at 24-weeks post-stroke), and alive on the originally implanted device, or transplanted or explanted due to patient recovery

Future Directions

- Blood pressure management appears to reduce neurologic events and is being studied in the ongoing ENDURANCE Supplemental Trial

Acknowledgements

- ENDURANCE Investigators
- Clinical site coordinators
- Patients and families