

Functional Assessment Outcomes in Heart Failure



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Disclosure

- Consultant, ResMED >\$10,000
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- FDA Advisory Committee, Consultant / no income received
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- HFSA has no conflict to disclose

MEDCAC Question 4

- How confident are you that functional assessments [e.g., 6 min walk test (6MWT), VO2max, ventilator threshold]:
 - Are adequate measures which reflect the patient experience;
 - Should be included as the standalone, meaningful primary health outcomes in research studies;
 - Should be included as a composite standalone, meaningful primary health outcomes in research studies?

MEDCAC/CMS Evaluation of Endpoints in Heart Failure

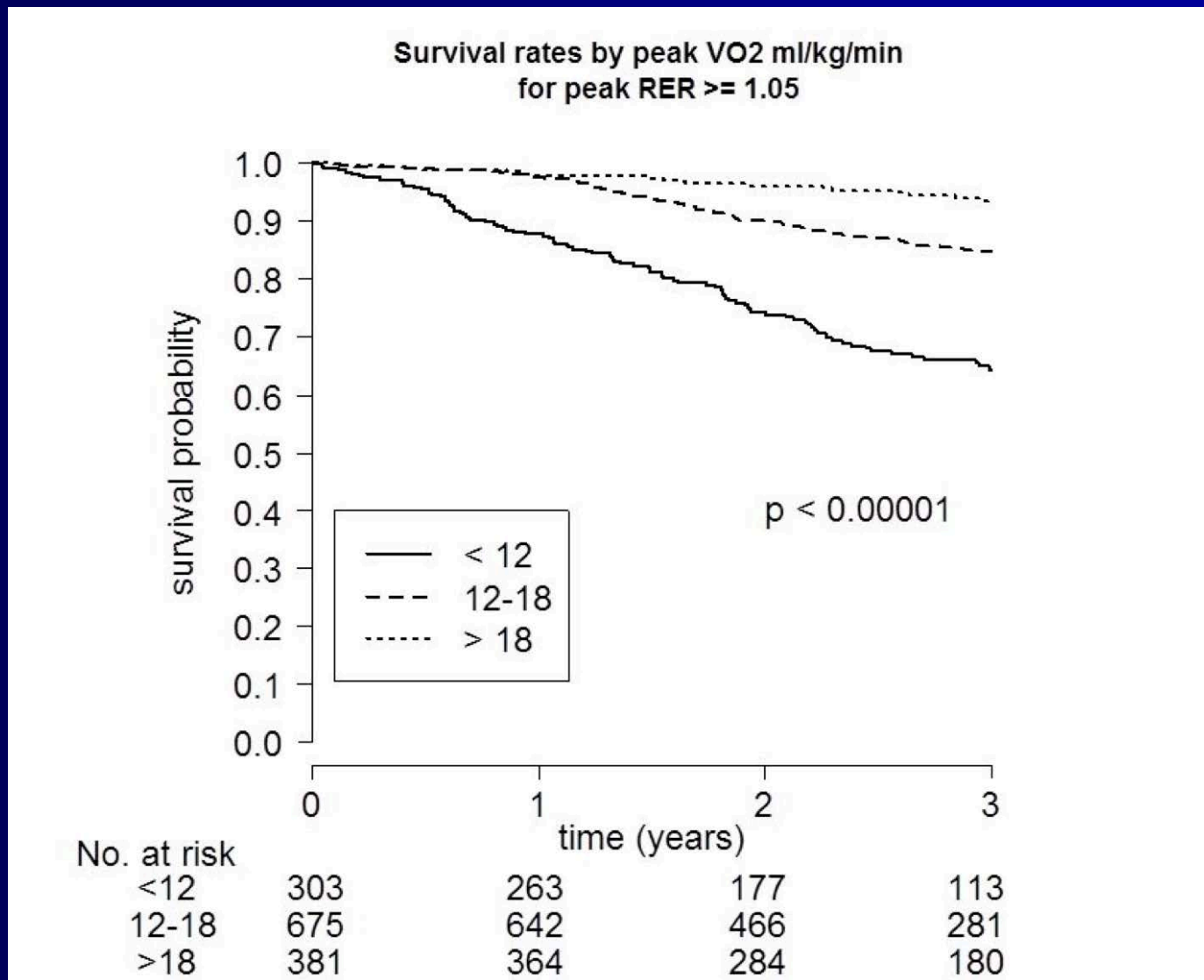
- Can functional assessments stand alone as primary endpoints or as composite endpoints in the evaluation of medical technology for HF patients?
- HF-ACTION database is the most robust database of HFrEF patients with 2000 serial measurements of 6 minute walk test and CPET variables along with adequate number of clinical endpoints

O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301(14):1439–50.

Functional Outcomes Predict Clinical Outcomes

- Peak VO₂
- Six minute walk test
- CPET Variables(Ventilatory Threshold, Exercise Oscillatory Ventilation,Treadmill time)
- Gait Speed

Peak VO2 and Outcome : HF-Action

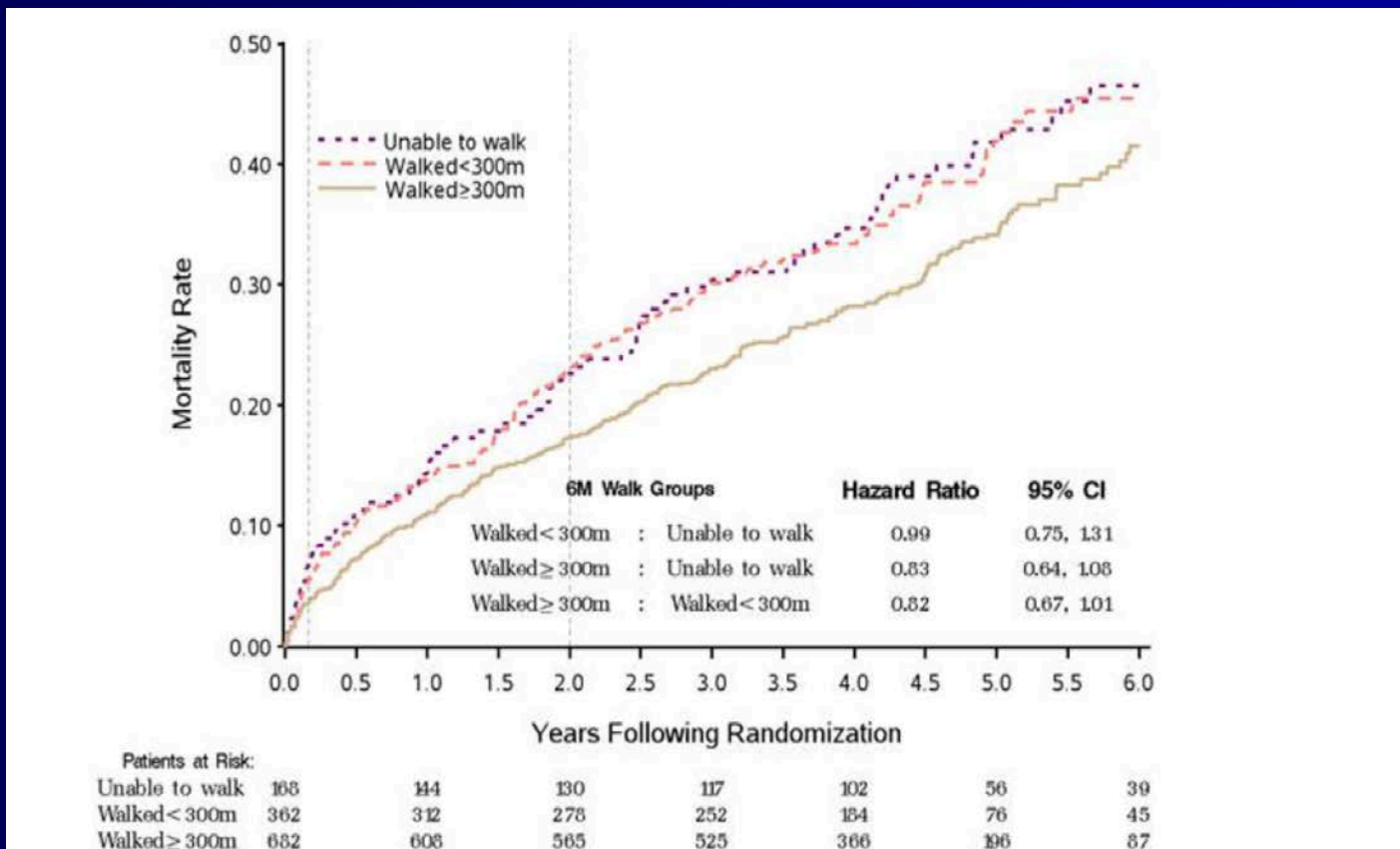


HF ACTION :Uber-Model

Table 3. Simplified Predictive Model for Mortality End Point

Parameter	Average χ^2	<i>P</i>	HR (95% CI)
Exercise duration on CPX test (HR for 1-min increase)	151.7	<0.0001	0.82 (0.80–0.85)
Serum urea nitrogen (HR for 10-mg/dL increase)	35.9	<0.0001	1.08 (1.05–1.11)
Sex=female	32.7	<0.0001	0.48 (0.37–0.61)
BMI (HR for 2-kg/m ² increase, truncated >25 kg/m ²)	17.9	<0.0001	0.79 (0.70–0.88)

Six Minute Walk Test and Outcome



HF Action and Functional Outcomes

Prognostic Utility of 6MWD vs. CPX Indices in Predicting All-Cause Mortality

Model	Parameter	Chi Square statistic	P value	Hazard Ratio ^{**} (95% confidence interval)	C-Index (95% confidence interval)	IDI
Unadjusted Univariate predictors	6MWD	94	<.0001	0.61 (0.55, 0.67)	0.65 (0.62, 0.68)	
	Peak VO ₂	123	<.0001	0.48 (0.42, 0.55)	0.68 (0.65, 0.71)	
	VE/Vco ₂ Slope	130	<.0001	1.58 (1.46, 1.71)	0.65 (0.61, 0.68)	
Adjusted ^{**}	6MWD	55	<.0001	0.65 (0.57, 0.73)	0.72 (0.69, 0.75)	0.005
	Peak VO ₂	77	<.0001	0.51 (0.44, 0.59)	0.73 (0.71, 0.76)	0.010
	VE/VCO ₂ Slope	45	<.0001	1.37 (1.25, 1.51)	0.71 (0.68, 0.74)	0.004

6MWD-6 minute walk distance; VO₂-oxygen consumption; VE/VCO₂-minute ventilation-carbon dioxide production; IDI-Integrated Discrimination Improvement

Functional Outcomes

- **Functional outcomes highly predictive of clinical outcomes**
- **Peak VO₂ and 6 MWT best independent predictors**
- **Change in these variables relate to outcome**

Study Design

Chronic heart failure, NYHA Class II-IV, LVEF $\leq 35\%$,
optimal HF medical therapy, capable of exercising

Pre-randomization CPX and ECHO

Randomization 1:1
(Stratified by center and HF etiology)

Usual Care

Median Follow-up 2.5 years

Exercise Training

Whellan DJ, O' Connor CM, Lee KL et al.
Am Heart J 2007;153:201-211.



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Median Change in 6-Minute Walk and Cardiopulmonary Exercise (CPX) Tests

Baseline to 3 months*	Usual Care	Exercise Training	<i>P</i> -value
6-minute walk distance (m)	5	20	<0.0001
CPX exercise duration (min.)	0.3	1.5	<0.0001
Peak VO ₂ (mL/min/kg)	0.2	0.6	<0.0001

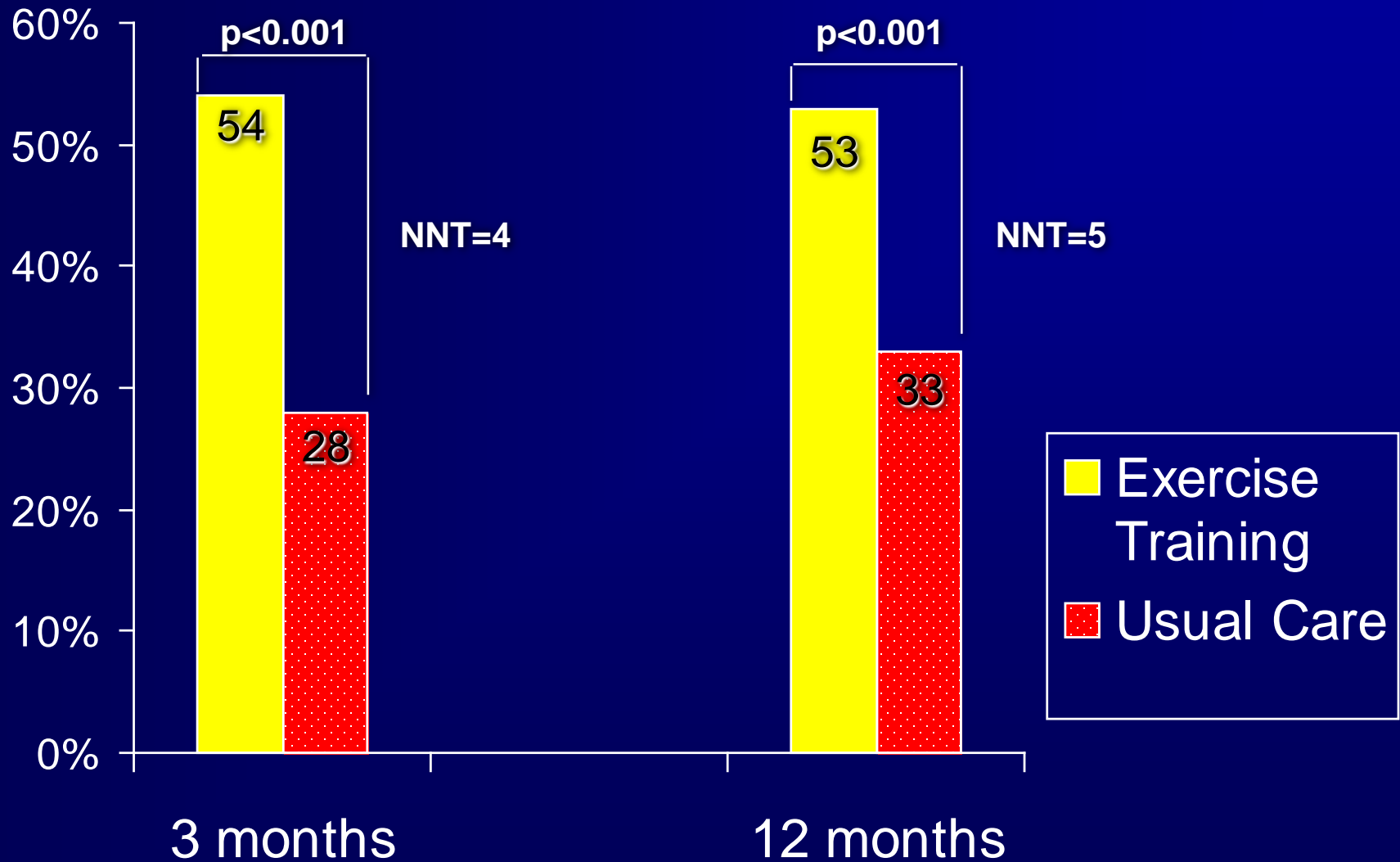
* Complete case analysis



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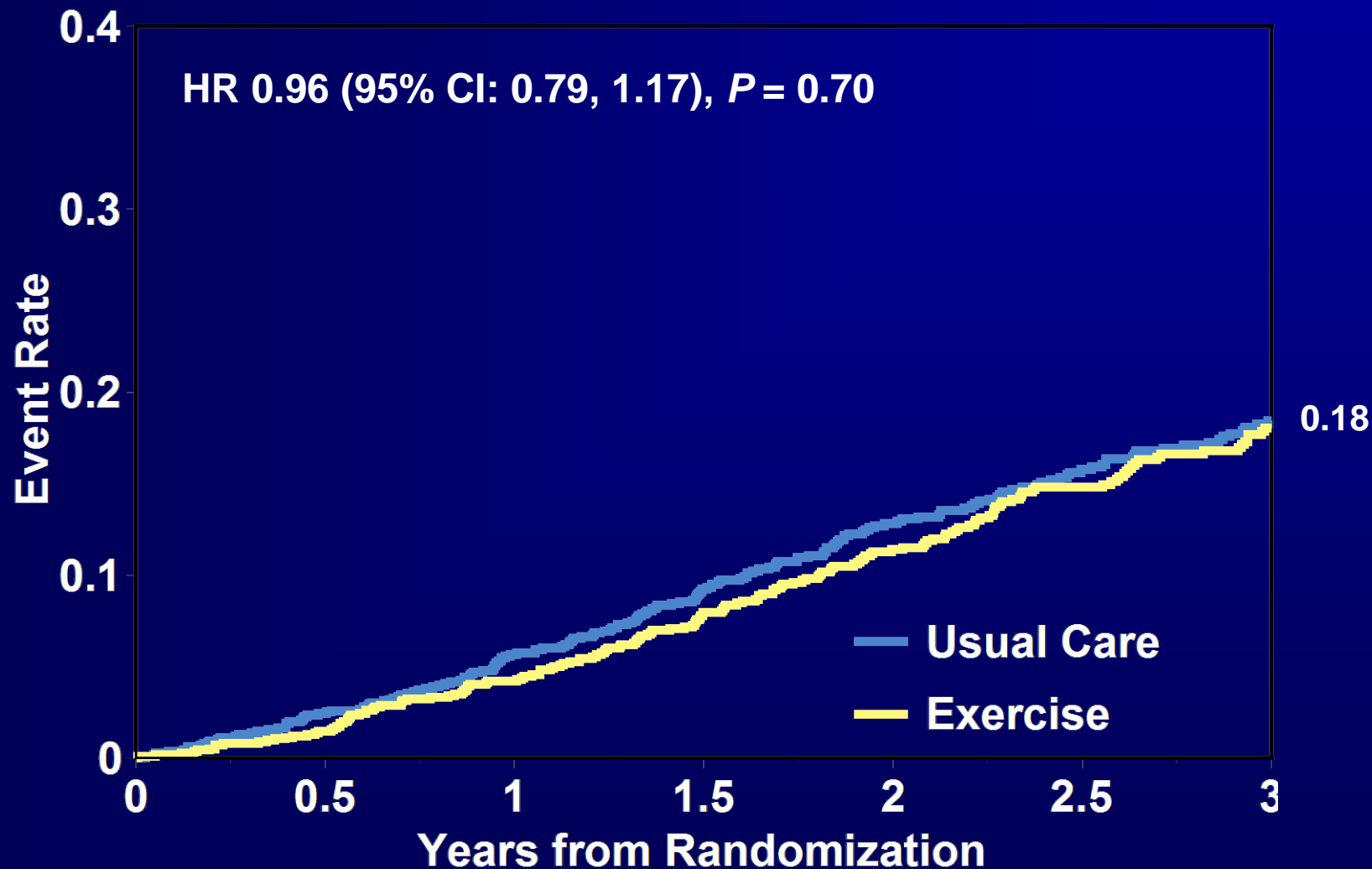
Percent of Patients with Clinical Improvement



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All-Cause Mortality



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HF-Action Clinical Outcomes

Table 1
Clinical events in HF-ACTION presented as unadjusted and adjusted for stratification effect

Event	% of Patients		Unadjusted HR (95% CI)	P Value for Unadjusted Analysis	Adjusted HR (95% CI)	P Value for Adjusted Analysis
	Usual Care (n = 1171)	Exercise Training (n = 1159)				
All-cause mortality or hospitalization (primary end point)	68	65	0.93 (0.84–1.02)	0.13	0.89 (0.81–0.99)	0.03 ^a
CV mortality or hospitalization	58	55	0.92 (0.83–1.03)	0.14	0.91 (0.82–1.01)	0.09
CV mortality or HF hospitalization	34	30	0.87 (0.75–1.00)	0.06	0.85 (0.74–0.99)	0.03 ^a



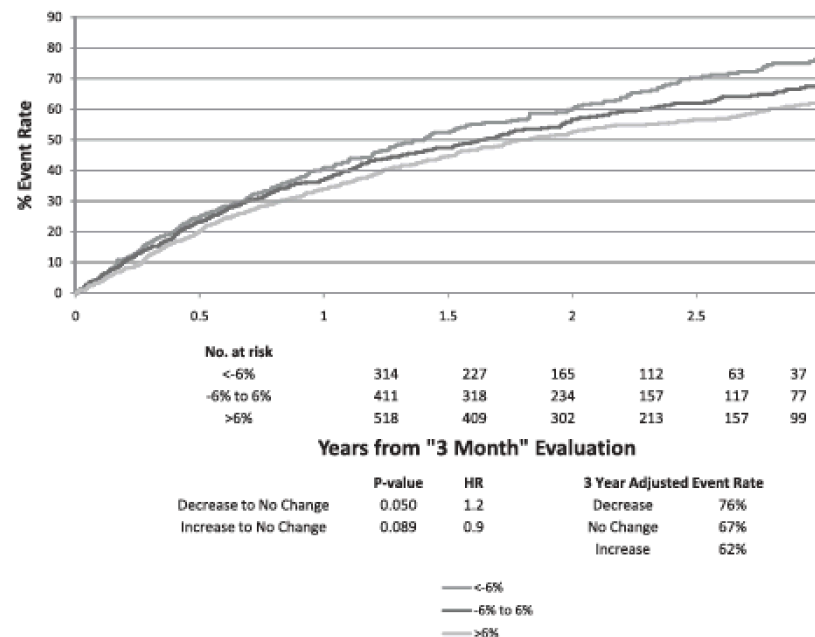
Change in VO₂ :HF-Action

Table 3. Trend Tests for Clinical Outcomes Across Tertiles of Peak VO₂ Change

Clinical Outcome	Estimate	χ^2	P
All-cause mortality or all-cause hospitalization	-0.15	13.08	<0.001
Cardiovascular mortality or hospitalization	-0.12	7.35	0.007
Cardiovascular mortality or HF hospitalization	-0.15	5.88	0.061
Mortality	-0.18	4.62	0.032

VO₂ indicates oxygen uptake; HF, heart failure.

Primary Endpoint of Time to All-Cause Mortality or All-Cause Hospitalization by % Change in 3 month Peak VO₂ (mL/kg/min)



Functional Assessment Outcomes as Stand Alone Endpoints

- Could be a primary endpoint in highly prevalence disease states if harm(mortality) ruled out
- HFrEF(3 million), HFpEF(3 million), ADHF(1 million)
- Most angina drugs(high prevalence) have been approved on a 1 minute improvement in exercise time
- Acceptable primary for phase 2 studies

Functional Endpoint as part of Composite Endpoint

- In common diseases when event rates low(Stage A HF)
- In rare diseases as primary endpoint
- Phase 2 studies
- Components same direction



- Evaluate the effect of minute ventilation-targeted adaptive servo-ventilation (ASV) in acute decompensated heart failure (HF) patients on outcomes at 6 months.
- **Primary Outcome**
 - Global Rank Endpoint: Rank order response based on survival free from CV hospitalization and improvement in functional capacity measured by 6MWD
- **Key Secondary Outcomes**
 - CV and all-cause death
 - SDB parameters
 - Change in 6MWD
 - Echo parameters
 - Arrhythmia parameters
 - Quality of Life



Primary Endpoint

Wilcoxon p-value: 0.92

0.70

0.12

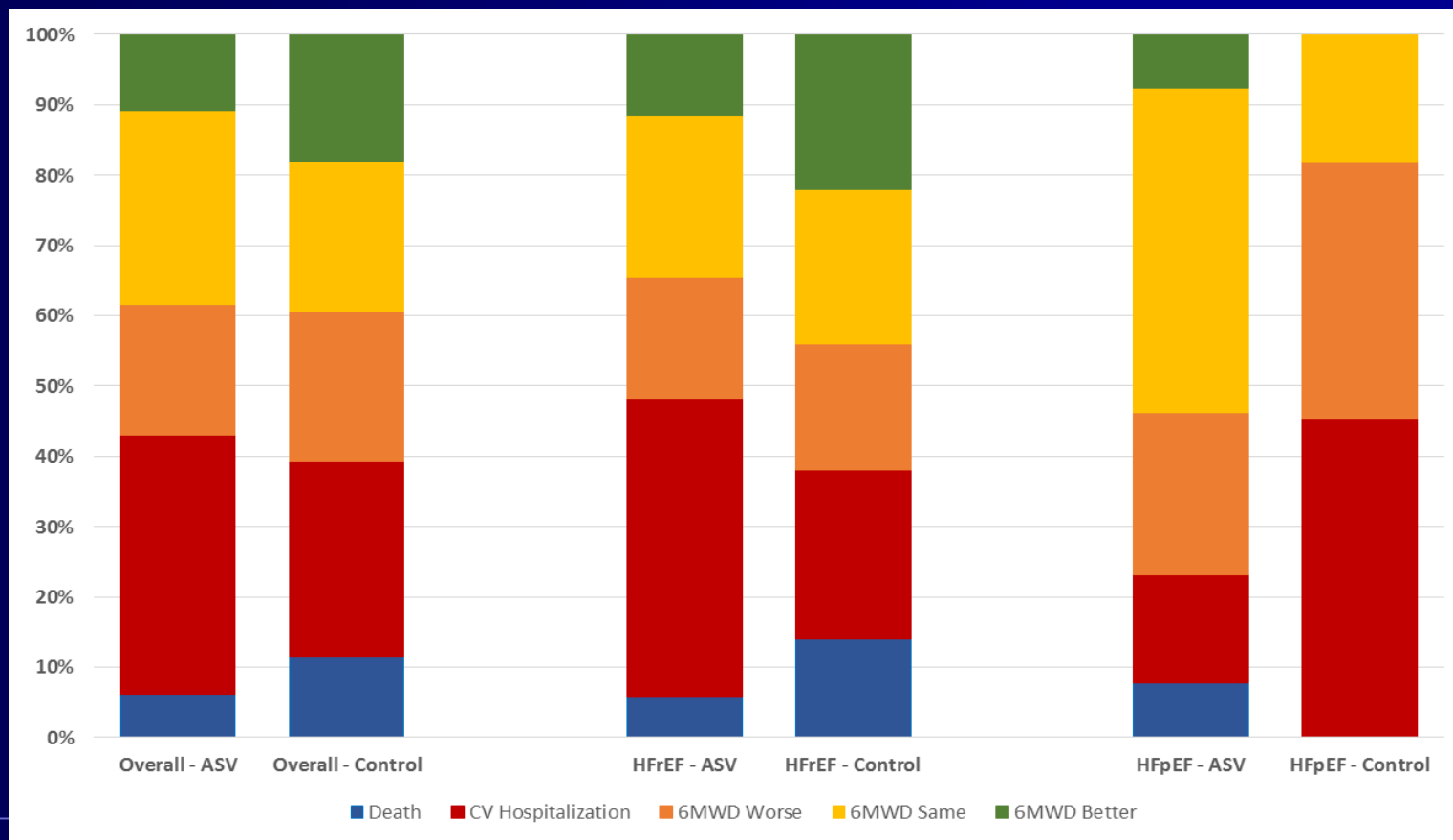
Interaction p-value: 0.22

Cox p-value: 0.74

0.40

0.036

Interaction p-value: 0.10



Functional Outcomes as Stand Alone Endpoints Acceptable in Small Population Cardiomyopathy

- Small population diseases(<50,000)
- Duchenne Muscular Dystrophy CM
- Mitochondrial Cardiomyopathy
- ARVD Cardiomyopathy
- Left Ventricular Non-compaction Cardiomyopathy(LVNC)

Functional Outcomes : Summary

- Six Minute Walk Test and Peak VO2 best data
- Possible indication for use as primary stand alone endpoint in high prevalent disease(HFrEF, HFpEF, ADHF) if harm(mortality) ruled out
- Reasonable primary endpoint in rare cardiomyopathies or very advanced disease where mortality less important
- Composite as a global rank reasonable in low mortality conditions and special subgroups(elderly)

Collaborating Organizations



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