



A Dose-Response Analysis of Patients with Heart Failure Enrolled in A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)

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Funding-

Main trial: National Heart Lung Blood Institute (NHLBI)

Ancillary studies: GE Healthcare and Roche Diagnostics



Presenter Disclosure Information

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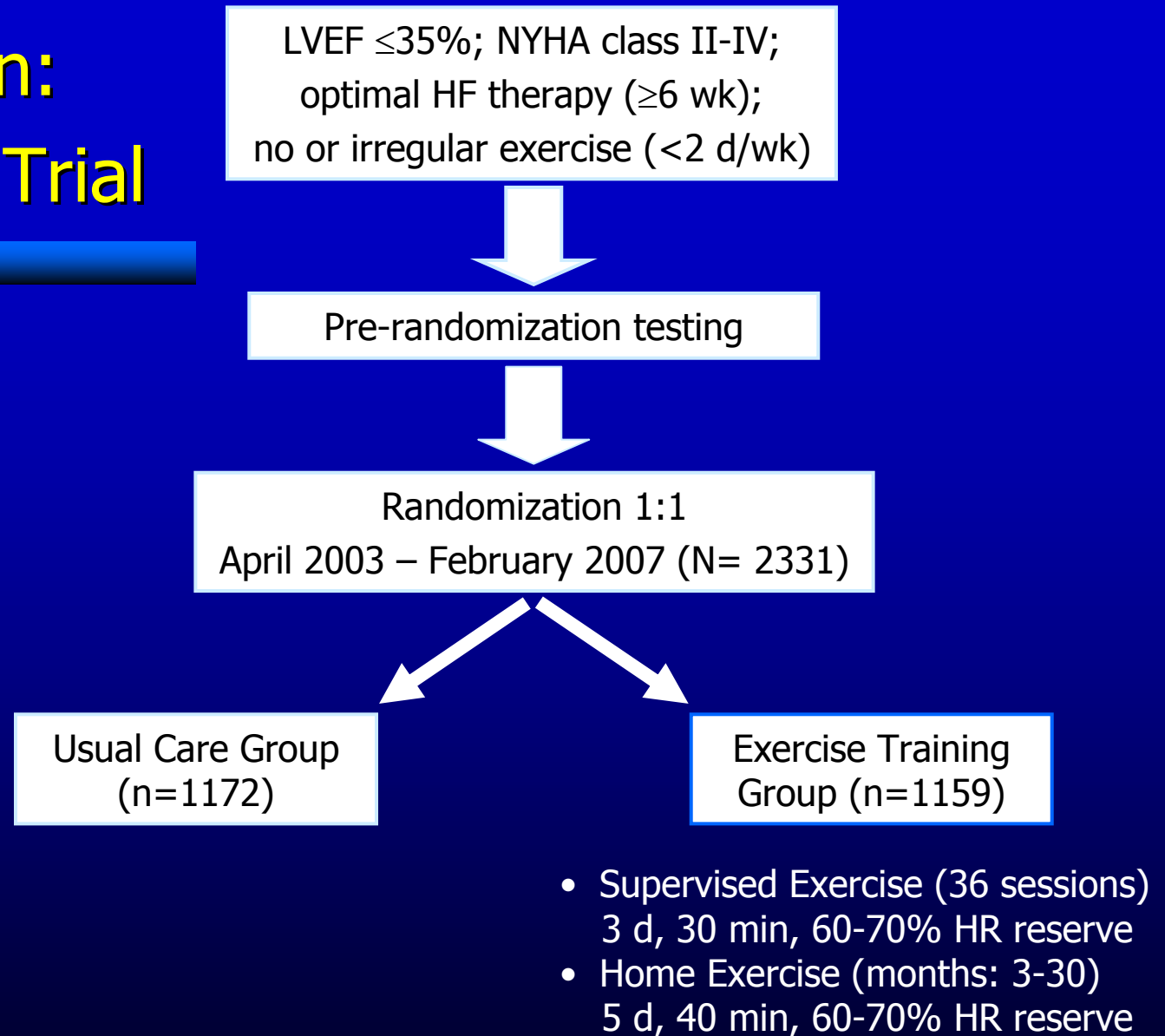
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Financial Disclosures: None

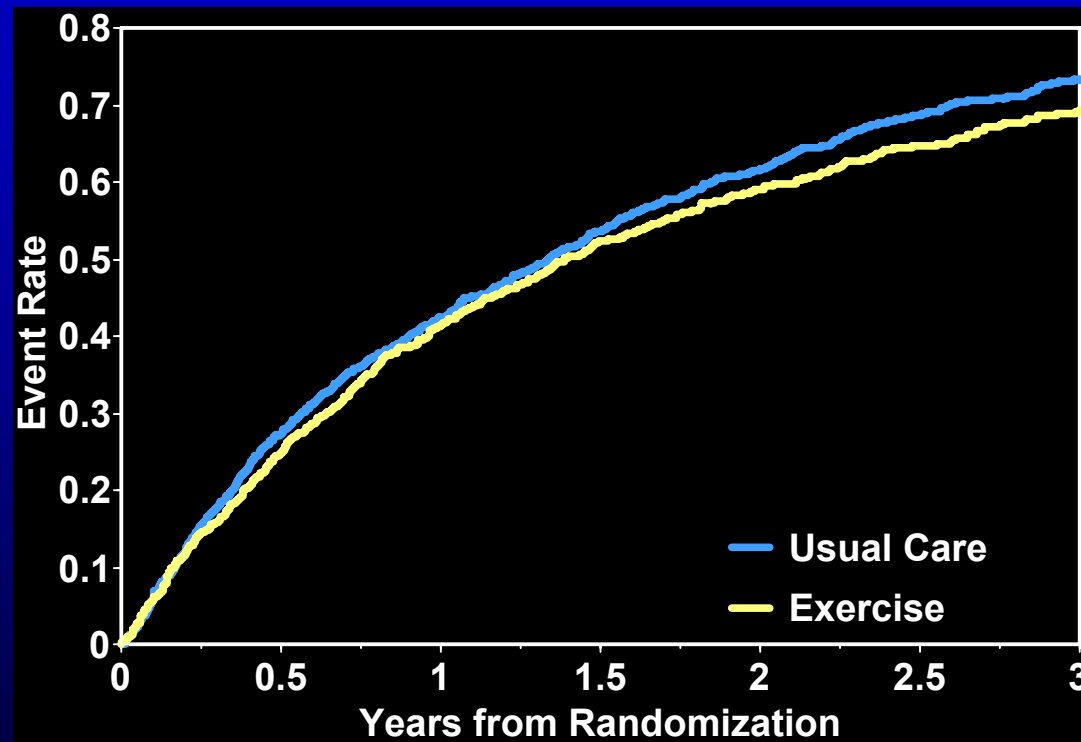
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Study Design: HF-ACTION Trial



Background: HF-ACTION Primary Endpoint (All-Cause Mortality or All-Cause Hospitalization)

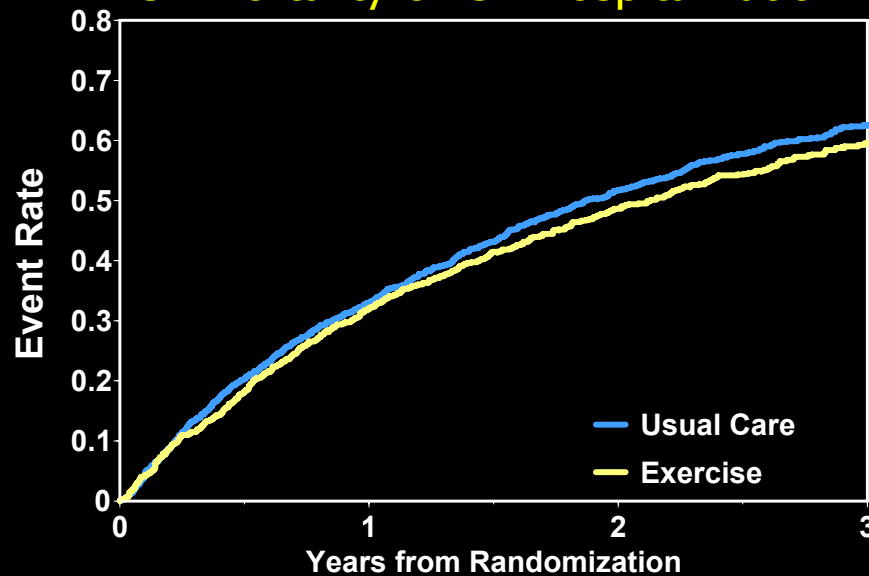


(Primary) HR 0.93 (95% CI: 0.84, 1.02), p = 0.13
*Adjusted HR 0.89 (95% CI: 0.81, 0.99), p = 0.03

*Adjusted for key prognostic factors at baseline: etiology + atrial fibrillation, exercise duration, Beck depression score, ejection fraction.

Background: HF-ACTION Secondary Endpoints

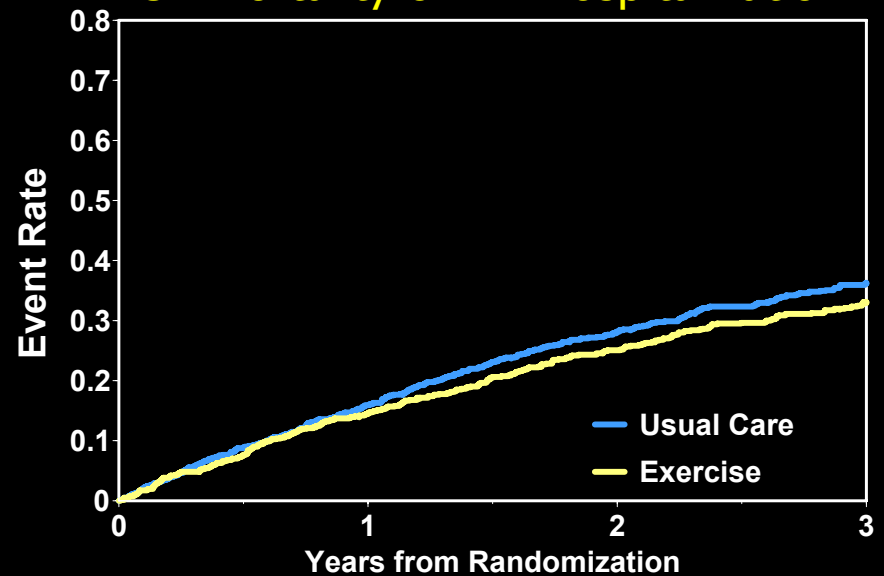
CV Mortality or CV Hospitalization



HR 0.92 (95% CI: 0.83, 1.03), $p = 0.14$

* Adjusted HR 0.91 (95% CI: 0.82, 1.01), $p = 0.09$

CV Mortality or HF Hospitalization

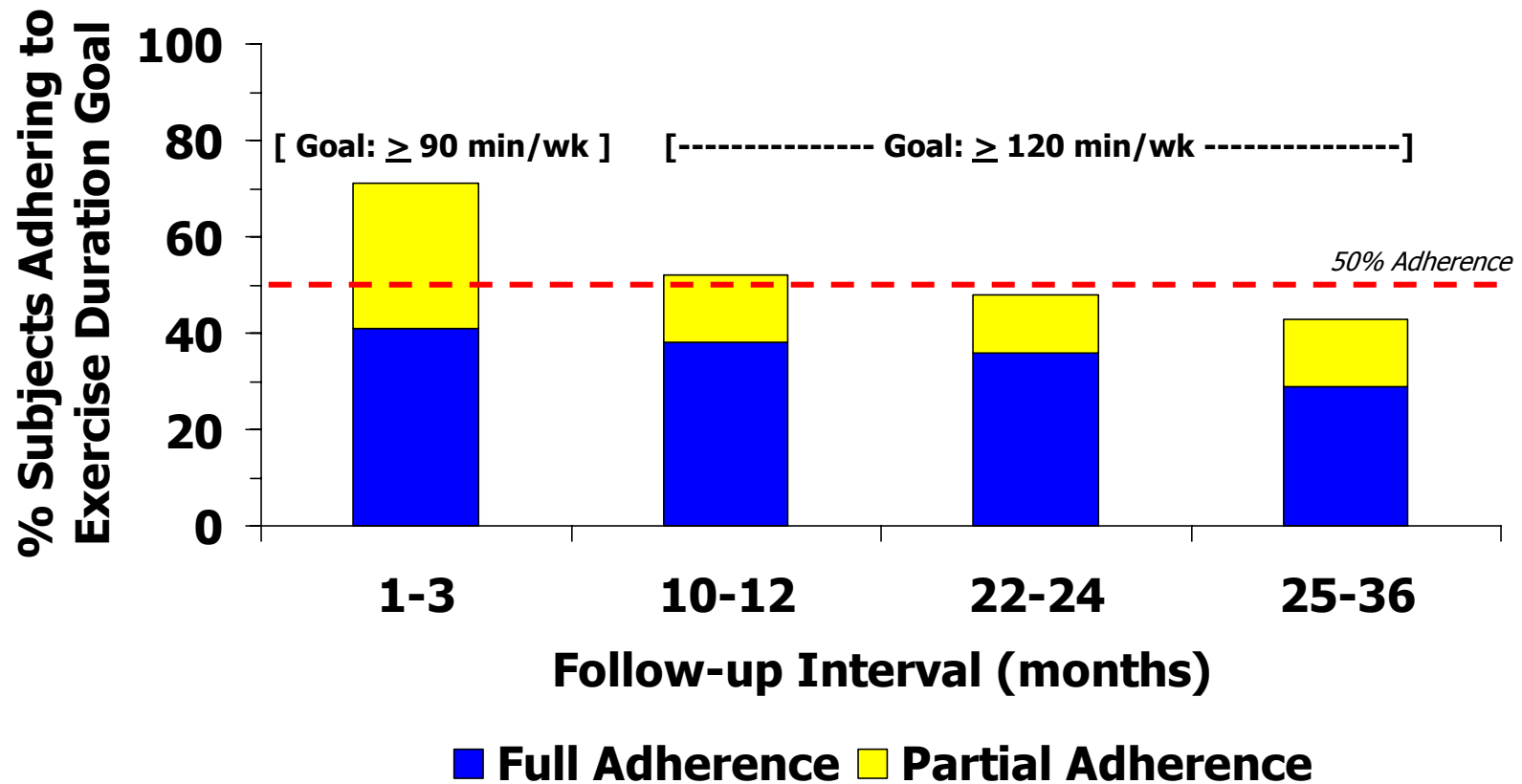


HR 0.87 (95% CI: 0.75, 1.00), $p = 0.06$

* Adjusted HR 0.85 (95% CI: 0.74, 0.99), $p = 0.03$

* Adjusted for key prognostic factors at baseline: etiology + atrial fibrillation, exercise duration, Beck depression score, ejection fraction.

Background: Adherence to Prescribed Exercise in HF-ACTION



Hypothesis ...

- ... an increase in the volume of exercise completed per week would be associated with a reduction in clinical events, as well as an improvement in exercise capacity and health status.

Study Outcomes

- Clinical Events
 - All-cause death or all-cause hospitalization
 - Cardiovascular death or cardiovascular hospitalization
 - Cardiovascular death or heart failure hospitalization
- Exercise Capacity
 - Peak VO_2 ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)
 - Six-minute walk distance (m)
- Self-Reported Health Status
 - Kansas City Cardiomyopathy Questionnaire (KCCQ)
 - Scale: 0-100; higher score = better health status

Quantifying Exercise Dose

Volume: MET-hours per week

- Hours per week \times average exercise intensity during training (METs)

Example: (typical study subject)

2.0 hr/wk

X 2.0 MET activity (e.g., walk @ 1.4 mph)

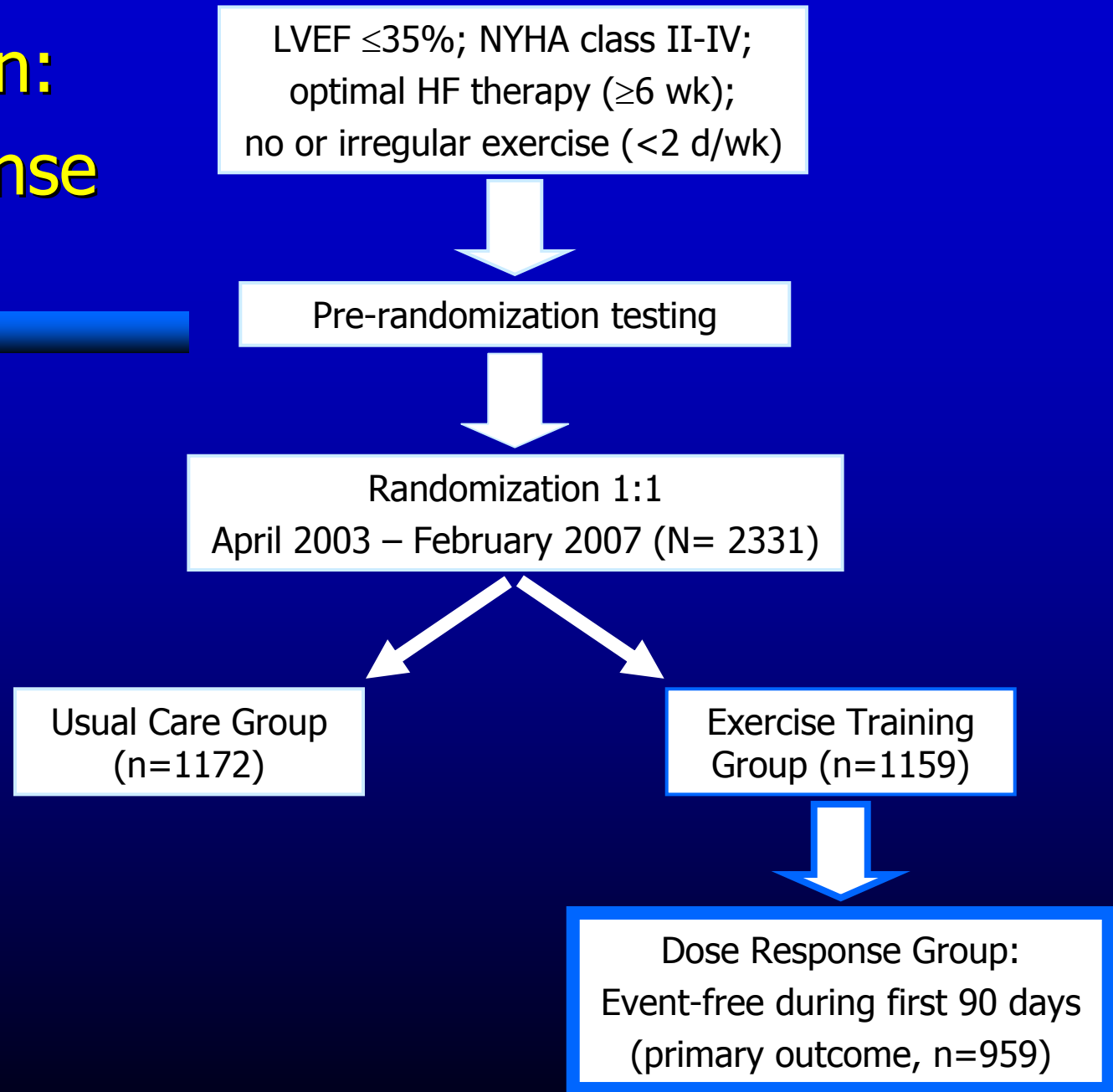
4.0 MET-hr/wk

2008 *DHHS, Physical Activity Guidelines Advisory Report*: Target for Healthy Adults = \sim 8 MET-hr/wk
[e.g., brisk (3 mph) walk for 30 minutes, five days per week]

Statistical Methods

- Methods for determining covariates: pre-defined list of 32 variables; reduced using backward elimination.
- Assess the relationship between the volume of exercise per week and the occurrence of clinical events after 90 days.
 - “Landmark-type Analysis”
- Statistical analysis
 - Clinical events: Cox proportional hazards model
 - Exercise capacity: Multivariable linear regression (complete case analysis)
 - Health status: Longitudinal linear mixed model

Study Design: Dose Response Group



Results: Baseline Characteristics of Dose Response Group (n = 959)

Age (yr) *	59 (51, 67)
Female (%)	31
African American (%)	32
NYHA Class II / III / IV (%)	65 / 34 / 1
LVEF (%) *	25 (20, 30)
Ischemic Etiology (%)	50
Diabetes (%)	32
Atrial Fibrillation/Flutter (%)	21
History of Stroke (%)	10
Body Mass Index (kg·m ⁻²) *	30 (26, 35)
Peak VO ₂ (mL·kg ⁻¹ ·min ⁻¹) *	14.7 (11.6, 17.8)
Beck Depression Inventory II Score	8 (5, 15)
CPX Duration (min) *	10 (7, 12)

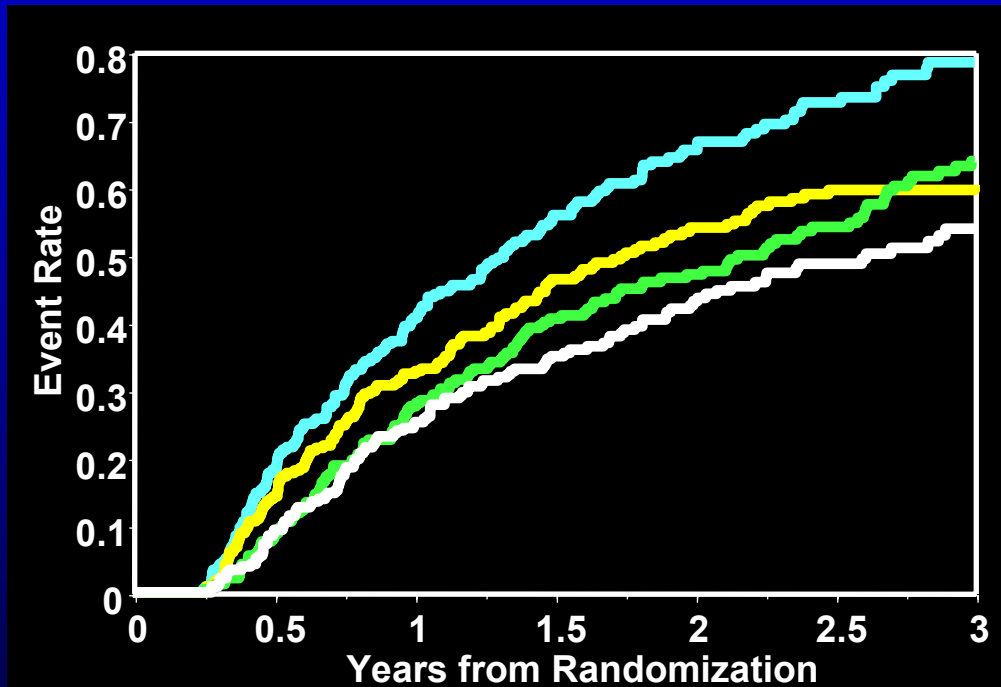
* Median (25th, 75th)

Baseline Characteristics, Volume of Exercise, and Risk for All-Cause Death or All-Cause Hospitalization After 90 Days

<i>Covariate</i>	<i>HR (CI)</i>	χ^2	<i>p-value</i>
Peak VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	0.95 (0.93-0.97)	19.2	<0.0001
Exercise Volume (MET-hr/wk)*	0.95 (0.92-0.98)	8.8	0.003
Beck Depression Inventory II Score	1.02 (1.01-1.03)	8.1	0.005
LV Ejection Fraction (%)	0.98 (0.97-1.00)	7.8	0.005
History of Atrial Fibrillation/Flutter	1.33 (1.07-1.64)	6.7	0.010
Beta-Adrenergic Blockade Therapy	0.67 (0.48-0.94)	5.5	0.020
Female Gender	0.77 (0.62-0.96)	5.3	0.022
Statin Therapy	0.83 (0.69-1.00)	4.0	0.045
Resting Heart Rate (min ⁻¹)	0.99 (0.98-1.00)	3.3	0.068
Non Ischemic Etiology	0.94 (0.77-1.14)	0.4	0.53
Bi-Ventricular Pacemaker	0.95 (0.73-1.25)	0.12	0.73
Conduction in Resting ECG	[Multi-level]		0.033
Smoking Status	[Multi-level]		0.086

* Median exercise volume performed = ~ 4 MET-hr/wk

Unadjusted Kaplan-Meier Curves of the Primary Endpoint by Quartiles of MET-hr/wk



	MET-hr/wk
— Quartile 1	≤ 1.9
— Quartile 2	$1.9 < 3.9$
— Quartile 3	$3.9 < 6.2$
— Quartile 4	> 6.2

Volume of Exercise and Risk for Clinical Events after 90 Days

Risk Reduction Per 1 MET-hr/wk			
	<i>HR (CI) *</i>	χ^2	<i>p-value</i>
All-Cause Death or All-Cause Hospitalization	0.95 (0.92-0.98)	8.8	0.003
CV Death or CV Hospitalization	0.95 (0.92-0.99)	6.8	0.009
CV Death or HF Hospitalization	0.89 (0.84-0.94)	16.7	<0.0001

* Adjusted Cox proportional hazards model

Volume of Exercise and Improvement in Exercise Capacity and Health Status at 90 Days

	Increase at 90 days per 1 MET-hr/wk of exercise*	p-value
Peak VO ₂ (mL·kg ⁻¹ ·min ⁻¹)	0.18 (0.028)	<0.0001
Six-min walk distance (m)	4.23 (0.76)	<0.0001
KCCQ score (points)	0.73 (0.12)	<0.001

*Slope estimate (SE)

Possible Clinical Implications for Typical Patients from HF-ACTION

Two Typical Subjects:
Each 59 yr, ischemic CMY,
NYHA class II,
LVEF = 25%,
 $VO_{2\text{peak}} = 14 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$

One walks 2 mph, 30 min,
3 d/wk = 4 MET-hr/wk

Clinical risk: $\downarrow \sim 18\%$ (6% – 28%)
 $\Delta \text{Peak } VO_2: + 0.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
 $\Delta \text{KCCQ}: + 2.9 \text{ points}$

Another walks 2.5 mph, 25 min,
5 d/wk = 6 MET-hr/wk

Clinical risk: $\downarrow \sim 26\%$ (9% – 39%)
 $\Delta \text{Peak } VO_2: + 1.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
 $\Delta \text{KCCQ}: + 4.4 \text{ points}$

Study Limitations

- Patients were not randomized to different doses of exercise
 - Confounding due to unobserved factors
 - Results must be interpreted with caution
- Some covariates (e.g., BNP, creatinine) which influence clinical outcomes were not available on all subjects and therefore were not included in the analysis.



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Conclusion: In patients with chronic heart failure, a 1 MET-hr increase in the volume of exercise performed per week is associated with ...

- ~ 5% lower estimated risk for all-cause death or all-cause hospitalization
- ~ 0.2 mL·kg⁻¹·min⁻¹ higher peak VO₂ at 90 days
- ~ 0.7 point higher KCCQ score at 90 days





Conclusion

This analysis:

- Quantifies the dose response relationship between regular aerobic exercise and patient outcomes among subjects in HF-ACTION.
- Provides insight as to how volume of exercise may have contributed to the modest improvement in clinical, fitness and health status outcomes observed in the main HF-ACTION Trial.
- Provides additional information regarding the use of regular aerobic exercise in the management of patients with heart failure due to left ventricular systolic dysfunction.

