



Efficacy and Safety of Exercise Training as a Treatment Modality in Patients With Chronic Heart Failure: Results of A Randomized Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION)

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*Funded by NHLBI
Ancillary studies funded by GE Healthcare and Roche Diagnostics*



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Presenters' Disclosure Information

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Financial Disclosure

- Grants/Research Support: NHLBI, Roche Diagnostics, GE Healthcare
- Speaker Bureau: None
- Unlabeled/Unapproved Use Disclosures: None



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Background

- **Several studies have demonstrated that exercise training improves functional capacity in patients with heart failure:**
 - **Increased exercise capacity**
 - **Improved quality of life**
 - **Improved biomarkers**

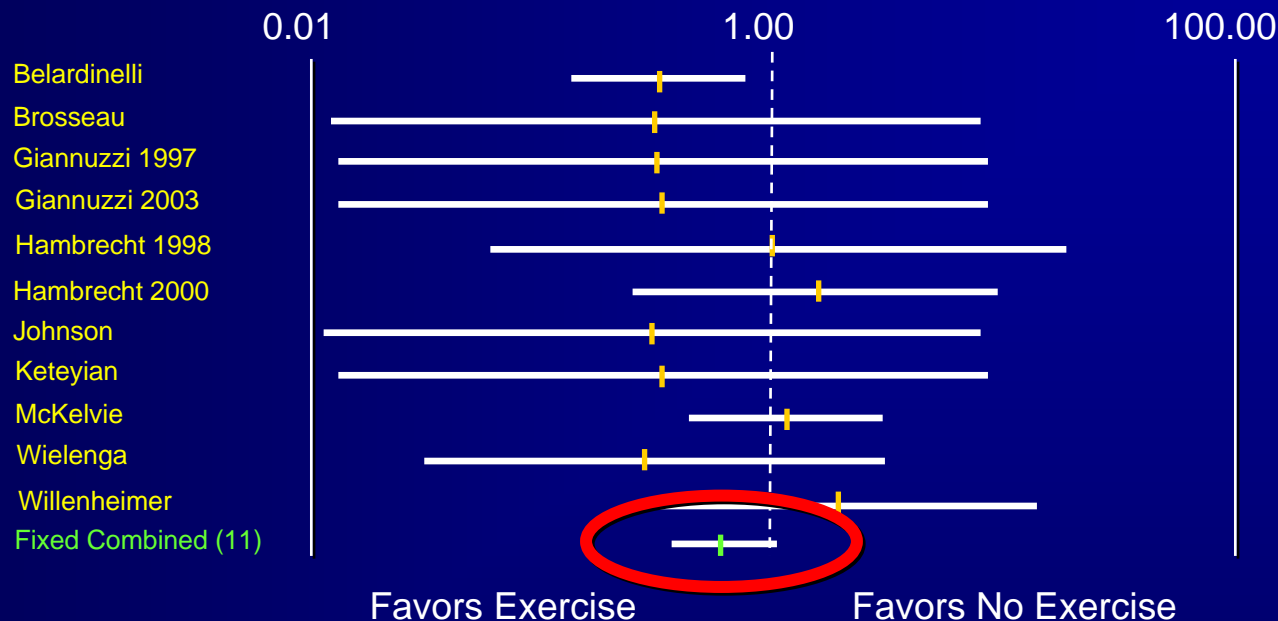
Belardinelli R et al. *Circ* 1999; 99:1173-1182; Coats AJ et al. *Circ* 1992; 85:2119-2131; Hambrecht R, et al. *J Am Coll Cardiol* 1995; 25:1239-1249; McKelvie RS. *Heart Fail Rev* 2008; 13:3-11.



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Influence of Exercise Training on Mortality



Meta-analysis 11 studies (729 subjects)

HR = 0.61 (95% CI: 0.37, 1.02), P = 0.06

Smart N et al. *Am J Med* 2004;116:693-706.



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Limitations of Prior Studies

- Relatively small
- Majority single-center
- Underpowered to evaluate mortality and morbidity
- Lack of adequate control groups
- Limited safety data



HF-ACTION Primary Hypothesis

Patients with left ventricular systolic dysfunction and New York Heart Association class II-IV symptoms who undergo exercise training in addition to usual care will have a 20% lower rate of **all-cause death or hospitalization (primary endpoint)** over two years than patients who receive usual care alone.

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



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HF-ACTION Secondary Endpoints

- CV mortality + CV hospitalization
- CV mortality + HF hospitalization
- Mortality
- Safety
- Exercise capacity
- QOL
- Cost



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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Treatment Groups

■ Usual Care

- Optimized medical treatment
- Patient education
- Phone calls

■ Exercise Training

- Optimized medical treatment
- Patient education
- Phone calls
- Supervised training
- Home training



Statistical Power / Sample Size

- The study was designed to provide 90% power to detect a 20% ↓ over 2 years *if patients were compliant with the exercise intervention*
- **Assumptions:**
 - Annual event rate of 30% in the usual care group
 - Non-adherence rates of 30% in the first year of follow-up and 12.5% annually thereafter
 - Annual crossover rate of 5% from usual care to exercise
 - Planned median follow-up of 2.5 years
- To account for non-adherence and crossover, the study was actually powered to detect an 11% ↓
- Two-sided $\alpha = 0.05$
- Target sample size 3000; later reduced to 2300 based on higher than projected aggregated event rate



Statistical Analysis

- Intention-to-treat
- Treatments compared using time-to-event analysis based on the log-rank test, stratified by HF etiology
- Relative risks derived from Cox proportional hazards model, reported as HR (95% CI)



Adjusted Analysis

- Prespecified in protocol (secondary)
- Adjustment for highly prognostic factors may improve the accuracy of the estimated treatment effect.
- Strongest prognostic factors for the primary endpoint, selected without using treatment information
 - CPX duration
 - LVEF
 - Beck Depression Inventory
 - History of atrial fibrillation and flutter



Baseline Characteristics

	Usual Care N=1172	Exercise Training N=1159
Age, y *	59 (51, 68)	59 (51, 68)
Female, %	27	30
African American, %	32	33
NYHA Class, % II / III / IV	64 / 35 / 1	62 / 36 / 1
LVEF, % *	25 (20, 30)	25 (20, 30)
Ischemic etiology, %	51	52
Diabetes, %	32	33
Afib/flutter, %	21	21
History of Stroke, %	11	10
BMI, kg/m ² *	30 (26, 35)	30 (26, 35)
Serum Creatinine, mg/dL *	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)
Peak VO ₂ , mL/min/kg *	14.5 (11.6, 17.8)	14.4 (11.3, 17.6)
CPX duration, minutes *	9.7 (7.0, 12.1)	9.5 (6.9, 12.0)

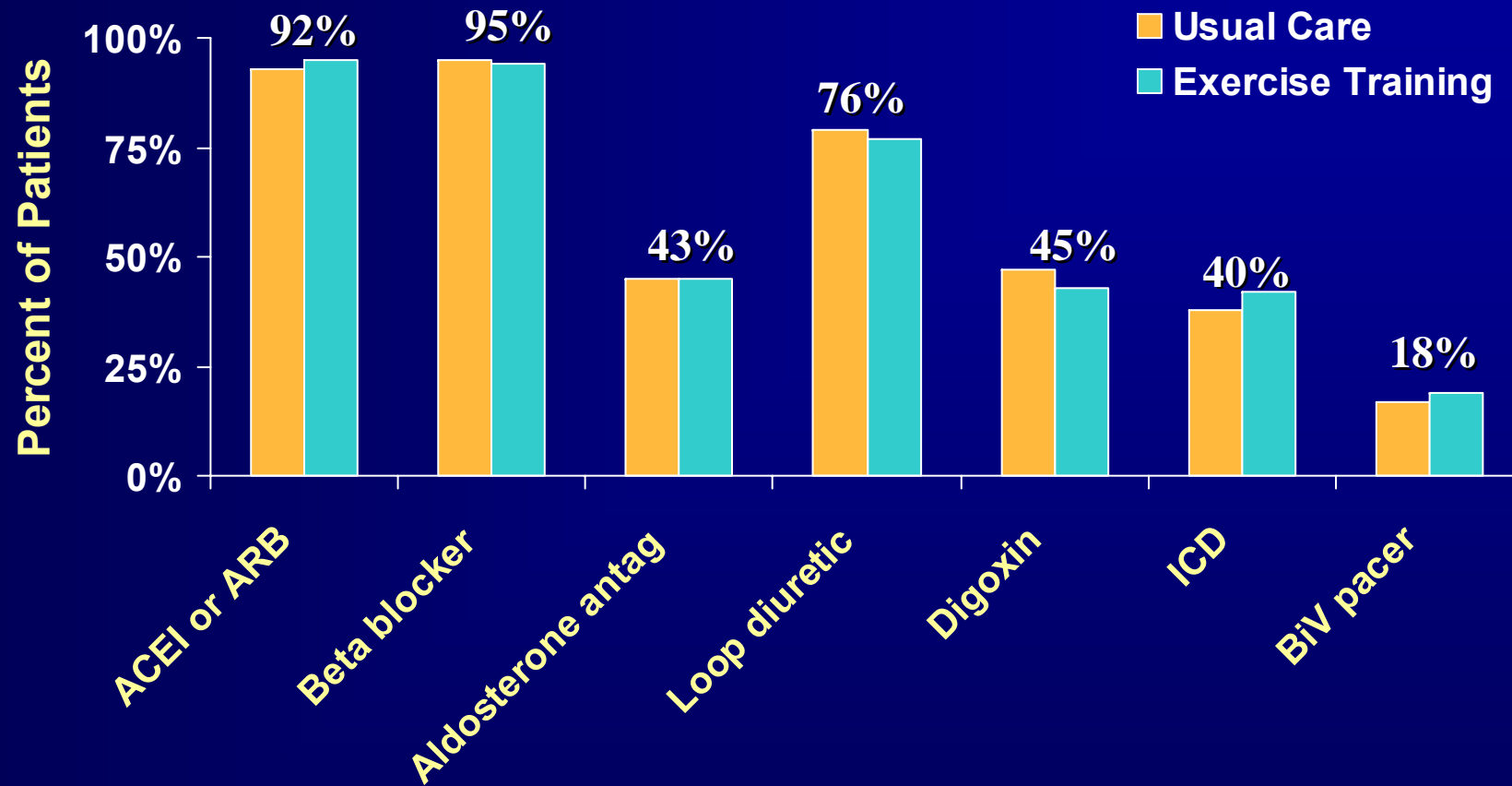
*Median (25th, 75th)



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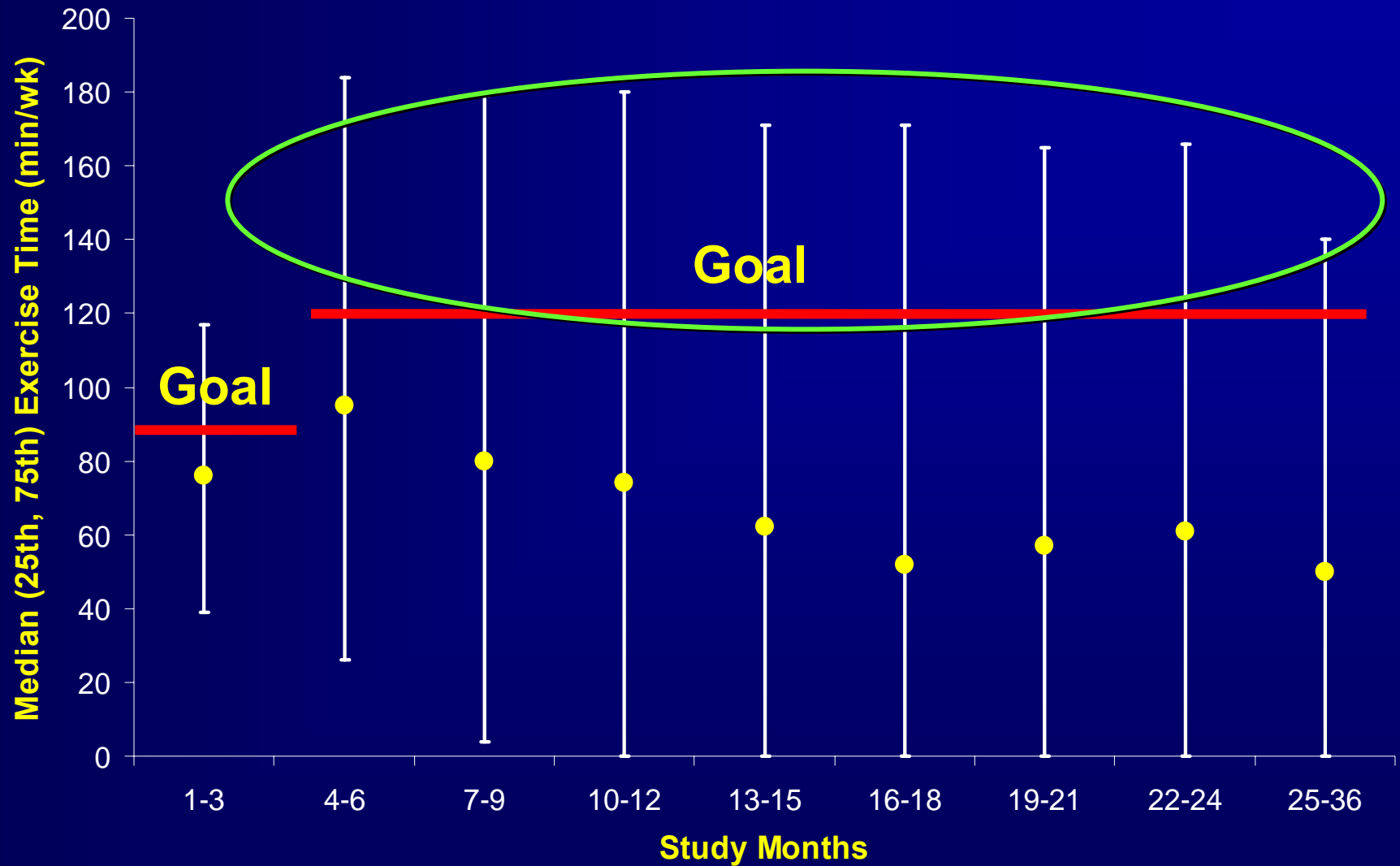
Baseline Medications and Devices



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Exercise Training: Minutes Per Week



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

Baseline to 3 months*	Usual Care	Exercise Training	P-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

Baseline to 12 months*	Usual Care	Exercise Training	P-value
6-minute walk distance (m)	12	13	0.26
CPX exercise duration (min.)	0.2	1.5	<0.0001
Peak VO ₂ (mL/min/kg)	0.1	0.7	<0.0001

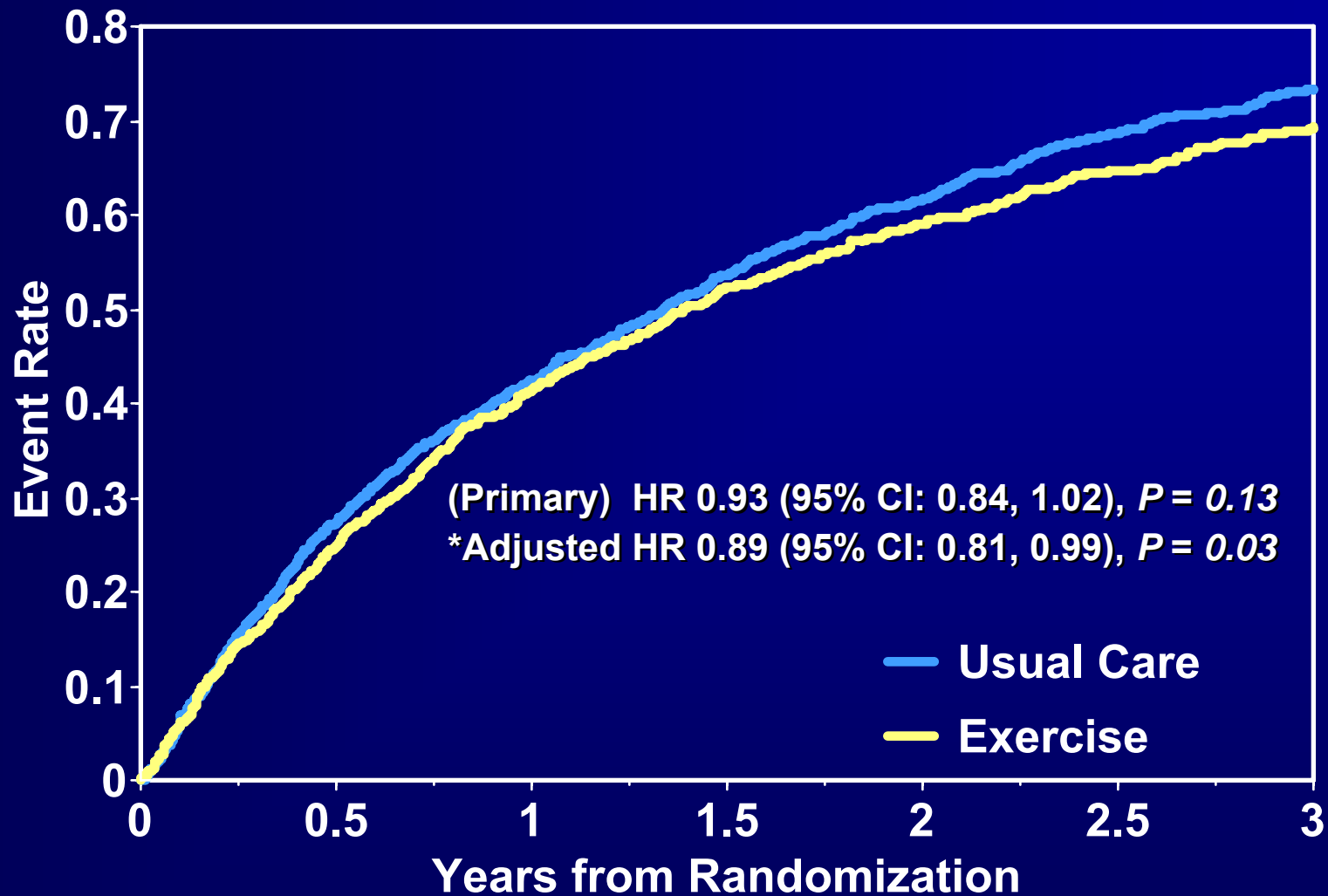
* Complete case analysis



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All-Cause Mortality or All-Cause Hospitalization



* Adjusted for key prognostic factors



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CV Mortality or CV Hospitalization



* Adjusted for key prognostic factors



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CV Mortality or HF Hospitalization



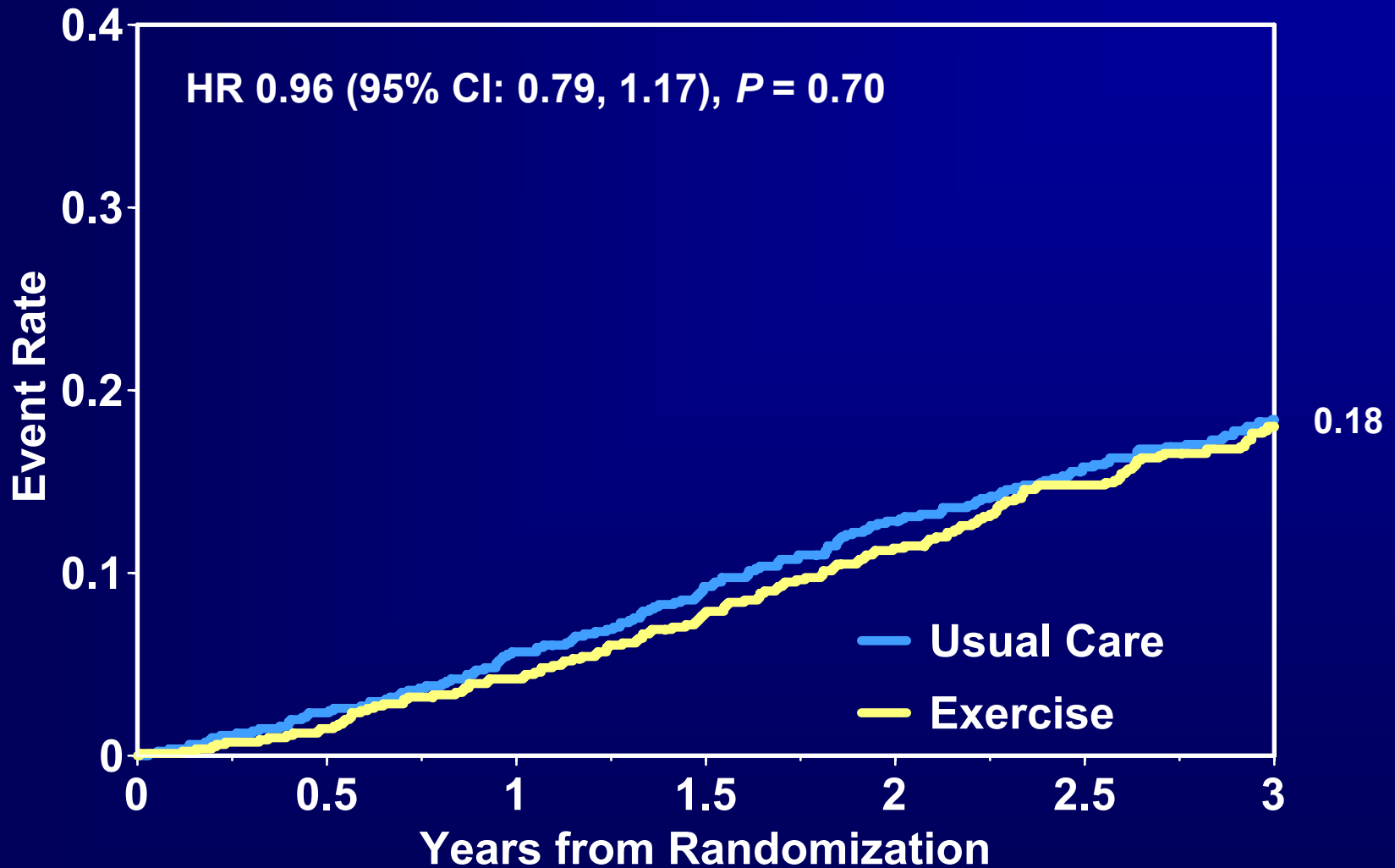
* Adjusted for key prognostic factors



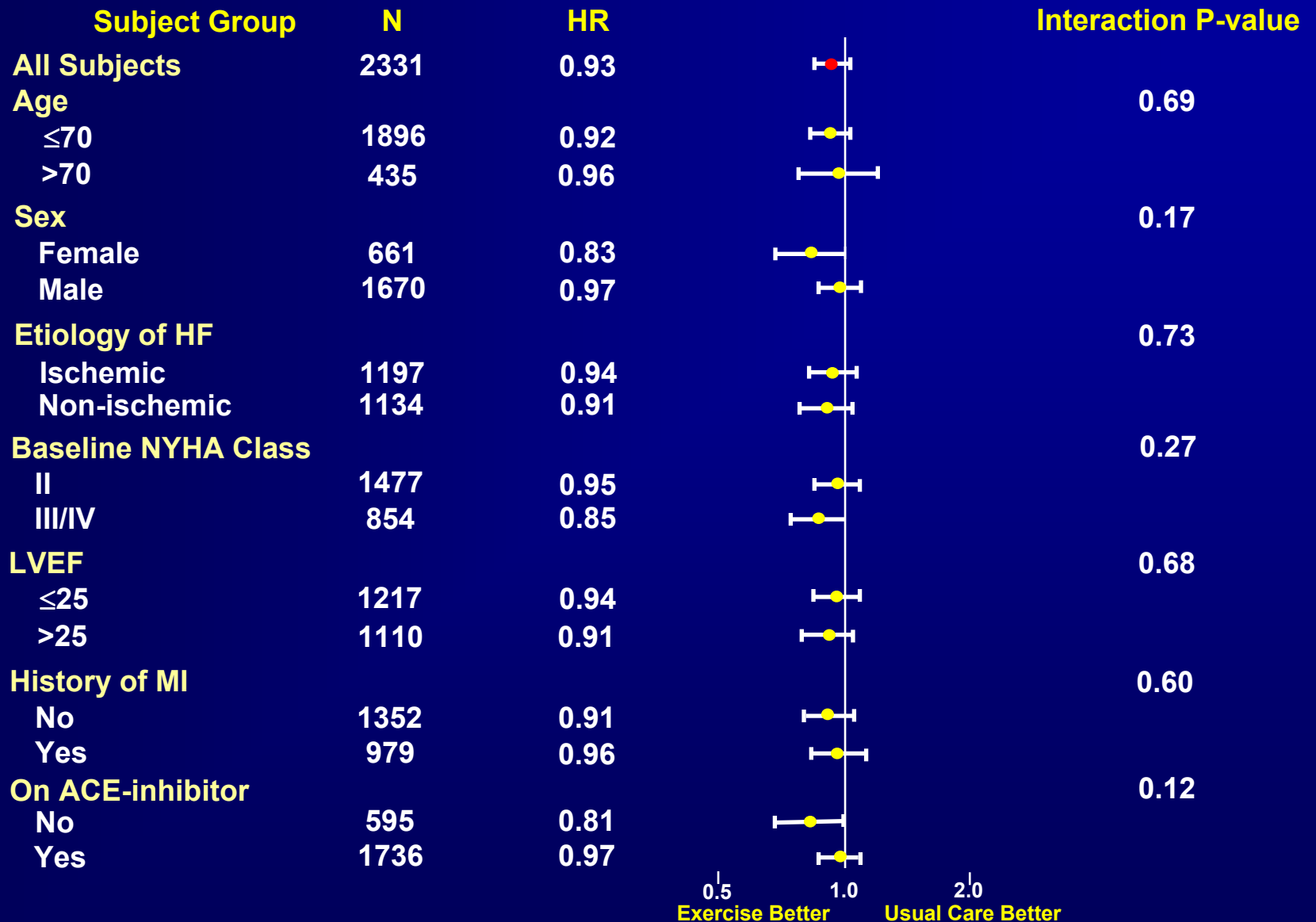
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All-Cause Mortality



Subgroup Analysis



Serious Adverse Events

	Usual Care N=1172	Ex Training N=1159
At least one CV event *	40%	37%
At least one ICD firing	23%	22%
Hospitalized after physical activity	2%	3%
Hospitalized for fracture of hip/pelvis	0.6%	0.3%
Deaths identified as possibly occurring within 3 hours of physical activity	0.4%	0.4%

* Worsening HF, MI, unstable angina, serious adverse arrhythmia, stroke, TIA



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Limitations

- **Suboptimal adherence in the exercise training group and physical activity by the usual care group may have diminished the benefit of exercise training**
- **Blinding of subjects and research personnel not possible**
 - **Core labs blinded**
 - **Clinical Endpoint Committee blinded**



Conclusions

- **HF-ACTION is the largest randomized trial of exercise training in patients with heart failure.**
- **Regular exercise training is safe in patients with heart failure.**
- **Exercise training provided modest improvements in physiologic endpoints.**



Conclusion (continued)

- Based on the main analysis adjusted for HF etiology, exercise training produced a modest, non-significant decrease in the primary endpoint (all-cause mortality or all-cause hospitalization) and key secondary clinical endpoints.
- In protocol-specified analyses adjusted for prognostic factors, the treatment effect was statistically significant for the primary endpoint and for the secondary endpoint of CV mortality or HF hospitalization.



Conclusion (continued)

Based on the safety of exercise training and the modest reduction in clinical events, the HF-ACTION study results support a prescribed exercise training program for patients with reduced LV function and HF symptoms in addition to evidence-based therapy.



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ACTION



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Back up slides



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Usual Care Crossover

- **Participating in any formal or non-formal exercise program**
 - 23% said yes on all calls first 3 months
 - 8% said yes on all calls after 3 months
- **Estimated that usual care group exercising 30% of the time based on phone call data.**
- **Median Time Exercising based on PAQ**
 - 6 months: Vigorous - 0, Moderate - 0, Walking - 65
 - 12 months: Vigorous - 0, Moderate - 0, Walking - 75



Surveillance Measures, First Nine Months

Surveillance Measures (all measures calculated per month)	Usual Care Group (N=961)	Exercise Group (N=981)
Completed HF-ACTION phone calls ¹	1.68 (1.15, 1.96)	1.73 (1.26, 2.03)
Patients with at least one provider contact ² in 9 months	533 (60%)	652 (70%)
Patients with at least one contact resulting in medication ³ change	311 (36%)	383 (43%)
Patients with at least one contact resulting in increased diuretic dose	134 (16%)	168 (19%)
Patients with at least one contact resulting in decreased diuretic dose	55 (6%)	79 (9%)

1. Phone calls the study coordinator makes to the patient per protocol.

2. "Provider contacts" refers to times in which the patient, the patient's family/friend, study personnel, exercise trainer, etc., have contacted the patient's provider due to changes in the patient's health or symptoms.

3. Changes to medications other than diuretics.



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Exercise Training Program

Training Phase	Location	Week*	Sessions / week	Aerobic minutes	Intensity (% HR reserve)	Training Mode
Initial supervised	Clinic	1-2	3	15-30	60%	Walk/Cycle
Supervised	Clinic	3-6	3	30-35	70%	Walk/Cycle
Supervised & Home	Clinic & Home	7-12	3 & 2	30-35	70%	Walk/Cycle
Maintenance	Home	13-end	5	40	60-70%	Walk/Cycle

*Week intervals shown are goals and may vary for individual participants.



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Eligibility Criteria

■ Inclusion

- LVEF \leq 35%
- NYHA class II-IV
- Optimal HF therapy at stable doses for 6 weeks

■ Exclusion

- Age <18 yrs
- Comorbidity that interferes with exercise training
- Major CV event or procedure < 6 weeks
- Expected cardiac transplant
- HF due to uncorrected primary valvular or congenital heart disease

■ Exclusion (cont).

- Exercise training >1x/wk at moderate/vigorous intensity
- Devices that limit attainment of target heart rates
- Exercise testing results that indicate exercise training may be unsafe

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



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Protocol-Specified Adjusted Analyses

Adjusted For:

	Hazard Ratio	95% CI	P-value
All-cause mortality and hospitalization (primary)			
HF etiology ¹	0.93	0.84, 1.02	0.13
Prognostic factors	0.89	0.81, 0.99	0.03
CV Mortality and CV hospitalization			
HF etiology	0.92	0.83, 1.03	0.14
Prognostic factors	0.91	0.82, 1.01	0.09
CV Mortality and HF hospitalization			
HF etiology	0.87	0.75, 1.00	0.06
Prognostic factors	0.85	0.74, 0.99	0.03

¹ specified as primary analysis



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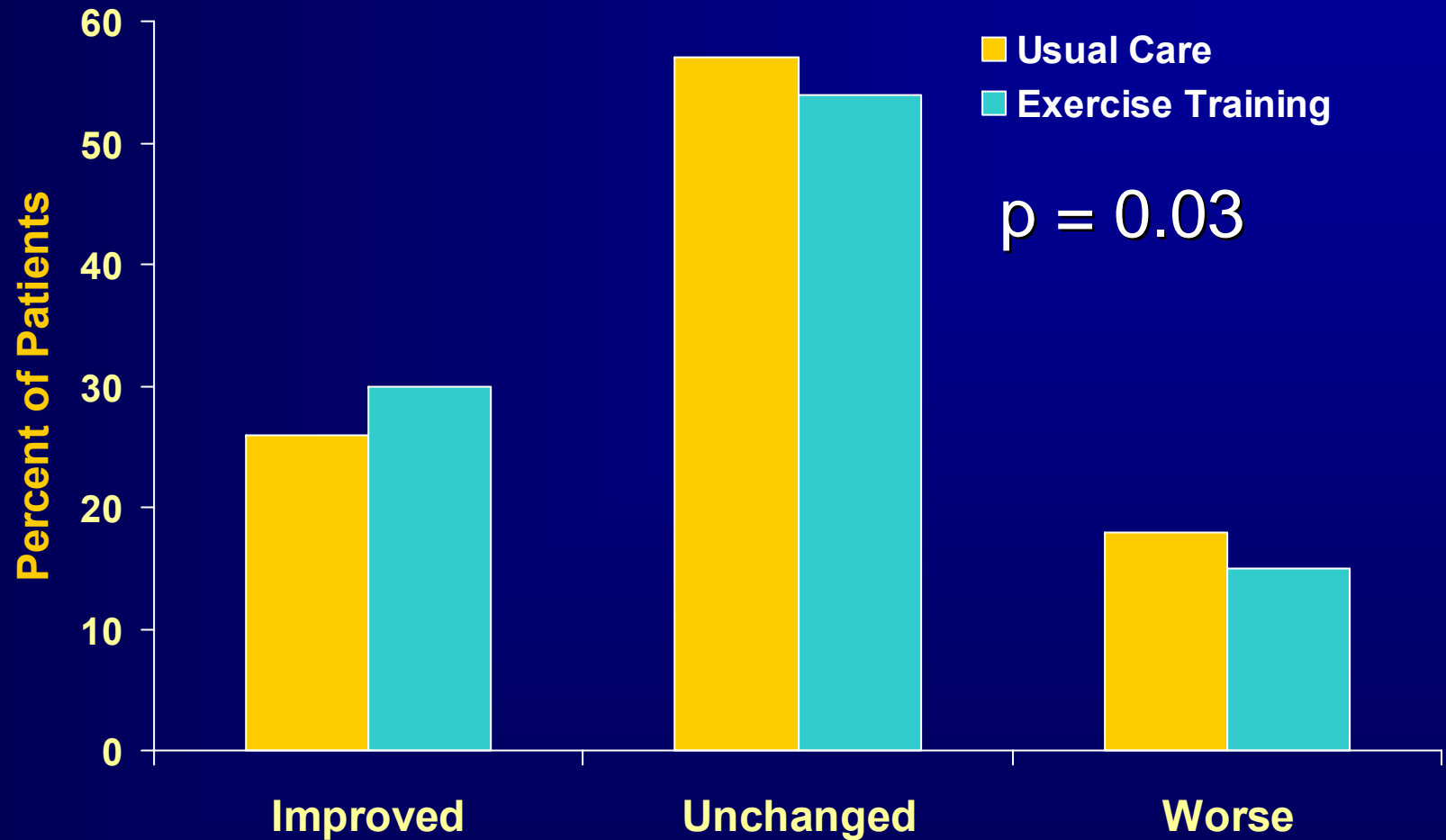


Clinical Outcomes

	Usual Care N=1172	Exercise Training N=1159	HR (95% CI)	P- value
All-cause mortality or hosp, N (%)	796 (68%)	759 (65%)	0.93 (0.84, 1.02)	0.13
CV mortality or CV hosp, N (%)	677 (58%)	632 (55%)	0.92 (0.83, 1.03)	0.14
CV mortality or HF hosp, N (%)	393 (34%)	344 (30%)	0.87 (0.75, 1.00)	0.06
All-cause mortality, N (%)	198 (17%)	189 (16%)	0.96 (0.79, 1.17)	0.70
CV mortality, N (%)	143 (12%)	131 (11%)	0.92 (0.74, 1.15)	0.47



Change in NYHA Class From Baseline to Most Recent Follow-Up



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Guideline Positions on Exercise Training in Heart Failure

■ ACC/AHA

- Exercise training is beneficial as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF and reduced LVEF (Class I, Level of Evidence B).

Hunt SA et al. *Circ* 2005;112:e154-e235

■ ESC

- Exercise training is recommended, if available, to all stable chronic HF patients. (Class I, Level of Evidence B).

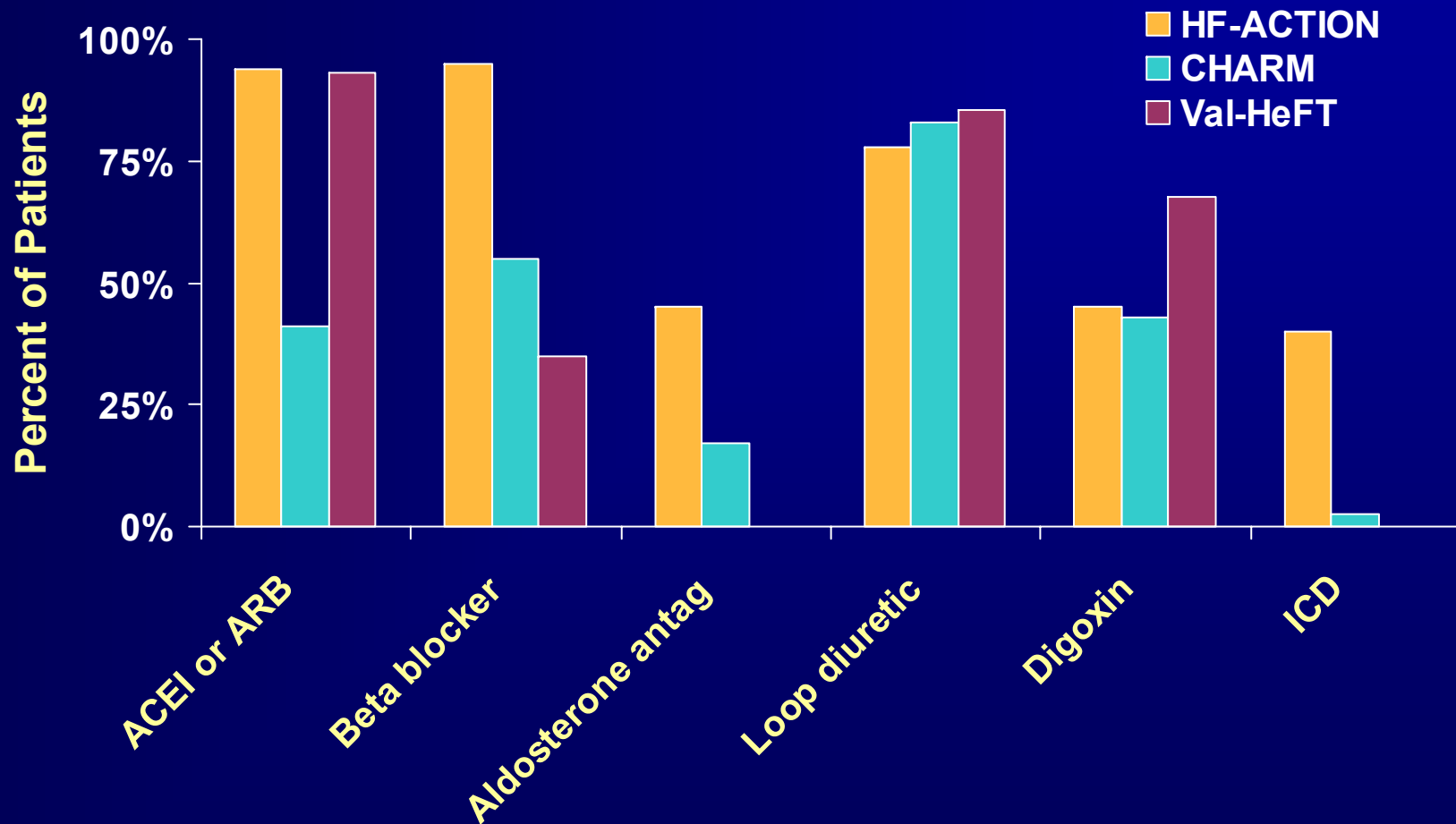
Dickstein K et al. *Eur Heart J* 2008;29:2388-2442.



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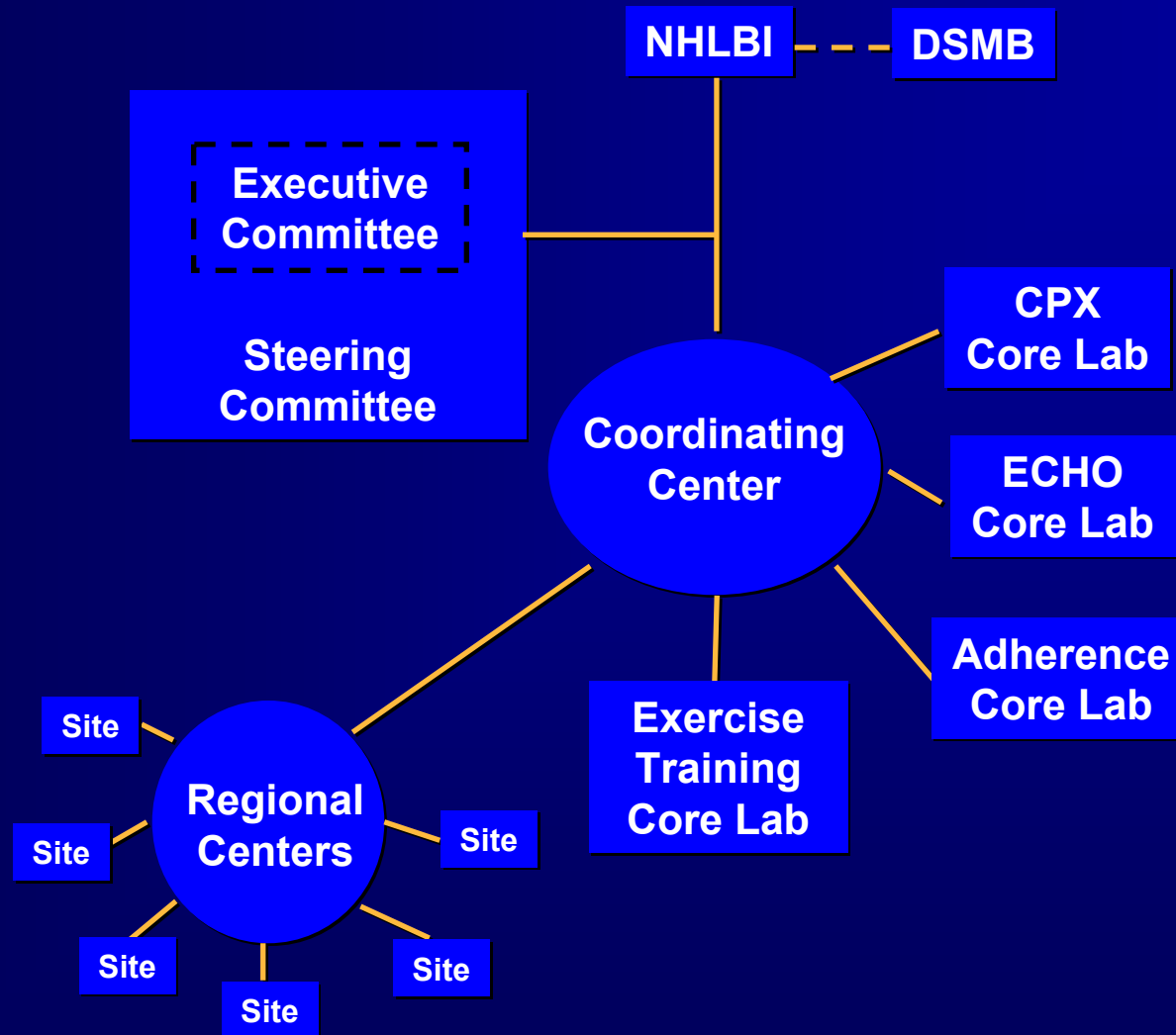
Comparison of Background Therapy: HF-ACTION, Val-HeFT, and CHARM



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Study Organization



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



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Prior CV Procedures

	Usual Care N=1172	Exercise Training N=1159
Hospitalization within 6 months, %	40	39
PTCA/Stent, %	22	24
CABG, %	25	26



Comparison of Adherence in HF-ACTION and Other Randomized Trials

Trial	Adherence Methodology	Adherence Findings
HF-ACTION	Follow-up phone calls and Physical Activity Questionnaire	29-42% performing exercise training as prescribed after month 3
Evangelista et al; JCF 2005	Pedometers (10% improvement in scores)	20/38 (53%) patients found to be adherent
Corvera-Tindel et al; AHJ 2004	Pedometers (actual walking time/prescribed time)	Overall mean compliance 74.3 ± 37% (N=42 in exercise training arm)
McKelvie RS et al; AHJ 2002	Pre-randomization screening	43% attended >80% of sessions, 16% attended <50% of sessions. Pts exercised 2.3 ± 0.4 sessions/wk during the 1 st mo and 1.7 ± 0.4 sessions/wk by month 12.
Oka et al; AJC 2000	Activity logs and telephone contact	Average adherence 110% for aerobic, 87% for upper body, and 75% for lower body
Coats AJS et al; Circ 1992	Percentage of expected bicycle wheel revolutions	Mean compliance 77.3% (range 26-116%)

Barbour KA and Houston Miller N. *Heart Fail Rev* 2008;13:81-89.



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401 Malcolm Arnold, MD, Julie K Smith, RN, *London Health Sciences, London, OH, CA*; 402 Eduardo Azevedo, MD, Glen Drobot, MD, Estrellita Estrella-Holder, RN, BN, MSA, CCN(C), *Saint Boniface General Hospital, Winnipeg, MB, CA*; 403 Jonathan Howlett, MD, Darlene Cooley-Warnell, Sheila Yarn RN, *Queen Elizabeth II Health Sciences, Halifax, NS, CA*; 404 Debra Isaac, MD, Jane Grant, RN, Kim Lyzun, *Foothills Hospital, Calgary, AB, CA*; 405 Marie-Helene LeBlanc, MD, Rachel Vienneau, RN, BSc, *Laval Hospital, Sainte Foy, QC, CA*; 406 Robert S. McKelvie, MD, Linda Beare, Jill Hancock, LRN, *Hamilton Health Sciences Corporation, Hamilton, ON, CA*; 408 Gordon Moe, MD, Delores Golob, RN, BA, *Saint Michaels Hospital, Toronto, OH, CA*; 409 Kenneth Melvin, MD, Anne Cymet, RN, Judith Renton, RN, *Toronto General Hospital, Toronto, OH, CA*; 411 Anil Nigam, MD Julie LaLonge, Research Technician, *Montreal Heart Institute, Montreal, QC, CA*

France (6 centers)

501 Karim Djaballah, MD, *Hôpital Brabois, Vandoeuvre Les Nancy, France*; 503 Patrick Aebehard, MD, *Centre Cardiologie du Nord, Saint Denis, France*; 504 Marie Christine Iliou, MD, *Hôpital Broussais, Paris, France*; 505 Remi Sabatier, MD, Annette Belin, MD, *CHU de Caen, Caen, France*; 506 Alain Cohen-Solal, MD, *Hôpital Beaujon Cardiologie, Clichy Cedex, France*; 507 Luc Hittinger, MD, *Hôpital Henri Mondor-Service de Cardiologie, Creteil, France*



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