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RESEARCH LETTER

Differences Between Patients Enrolled Early and Late During Clinical Trial Recruitment

Insights From the HF-ACTION Trial

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The duration of clinical trials has increased with time given increasing trial complexity, recruitment challenges, and lowering event rates.[1] Although inclusion and exclusion criteria of clinical trials are used in part to homogenize enrolled patients, limited data are available whether patient characteristics and outcomes change over the course of a clinical trial. We hypothesized that significant changes in patient characteristics and response to intervention occurred over the course of enrollment in a clinical trial.

We analyzed patients in the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training; URL: http://www.clinicaltrials.gov. Unique identifier: NCT00047437), which recruited from April 2003 to February 2007, randomizing outpatients with heart failure (HF) with reduced ejection fraction to exercise training versus usual care.[2] There was a nonsignificant difference in the prespecified primary outcome (all-cause mortality and hospitalization) between the exercise and usual care arms in the original trial.[2] In the present analysis, prespecified primary and secondary outcomes were compared between the first half of enrolled patients (n=1166, April 2003 to March 2005, 23.2 months) and the second half (n=1165, March 2005 to February 2007, 23.4 months). Adjusted models included the treatment arm and prespecified HF-ACTION adjustment variables used consistently in prior analyses.[3] All data and materials have been made publicly available at the NHLBI's BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center) and can be accessed at https://biolincc.nhlbi.nih.gov/studies/hf_action/. HF-ACTION was approved by the institutional review boards of all participating sites.

Early enrollees were less likely to be white (60% versus 66%), from outside the United States (8% versus 15%), and had marginally lower median ejection fraction (24% versus 25%) with longer baseline cardiopulmonary exercise test times (10 minutes versus 9 minutes; P<0.01; Table 1). United States sites were activated earlier in the trial thus more blacks were enrolled early. There were no other differences in key baseline demographics, disease severity, or functional measures. Late enrollees received more evidence-based therapies such as β-blockers (96% versus 94%), mineralocorticoid receptor antagonists (48% versus 42%), implantable cardioverter defibrillators (50% versus 31%), cardiac resynchronization therapy (21% versus 15%; all P<0.05). Almost all characteristics were similar between randomized arms by time of enrollment except for higher implantable cardioverter defibrillator prevalence and increased burden of depressive symptoms in the control arm as compared with the intervention arm in patients enrolled late. Late enrollees had greater adjusted 1 to 3 month exercise adherence (effect estimate +9.81 minutes/week [95% confidence interval, 0.7–19.0]; P=0.04) and exercise duration (+40.3 minutes/week [95% confidence interval, 11.8–68.8]; P<0.01). There was no difference in the primary outcome of all-cause mortality or hospitalization between those enrolled early and late, and no treatment-by-subgroup interaction was noted

Key Words: cardiac resynchronization therapy ■ exercise test ■ heart failure ■ outpatients ■ prevalence

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Table 1. Baseline Patient Characteristics by Time of Recruitment and Randomized Treatment

		Early vs Late Recruitment			Early Recruitment			Late Recruitment		
					Randomized Therapy			Randomized Therapy		
Characteristic	All Patients (N=2331)	Early Recruitment (N=1166)	Late Recruitment (N=1167)	*P* Value	Treatment Arm (N=584)	Control Arm (N=582)	*P* Value	Treatment Arm (N=575)	Control Arm (N=590)	*P* Value
Demographics										
Age, y	59 (51–68)	59 (51–68)	59 (51–68)	0.354	59 (51–68)	59 (51–68)	0.544	60 (52–69)	59 (51–68)	0.586
Male	1670 (71.6%)	821 (70.4%)	849 (72.9%)	0.187	422 (72.5%)	399 (68.3%)	0.117	436 (73.9%)	413 (71.8%)	0.426
Hispanic or Latino ethnicity	928 (40.1%)	502 (43.4%)	426 (36.7%)	<0.001	251 (43.5%)	251 (43.4%)	0.959	207 (35.2%)	219 (38.3%)	0.276
Black	772 (33.1%)	431 (37.0%)	341 (29.3%)	<0.001	213 (36.6%)	218 (37.3%)	0.796	169 (28.6%)	172 (29.9%)	0.634
White	1468 (63.0%)	694 (59.5%)	774 (66.4%)	<0.001	346 (59.5%)	348 (59.6%)	0.961	403 (68.3%)	371 (64.5%)	0.172
Other	82 (3.6%)	44 (3.8%)	38 (3.3%)	0.515	26 (4.5%)	18 (3.1%)	0.212	13 (2.2%)	25 (4.4%)	0.037
Country				<0.001			0.899			0.904
United States	2068 (88.7%)	1077 (92.4%)	991 (85.1%)		537 (92.3%)	540 (92.5%)		504 (85.4%)	487 (84.7%)	
Canada	188 (8.1%)	89 (7.6%)	99 (8.5%)		45 (7.7%)	44 (7.5%)		48 (8.1%)	51 (8.9%)	
France	75 (3.2%)	0 (0.0%)	75 (6.4%)		0 (0.0%)	0 (0.0%)		38 (6.4%)	37 (6.4%)	
Clinical characteristics										
BMI	30 (26–35)	30 (26–35)	30 (26–35)	0.781	30 (26–35)	30 (26–35)	0.528	30 (26–35)	30 (26–35)	0.705
NYHA class				0.907			0.222			0.489
II	1477 (63.4%)	743 (63.7%)	734 (63.0%)		373 (64.1%)	370 (63.4%)		381 (64.6%)	353 (61.4%)	
III	831 (35.6%)	411 (35.2%)	420 (36.1%)		206 (35.4%)	205 (35.1%)		203 (34.4%)	217 (37.7%)	
IV	23 (1.0%)	12 (1.0%)	11 (0.9%)		3 (0.5%)	9 (1.5%)		6 (1.0%)	5 (0.9%)	
CCS angina class				0.007			0.351			0.374
No angina	1950 (83.8%)	949 (81.4%)	1001 (86.1%)		480 (82.5%)	469 (80.3%)		514 (87.3%)	487 (85.0%)	
I	200 (8.6%)	117 (10.0%)	83 (7.1%)		59 (10.1%)	58 (9.9%)		36 (6.1%)	47 (8.2%)	
II	178 (7.6%)	100 (8.6%)	78 (6.7%)		43 (7.4%)	57 (9.8%)		39 (6.6%)	39 (6.8%)	
Ischemic cause of HF	1197 (51.4%)	586 (50.3%)	611 (52.4%)	0.290	291 (50.0%)	295 (50.5%)	0.861	308 (52.2%)	303 (52.7%)	0.866
LVEF	25 (20–30)	24 (20–30)	25 (21–30)	0.006	24 (20–30)	24 (20–30)	0.667	25 (20–31)	25 (21–30)	0.625
Diabetes mellitus	748 (32.1%)	376 (32.2%)	372 (31.9%)	0.870	189 (32.5%)	187 (32.0%)	0.868	181 (30.7%)	191 (33.2%)	0.353
Previous MI	979 (42.0%)	474 (40.7%)	505 (43.3%)	0.187	235 (40.4%)	239 (40.9%)	0.849	264 (44.7%)	241 (41.9%)	0.329
Hypertension	1388 (59.9%)	708 (61.0%)	680 (58.7%)	0.256	345 (59.6%)	363 (62.5%)	0.312	331 (56.5%)	349 (61.0%)	0.118
Atrial fibrillation or flutter	488 (20.9%)	227 (19.5%)	261 (22.4%)	0.080	111 (19.1%)	116 (19.9%)	0.733	130 (22.1%)	131 (22.8%)	0.771
Moderate or severe MR	256 (12.0%)	133 (12.4%)	123 (11.6%)	0.542	72 (13.4%)	61 (11.4%)	0.336	61 (11.3%)	62 (11.8%)	0.785
Beck Depression Inventory Score	8 (4–15)	8 (4–15)	8 (4–15)	0.445	8 (4–15)	8 (5–15)	0.843	8 (4–14)	9 (5–15)	0.029
Systolic blood pressure, mm Hg	111 (100–126)	112 (100–126)	110 (100–126)	0.277	112 (100–128)	112 (102–126)	0.764	110 (100–125)	110 (100–126)	0.482
Diastolic blood pressure, mm Hg	70 (60–78)	70 (60–80)	70 (60–78)	0.871	70 (60–80)	70 (60–78)	0.704	70 (60–78)	70 (62–78)	0.578
Sodium, mmol/L	139 (137–141)	139 (137–141)	139 (137–141)	0.673	139 (137–141)	139 (137–141)	0.316	139 (137–141)	139 (137–141)	0.784
BUN, mg/dL	20 (15–28)	20 (15–27)	21 (15–29)	0.191	20 (15–28)	20 (15–27)	0.963	21 (15–29)	21 (15–29)	0.719
Serum creatinine, mg/dL	1.20 (1.00–1.50)	1 (1.00–1.50)	1 (1.00–1.50)	0.874	1.20 (1.00–1.50)	1.20 (1.00–1.50)	0.609	1.20 (1.00–1.50)	1.20 (1.00–1.40)	0.183
Baseline meds, devices										
ACEI-ARB	1736 (74.5%)	889 (76.2%)	847 (72.7%)	0.050	440 (75.6%)	449 (76.9%)	0.607	421 (71.4%)	426 (74.1%)	0.295
β-blocker	2203 (94.5%)	1090 (93.5%)	1113 (95.5%)	0.029	549 (94.3%)	541 (92.6%)	0.242	563 (95.4%)	550 (95.7%)	0.850
Aldosterone receptor antagonist	1051 (45.1%)	494 (42.4%)	557 (47.8%)	0.008	250 (43.0%)	244 (41.8%)	0.685	278 (47.1%)	279 (48.5%)	0.632

(*Continued*)

Table 1. Continued

Characteristic	All Patients (N=2331)	Early vs Late Recruitment			Early Recruitment			Late Recruitment		
					Randomized Therapy			Randomized Therapy		
		Early Recruitment (N=1166)	Late Recruitment (N=1167)	*P* Value	Treatment Arm (N=584)	Control Arm (N=582)	*P* Value	Treatment Arm (N=575)	Control Arm (N=590)	*P* Value
Loop diuretic	1816 (77.9%)	915 (78.5%)	901 (77.3%)	0.509	467 (80.2%)	448 (76.7%)	0.143	454 (76.9%)	447 (77.7%)	0.747
Digoxin	1046 (44.9%)	576 (49.4%)	470 (40.3%)	<0.001	304 (52.2%)	272 (46.6%)	0.053	243 (41.2%)	227 (39.5%)	0.552
Nitrate	559 (24.0%)	296 (25.4%)	263 (22.6%)	0.112	150 (25.8%)	146 (25.0%)	0.762	127 (21.5%)	136 (23.7%)	0.385
ICD	938 (40.2%)	358 (30.7%)	580 (49.8%)	<0.001	177 (30.4%)	181 (31.0%)	0.830	271 (45.9%)	309 (53.7%)	0.008
Biventricular pacemaker	419 (18.0%)	177 (15.2%)	242 (20.8%)	<0.001	93 (16.0%)	84 (14.4%)	0.448	110 (18.6%)	132 (23.0%)	0.070
Functional measures										
Six-minute walk distance, m	371 (299–435)	372 (302–434)	369 (293–435)	0.519	374 (304–430)	369 (301–439)	0.989	373 (298–439)	366 (282–435)	0.366
Cpex time, min	10 (7–12)	10 (7–12)	9 (7–12)	0.006	10 (7–13)	10 (7–12)	0.932	10 (7–12)	9 (7–12)	0.229
Peak HR, min	120 (104–134)	120 (105–134)	119 (104–134)	0.400	120 (104–134)	120 (106–134)	0.931	120 (103–133)	118 (104–136)	0.933
Peak O_2 consumption, mL/kg per minute	14 (12–18)	14 (11–18)	15 (12–18)	0.428	14 (12–18)	14 (11–18)	0.433	15 (12–18)	14 (12–18)	0.449
VE/V_{CO_2}, mL/kg per minute	33 (28–39)	32 (28–39)	33 (28–38)	0.913	32 (28–38)	32 (28–39)	0.942	33 (28–38)	33 (28–39)	0.825
KCCQ summary score	68 (51–83)	69 (52–83)	67 (50–83)	0.165	69 (53–84)	69 (51–83)	0.957	68 (51–84)	66 (49–82)	0.134

Baseline characteristics by time of enrollment and randomization arm. Values are presented as n (%), or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CCS, Canadian Cardiovascular Society; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; and NYHA, New York Heart Association.

for the primary outcome (Table 2). However, late enrollees experienced comparatively greater mortality benefit with exercise training than early enrollees.

Our data demonstrate that patient characteristics and treatment adherence can change over the course of a large clinical outcomes trial. Utilization of evidence-based therapies for HF improved over time, suggesting that despite strict inclusion/exclusion criteria, the enrolled population reflected changes in management similar to those experienced by the general population

Table 2. Association Between Randomized Treatment Group and Clinical Outcomes by Time of Enrollment (Control Is Reference Group)

Clinical Outcome	Incidence Rate (Per 365 Patient Days)		Adjusted	
	Intervention Arm	Control Arm	Rate Ratio (95% CI)	*P* Value
All-cause mortality/hospitalization*				
Interaction timing of treatment arm and enrollment				0.579
Intervention vs control in early enrollers	0.43 (0.39–0.47)	0.46 (0.42–0.51)	0.88 (0.76–1.02)	0.088
Intervention vs control in late enrollers	0.46 (0.42–0.52)	0.50 (0.45–0.56)	0.94 (0.79–1.11)	0.461
All-cause mortality*				
Interaction timing of treatment arm and enrollment				0.012
Intervention vs control in early enrollers	0.07 (0.06–0.09)	0.06 (0.05–0.08)	1.16 (0.90–1.48)	0.253
Intervention vs control in late enrollers	0.05 (0.04–0.07)	0.07 (0.06–0.09)	0.66 (0.46–0.95)	0.023
CV mortality†				
Interaction timing of treatment arm and enrollment				0.053
Intervention vs control in early enrollers	0.05 (0.04–0.06)	0.05 (0.04–0.06)	1.20 (0.86–1.67)	0.287
Intervention vs control in late enrollers	0.04 (0.03–0.05)	0.06 (0.04–0.07)	0.67 (0.42–1.09)	0.107

Clinical outcomes based on time of enrollment and randomized therapy. CI indicates confidence interval; and CV, cardiovascular.

*Adjustment model includes: Weber class, Kansas City Cardiomyopathy Questionnaire symptom stability score, country, sex, mitral regurgitation grade, ventricular conduction, blood urea nitrogen, left ventricular ejection fraction, and β-blocker dose.

†Adjustment model includes: exercise duration, creatinine, body mass index, sex, loop diuretic dose, left ventricular ejection fraction, Canadian Cardiovascular Society angina classification, and ventricular conduction.

during this time period.[4] However, baseline characteristics were largely similar between patient groups by randomization arm and time of enrollment. Late enrollees were also more adherent with the exercise intervention potentially because of increased focus on adherence by investigators and overall improvement in performance of study staff with time. All of these changes, including increased adherence in the late enrolled group, may have contributed to the mortality benefit observed with exercise in late enrollees, a benefit not noted in the overall trial.[2]

These findings have important implications for trial design and interpretation. Based on our analysis of the ClinicalTrials.gov database, phase 3 to 4 cardiovascular trials completed between 1991 and 2016 (n=1282) lasted for 3.4 years on average, enrolling 964 subjects, compared with 4.9 years for HF-ACTION. Thus, with an average duration of 3 to 4 years, temporal changes in the state-of-the-art management of conditions such as cardiovascular disease may affect trial findings despite randomization and blinding. Although our findings are hypothesis generating and we cannot rule out residual confounding factors, they suggest that time of enrollment could be included in the variables used for covariate adjustment within the outcome analysis of long duration trials during which background therapy, clinical characteristics or adherence to therapy may change. These findings are important particularly given that many trials implement strategies and protocols that may be subject to variable implementation and adherence similar to the exercise intervention in HF-ACTION.

Our results point to the importance of timely enrollment and the importance of maintaining intervention adherence, both to avoid such confounding interactions and to render the overall findings more appropriately applicable to the contemporary population at the time of publication. However, given the exploratory nature of this analysis, additional analyses exploring this concept in other data sets would help support the potential implications of time of enrollment over the duration of a long-term outcome trial.

ARTICLE INFORMATION

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