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Response to Exercise Training and Outcomes in Patients with Heart Failure and Diabetes Mellitus: Insights from HF-ACTION

Adam Z. Banks, MD[*], **Robert J. Mentz, MD**[*,†], **Amanda Stebbins, PhD**[†], **Catherine R. Mikus, PhD**[*], **Phillip J. Schulte, PhD**[†], **Jerome L. Fleg, MD**[‡], **Lawton S. Cooper, MD**[‡], **Eric S. Leifer, PhD**[‡], **Dalynn T. Badenhop, PhD**[$], **Steven J. Keteyian, PhD**[‖], **Ileana L. Piña, MD, MPH**[¶], **Dalane W. Kitzman, MD**[#], **Mona Fiuzat, PharmD**[*,†], **David J. Whellan, MD, MHS**[††], **William E. Kraus, MD**[*], and **Christopher M. O'Connor, MD**[*,†]

Adam Z. Banks: adam.z.banks@duke.edu

[*]Duke University Medical Center, Durham, NC

[†]Duke Clinical Research Institute, Durham, NC

[‡]National Heart, Lung, and Blood Institute, Bethesda, MD

[$]University of Toledo Medical Center, Toledo, OH

[‖]Henry Ford Hospital, Detroit, MI

[¶]Montefiore-Einstein Medical Center, New York, NY

[#]Wake Forest School of Medicine, Winston Salem, NC

[††]Thomas Jefferson University, Philadelphia, PA

Abstract

Background—In the HF-ACTION trial, exercise training improved functional capacity in heart failure with reduced ejection fraction (HFrEF). Previous studies have suggested that diabetes mellitus (DM) may be associated with an attenuated response to exercise. We explored whether DM attenuated the improvement in functional capacity with exercise.

Methods/Results—HF-ACTION randomized 2,331 patients with HFrEF to medical therapy with or without exercise training over a median follow-up of 2.5 years. We examined the interaction between DM and exercise response measured by change in 6-minute walk distance (6MWD) and peak VO_2. We also examined outcomes by DM status. In HF-ACTION, 748 (32%) patients had DM. DM patients had lower functional capacity at baseline and had lower exercise volumes at 3 months. There was a significant interaction between DM status and exercise training for change in peak VO_2 (interaction p=0.02), but not 6MWD. In the exercise arm, DM patients had a smaller mean increase in peak VO_2 than non-DM patients (p=0.03). There was no interaction

Corresponding Author: Dr. Adam Banks. 2530 Erwin Road Apt 513, Durham, NC 27705, (P)281-382-4667. (F) 919-668-7078. Adam.Z.Banks@duke.edu.

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between DM and exercise on clinical outcomes. After risk adjustment, DM was associated with increased all-cause mortality/hospitalization (p=0.03).

Conclusions—In HF-ACTION, DM was associated with lower baseline functional capacity, an attenuated improvement in peak VO_2 and increased hospitalizations.

Keywords

Diabetes Mellitus; Chronic Heart Failure; Functional Capacity

Introduction

Despite effective pharmacologic therapies for patients with heart failure with reduced ejection (HFrEF), these patients continue to have high rates of morbidity and mortality. Fifty percent of HFrEF patients die within 5 years of diagnosis; thus, there is a need for individual and population-based interventions to improve outcomes (1). A treatment strategy that influences comorbidities, such as diabetes mellitus (DM), chronic obstructive pulmonary disease, and chronic kidney disease, may represent an effective approach to improve outcomes in HF (2).

DM is a common comorbidity, seen in approximately 40–45% of patients with HFrEF (3,4). Prior studies suggest that DM is associated with an increased incidence of HF, more comorbidities and worse outcomes (4–7). However, the data on outcomes in HF patients with DM is conflicting. Several HF registries demonstrate an association between DM and increased all-cause mortality (8,9), while others demonstrate an association with increased risk of hospitalization but similar mortality (4,5). In addition, most prior studies had relatively short-term follow up, with a median duration of less than 10 months.

Thus, there is an unmet need to determine long-term clinical outcomes and assess interventions to reduce events in HF patients with DM. Heart Failure: a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was a randomized trial of 2,331 ambulatory HFrEF patients with long-term follow up, high usage of evidence-based HF therapies, and a large population of DM patients (10). In addition, HF-ACTION was the largest randomized trial to date of exercise in patients with HFrEF, which enables us to describe the baseline functional capacity of patients with HFrEF and DM, as well as their response to exercise training. In HF-ACTION, 3 months of exercise training was associated with a modest increase in 6-minute walk distance (6MWD) (median of 15 meters) and peak oxygen uptake (VO_2) (median 0.4 mL/kg/min) compared with usual care (both $p<0.001$). Previous studies in the general population suggest that type 1 or 2 DM patients experience an attenuated physiologic response to exercise (10,11). Despite this attenuated physiologic response, a previous study of cardiac rehabilitation in patients with coronary artery disease demonstrated that both DM and non-DM patients benefitted from exercise training with similar improvements in exercise capacity observed in both groups (12). However, no large-scale study to our knowledge has examined the efficacy of exercise training in HFrEF patients with DM.

We, therefore, explored whether DM attenuated the benefit of exercise in patients with HFrEF. We hypothesized that improvement in functional capacity, as measured by change 6MWD and change peak VO_2 after 3 months, would be attenuated in the exercise group with DM. We also evaluated long-term medical outcomes stratified by DM status, and assessed whether there is an interaction between DM status and exercise training on clinical outcomes.

Methods

The design and analysis of the HF-ACTION study has been previously published (clinicaltrials.gov, NCT00047437) (13,14). HF-ACTION randomized 2,331 patients with HFrEF (EF≤35%) and New York Heart Association (NYHA) class II–IV symptoms to aerobic exercise training vs. usual care with a median follow-up of 2.5 years. DM status was prospectively recorded at study enrollment by self-report and confirmed by the clinician-investigator based on clinical evidence and knowledge of past medical history by chart review. In addition, the use of insulin and oral hyperglycemic agents were documented at the time of enrollment. HF-ACTION was approved by local institutional review boards, and all patients provided informed consent.

Patients completed a cardiopulmonary exercise (CPX) test, 6-minute walk, and health status surveys at baseline and were subsequently randomized to exercise training vs. usual care. Patients randomized to exercise were scheduled to participate in 3 supervised exercise sessions/week for 3 months. Patients exercised using a treadmill or stationary cycle ergometer as their training mode. Patients were encouraged to begin home-based exercise after 18 supervised sessions and to fully transition to home exercise after 36 supervised sessions. Adherence was defined as ≥90 min/wk of exercise during months 1–3 and ≥120 min/wk during subsequent months. MET-HRs/week data were recorded to assess exercise volume based on the supervised exercise sessions and self-reported home activity logs. Patients were instructed to continue home-based exercise training, along with one supervised session every 3 months. Exercise (CPX testing and 6- minute walk) and health status measures were repeated at 3 and 12 months after baseline. (13,14)

Statistical Methods

Baseline characteristics were assessed including DM status and stratification by insulin vs. non-insulin dependent DM. Continuous variables were described with the median and interquartile ranges (25^{th} and 75^{th} percentile) and compared for DM vs. Non-DM using the Wilcoxon rank-sum statistic. Discrete variables are presented as percentages and compared for DM vs. non-DM using the Pearson Chi-Squared statistic or Fisher's exact test. Exercise volume (MET-HRs/week) was measured after 3 months to assess adherence and compared between DM and non-DM patients using the Wilcoxon rank-sum test.

The co-primary outcomes for the present study were change in 6MWD and peak VO_2 after 3 months of training. We also evaluated the secondary outcomes of change in health status (i.e., Kansas City Cardiomyopathy Questionnaire) and time to clinical outcomes (all-cause mortality/hospitalization, all-cause mortality, cardiovascular (CV) mortality/HF hospitalization). We used linear regression to examine the interaction between DM and

exercise training as a predictor for change in 6MWD and peak VO_2 from baseline to 3 months adjusted only for baseline 6MWD and peak VO_2, respectively. Inverse weighted averages were used to account for patients with missing exercise data at 3 months. Figure 1 presents the study population. If the interaction P-value was significant ($P<0.05$), then the mean difference and 95% confidence interval for change in the exercise variable were reported. As a sub-analysis, we repeated the above statistical analysis comparing insulin- and non-insulin-dependent DM.

Adjusted Cox proportional hazard models were used to assess an interaction between DM status and exercise training for clinical outcomes. If the interaction P-value was significant, then the hazard ratio and 95% confidence interval were reported. The relationship between DM status and clinical outcomes was investigated, irrespective of treatment assignment, using unadjusted and adjusted Cox proportional hazard models. The hazard models were adjusted for a comprehensive set of covariates that have previously been identified for the HF-ACTION cohort using a stepwise variable selection based on a bootstrap-backward selection process (15).

A two-tailed P-value of <0.05 was considered to be statistically significant. There was no correction for multiple comparisons. All statistical analyses were performed by the Duke Clinical Research Institute (Durham, NC, USA) using SAS version 9.2 (Cary, NC, USA). The authors are solely responsible for the design and conduct of this study, all statistical analyses, and the drafting and editing of the manuscript.

Results

In HF-ACTION, 748 (32%) patients had DM. Table 1 presents the baseline characteristics stratified by DM status. DM patients were older, more likely to be African-American, had higher BMIs and worse NYHA class symptoms at baseline compared to non-DM patients. DM patients were more likely to be hypertensive and had higher creatinine and blood urea nitrogen at baseline. Guideline-directed medical- therapy for HF were high in both patient groups.

Table 2 presents exercise capacity and health status at baseline in patients stratified by DM and insulin use. Mean baseline peak VO_2, 6MWD and KCCQ clinical summary scores were lower in patients with DM. After adjustment for age, race, BMI, CKD, hypertension, and NYHA class the mean baseline peak VO_2 was still significantly lower in patients with DM. For comparison, the minimal clinically importance differences (MCID) for 6MWD, peak VO_2 and KCCQ clinical summary score have previously been estimated to be approximately 30 meters (16,17), 1 mL/kg/min or a 6% change from baseline (18,19) and 5 points, respectively (20). For the sub-analysis comparing insulin-dependent DM patients vs. non-insulin-dependent DM patients, the mean baseline functional capacity was significantly lower for the insulin-dependent patients as measured by 6MWD and peak VO_2 (Table 2). Heart rate (HR) at peak exercise and HR reserve (HR at peak exercise minus resting HR) were also significantly lower in the DM versus non-DM patients and in the insulin-dependent versus non-insulin dependent DM patients. However, this may be at least partially driven by an increased mean beta-blocker dose in the DM patients. During the first 3 months

following randomization, exercise volume was lower in DM versus non-DM for patients in the exercise arm (2.5 MET-HRs/week IQR (0.1–4.7) versus 3.3 (0.6–5.9), p <0.001). This difference in adherence may be partially driven by the older age, higher BMI, and higher NYHA class within the DM group.

There was a statistically significant interaction between DM status and exercise training for change in peak VO_2 (interaction p=0.02), but not 6MWD (interaction p=0.53) after adjustment for baseline peak VO_2 and 6MWD, respectively. Table 3 displays the median baseline and 3-month values for the explored exercise variables. The mean increase in 6MWD and peak VO_2 after 3 months can be seen in Table 4 for the exercise and usual care arm. In the exercise arm, DM patients had a smaller mean increase in peak VO_2 than non-DM patients (0.5 ± 2.4 vs. 0.9 ± 2.6 mL/kg/min, p=0.03). Despite this attenuated exercise response in the DM patients compared to non-DM patients, the DM patients in the exercise arm of HF-ACTION still had a statistically significant improvement in both peak VO_2 (0.5 vs. 0.3 ml/kg/min, p <0.001) and 6MWD (17.4 vs. 5.8 meters, p<0.001) after 3 months of exercise training as compared to usual care. Since exercise volume was significantly lower in the DM patients, we retrospectively adjusted our primary analysis for exercise volume (MET-HRs/week). After adjustment for exercise volume the interaction between DM status and exercise training for peak VO_2 remained significant (interaction p=0.04). The DM patients within HF-ACTION were also older, more likely to be African-American, had more CKD and hypertension, with higher BMIs and worse heart failure symptoms at baseline. However, after adjustment for age, race, BMI, CKD, hypertension, and NYHA class, the interaction between DM status and exercise training for change in peak VO_2 demonstrated a trend for significance (interaction p=0.05). There was no interaction between DM status and exercise training on health status, as measured by KCCQ clinical summary score. There was no interaction between insulin status and exercise training on functional capacity, as measured by 6MWD (interaction p=0.43) or peak VO_2 (interaction p=0.41).

After a median follow-up of 2.5 years, DM was associated with increased all-cause mortality/hospitalization, all-cause mortality and CV mortality/HF hospitalization (Table 5). Kaplan-Meier event curves for all-cause mortality/hospitalization, all-cause mortality and CV mortality/HF hospitalization are displayed in Figure 2. After adjustment for the HF-ACTION risk model covariates, DM was associated with a significant increase in all-cause mortality/hospitalizations, but similar all-cause mortality and CV mortality/HF hospitalization (Table 5). Hospitalization was retrospectively evaluated as a separate clinical outcome. By censoring at death, the cause-specific hazard for hospitalization identified a significant association between DM and hospitalization (Wald Chi-Square- 4.02, p=0.05). The composite outcome of CV mortality/HF hospitalization was not significantly different between the DM and non-DM patients. These observations suggest that the between-group difference in DM vs. non-DM patients was specifically due to an increase in non-HF hospitalizations. There was no evidence of an interaction between DM and exercise training on any of the clinical outcomes.

Discussion

In HF-ACTION, approximately one third of HFrEF patients had concomitant DM. DM was associated with reduced baseline exercise capacity and functional status, as well as lower adherence to exercise training. Insulin-dependent DM patients had even lower exercise and functional capacity, as compared to the non-insulin dependent DM patients. Our primary hypothesis was supported and DM was associated with an attenuated improvement in peak VO_2 after 3 months of exercise. However, DM patients had similar improvement in 6MWD as compared to non-DM patients. After covariate adjustment, DM was associated with increased all-cause mortality/hospitalization due to an increased risk of hospitalization, but similar risk for other endpoints. Thus, DM was associated with lower baseline exercise capacity, lower adherence to exercise training, and an increased risk of all-cause mortality/hospitalization. Importantly, there was insufficient evidence to suggest a differential association between exercise training and clinical outcomes.

In previous studies, the association between DM status and clinical outcomes has been inconsistent. Several registries have shown an association between DM and increased mortality compared to non-DM patients (8,9), while others have shown increased rates of hospitalization with similar risk for mortality (4,5). In the unadjusted analysis of HF-ACTION, comorbid DM was associated with increased all-cause mortality/hospitalization, all-cause mortality, and CV mortality/HF hospitalization. After adjustment, comorbid DM was only associated with increased hospitalization. These findings are consistent with those prior studies suggesting that increased hospitalization is the primary difference in outcomes between DM and non-DM patients (4,9).

The effect of exercise on the change in functional capacity by DM status in HFrEF patients has not previously been investigated. In HF-ACTION, there was a statistically significant interaction between DM status and exercise on change in functional capacity as measured by peak VO_2, but not 6MWD. In the exercise training arm, DM patients had a smaller mean increase in peak VO_2 compared with non-DM patients, while in the usual care arm, the DM vs. non-DM changes for peak VO_2 and 6MWD were similar. This difference was modest and less than the previously recognized MCID for change in peak VO_2 of 1 ml/kg/min. Notably, this difference was after 3 months of exercise training; the long-term association between DM status and exercise training response in HFrEF patients is unknown. We did not assess the change in peak VO_2 or 6MWD at the 12 month time point because of greater missing CPX testing and 6MWD data at this time point, which could lead to increased confounding. In addition, after 3 months, adherence rates with the exercise training regimen decreased when HF-ACTION patients were transitioned from supervised exercise training to a home-based exercise regimen. Thus, the 3 month result, following supervised exercise training, provides the least confounded result.

The attenuated increase in exercise capacity in the DM patients within HF-ACTION is likely driven by a combination of lower adherence, higher BMI and physiologic maladaptations in patients with DM. The attenuated benefit of exercise in this cohort is likely due in part to reduced adherence, as a previous analysis of HF-ACTION has demonstrated that higher exercise volume (MET-HRs/week) is associated with larger improvements in exercise

capacity and improved outcomes (21). However, even after adjustment for exercise volume the exercise training benefit as quantified by change in peak VO_2 was attenuated in DM vs. non-DM patients. Several previously described physiologic maladaptations contribute to an attenuated benefit of exercise training in HF patients with DM. DM patients have cardiac, autonomic and peripheral dysfunction that contribute to decreased exercise tolerance. From a cardiac perspective, insulin resistance leads to increased uptake and utilization of fatty acids by myocytes. Increased fatty acid utilization causes increased oxidative stress in the myocardium leading to both myocyte apoptosis and interstitial fibrosis (11,22). As a result, myocardial contractility and relaxation are impaired in DM. This decreased myocardial reserve is exacerbated further by an attenuated autonomic response leading to an impaired exercise reserve for HR, contractility and relaxation (23). This is consistent with the attenuated peak exercise HR in the DM patients within our study. Finally, DM patients have impaired peripheral arterial dilation of both small and large vessels and reduced skeletal muscle capillary density. Several studies have demonstrated reduced cardiac output and oxygen utilization at exercise in DM patients due to peripheral dysfunction, independent of myocardial factors (24,25). These physiologic factors likely contributed to the reduction in exercise capacity and response in the DM patients in HF-ACTION. In addition, the DM patients had significantly higher BMIs compared to non-DM patients. Obesity is associated with reduced exercise capacity and may be partially responsible for the attenuated exercise training response in DM (26). However, after adjustment for comorbidities and symptom burden (age, BMI, CKD, hypertension, race, and NYHA class) the DM patients in HF-ACTION still exhibited a reduced training response.

The current data suggests that the clinical benefit of exercise is reduced in DM by physiologic maladaptations and reduced adherence in HF patients with DM. The DM patients within HF-ACTION did receive some attenuated benefit in functional capacity and at this point physicians should continue to promote aerobic exercise in HF patients with DM. However, future research needs to target different modalities and intensities of training in DM patients to improve both adherence and physiologic response to exercise.

This study should be interpreted in the context of several limitations. This was a retrospective analysis from a randomized controlled trial of exercise training. While there was adjustment for previously identified covariates, there are likely additional measured and unmeasured variables within the cohort that may have influenced our results. The use of self-reported exercise logs limits the reliability of our exercise volume data. In addition, measures of glycemic control, such as hemoglobin A1c, fasting glucose, or duration of DM, were not recorded in the trial dataset. However, DM status was self-reported and confirmed by clinician-investigators using available clinical data at the time of enrollment. In addition, use of insulin and oral hyperglycemic agents were recorded at baseline, which enabled us to explore characteristics of insulin vs. non-insulin dependent DM patients. HF-ACTION had strict exclusion and inclusion criteria to enroll an ambulatory cohort of chronic HFrEF patients. As a result, this cohort of patients was younger and had higher usage of evidence-based HF therapies than the general HF population (13,14).

Conclusions

In HF-ACTION, DM was associated with older age, higher BMI, an increased prevalence of hypertension, worse HF symptoms, reduced health status, lower adherence to exercise training, and reduced peak VO_2 and 6MWD at baseline. These differences were of greater magnitude in insulin-dependent DM. DM was associated with an attenuated improvement in peak VO_2, but similar improvement in 6MWD with exercise training. After risk adjustment, DM was associated with increased hospitalization, but similar all-cause mortality and CV mortality/HF hospitalization. These results suggest that DM patients have a differential functional response to exercise training, independent of reduced adherence, and may need to be considered as a separate cohort in the design and analysis of future randomized controlled trials of exercise training in HF patients. Future trials should explore whether response to exercise training in DM patients can be improved by different modalities or intensities of exercise training.

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Abbreviations

HFrEF	Heart Failure with Reduced Ejection Fraction
DM	Diabetes Mellitus
6MWD	6-minute walk distance
HRs	Hours
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
VO_2	oxygen uptake
NYHA	New York Heart Association
CPX	Cardiopulmonary Exercise
KCCQ	Kansas City Cardiomyopathy Questionnaire
CV	Cardiovascular
MCID	Minimally Clinical Important Difference

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Highlights

- DM was associated with lower adherence to exercise and reduced peak VO_2 and 6MWD at baseline
- DM patients have an attenuated response to exercise, independent of reduced adherence
- DM patients have cardiac and peripheral dysfunction that result in attenuated exercise tolerance
- DM was associated with increased hospitalization, driven by non-HF hospitalizations

Clinical Perspective

DM patients have cardiac, autonomic and peripheral dysfunction that contribute to decreased exercise capacity and tolerance. These physiologic maladaptations seem to be more pronounced in diabetic patients on insulin. In addition, HF patient with DM are at increased risk of non-adherence and hospitalization. They may benefit from more frequent outpatient follow up with an emphasis on a multidisciplinary approach including primary care, nutrition, endocrinology, and cardiology.

Translational Outlook

These results suggest that diabetic patients have a differential functional response to exercise training, independent of reduced adherence. DM status will need to be considered carefully in the design and analysis of future randomized controlled trials of exercise training in HF patients.

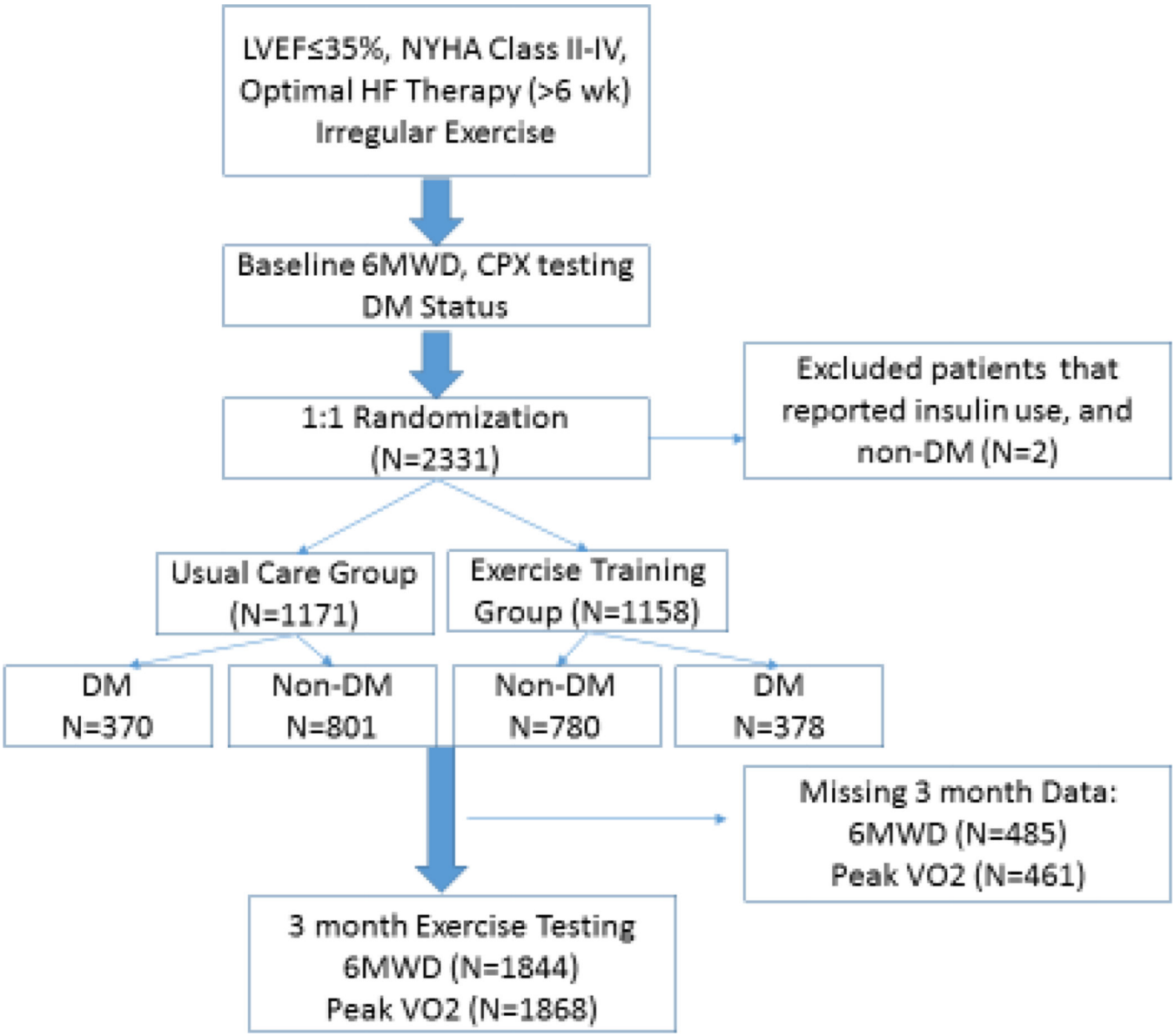

Figure 1. Study Flow Chart

Study Flow Chart showing flow of patients to 3-month CPX testing for our primary analysis.

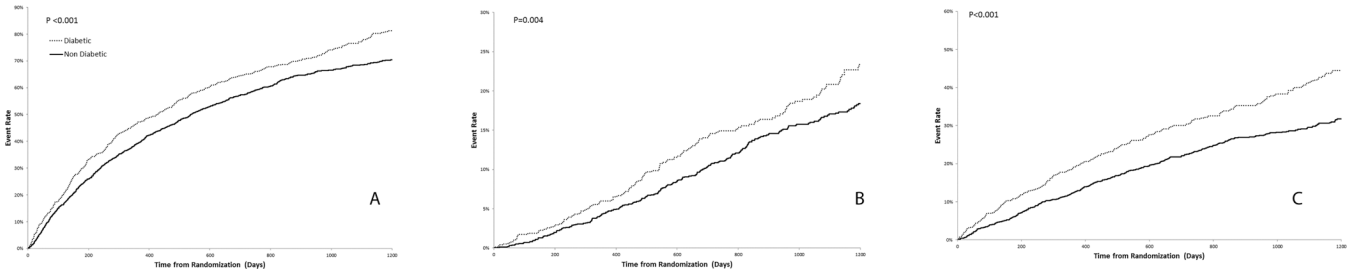

Figure 2. Kaplan-Meier event curves

Kaplan-Meier event curves for (A) All-Cause Mortality/Hospitalization (B) All-Cause mortality and (C) CV Mortality/HF Hospitalization prior to adjustment.

Table 1

Baseline characteristics of the study cohort based on DM Status

Variable	DM Status		P-value
	DM (n=748)	Non-DM (n=1583)	
Age, years	61 (54,68)	59(50,68)	<0.001
Female Sex, %	25.9	29.5	0.075
Race, %			0.008
Black or African American	36.6	30.8	
White	57.5	64.3	
Other	5.9	5.0	
New York Heart Classification, % III/IV	41.8	34.2	<0.001
BMI	33.1	30.1	<0.001
Ischemic cardiomyopathy, %	61.4	46.6	<0.001
Severe Mitral Regurgitation, %	8.2	12.3	0.003
Beck Depression Score at Baseline	8.0 (5.0–16.0)	8.0 (4.0, 15.0)	0.052
Hypertension, %	75.9	52.3	<0.001
Atrial Fibrillation or Flutter, %	21.7	20.6	0.545
Hemoglobin (g/dL)	13.3 (12.1, 14.3)	13.6 (12.4, 14.7)	<0.001
Creatinine, mg/dL	1.3 (1.0, 1.6)	1.2 (1.0, 1.4)	<0.001
Blood urea nitrogen, mg/dL	23.0 (17.0, 33.5)	19.0 (14.0, 26.0)	<0.001
Baseline Glomerular Filtration Rate (mL/hr)	61.5 (45.8, 79.3)	68.5 (54.2, 82.0)	<0.001
ACE-Inhibitor or Angiotensin II Receptor Blocker	93.0	94.9	0.064
Beta-blocker	94.8	94.4	0.686
Dose, mg/day carvedilol equivalent	50 (19.0, 50.0)	36.9 (13.0, 50.0)	<0.001
Aldosterone antagonist	43.4	45.9	0.274
Loop diuretic	85.3	74.4	<0.001
Implantable Cardioverter Defibrillator	41.8	39.5	0.277

Expressed as median interquartile range(IQR) or %.

Table 2

Baseline Health Status and Exercise Parameters by DM Status and insulin use.

Variable	Non-DM (n=1581)	DM			P-Value for DM vs. Non-DM	P-Value for Insulin vs. Non-Insulin DM
		Overall (n=748)	No Insulin (n=417)	Insulin (n=331)		
6-Minute Walk Distance, meters	384 (272, 410)	344 (311, 443)	356 (280, 426)	327 (259, 397)	<0.001	0.004
Peak VO_2, mL/kg/min	15.2 (12.3, 18.3)	13.0 (10.3, 16.3)	13.7 (10.9, 16.8)	12.0 (9.8, 15.6)	<0.001	<0.001
KCCQ Clinical Summary Score	76.0 (59.4, 87.5)	70.8 (53.6, 84.3)	73.8 (57.1, 87.5)	66.7 (49.0, 81.3)	<0.001	<0.001
Heart Rate at Peak Exercise (BPM)	121 (107, 136)	115 (100, 130)	120 (105, 133)	110 (96, 123)	<0.0001	<0.0001

Expressed as median (IQR).

Table 3

Baseline and 3 month Health Status and Exercise Parameters by DM Status and Exercise group.

	Exercise		Usual care	
Variables	**DM**	**Non-DM**	**DM**	**Non-DM**
6-Minute Walk Distance, meters				
• Baseline 6MWD	344	384	344	384
• 3-Month 6MWD	357	409	350	389
Peak VO_2, mL/kg/min				
• Baseline Peak VO_2	12.7	15.2	13.4	15.2
• 3-month Peak VO_2	13.6	16.2	13.8	15.4
KCCQ Clinical Summary Score				
• Baseline KCCQ	71.9	75.1	70.1	76.3
• 3-month KCCQ	72.3	76.0	71.3	74.5

Expressed as median.

Table 4

Interaction between DM Status, Exercise Training, and Functional Capacity

Outcome	Exercise training	Usual care	P-value for Interaction between DM Status and Treatment Assignment*
	Change after 3 months Mean (SD) [Confidence Interval]		
Variables			
6-Minute Walk Distance, meters			
• DM	17.4 (69.2)	5.8 (67.7)	0.53
• Non-DM	25.2 (74.0)	2.9 (69.5)	
Peak VO_2, mL/kg/min			
• DM	0.5 (2.4) [0.23–0.77]	0.3 (2.4) [0.02–0.58]	0.02
• Non-DM	0.9 (2.6) [0.70–1.10]	0.2 (2.6) [−0.01–0.41]	
KCCQ Clinical Summary Score			
• DM	5.0 (14.6)	2.6 (15.6)	0.23
• Non-DM	5.4 (14.5)	2.6 (13.6)	

*Adjusted only for Baseline 6MWD, Peak VO_2, and KCCQ Clinical Summary Score, respectively. Confidence intervals are listed for exercise variables with statistically significant interaction p-values.

Table 5

Association between DM Status and Clinical Outcomes

Outcome	Unadjusted		Adjusted*	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Mortality or Hospitalization	1.27 (1.14, 1.41)	<.001	1.14 (1.01, 1.30)	0.033
All-cause Mortality	1.35 (1.10, 1.66)	0.004	0.97 (0.78, 1.2)	0.80
CV Mortality or HF Hospitalization	1.52 (1.31, 1.77)	<0.001	1.08 (0.90, 1.30)	0.41

Adjustment variables:
All-Cause Mortality/Hospitalization: peak VO_2, KCCQ stability score, BUN, country, ejection fraction, sex, beta blocker dose, mitral regurgitation grade, ventricular conduction.
All-Cause Mortality: Baseline CPX test duration, creatinine, body mass index, sex, loop diuretic dose, left ventricular ejection fraction, canadian cardiovascular society anginal score, ventricular conduction.
CV Mortality/HF Hospitalization: Loop diuretic dose, ejection fraction, mitral regurgitation grade, ventricular conduction, KCCQ symptom stability score, BUN, race, sex, age.