Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

Manuscript: Effect of Isosorbide Mononitrate on Activity Tolerance in Heart Failure with Preserved Ejection Fraction

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Contents

NEAT-HFPEF TRIAL MEMBERS, INVESTIGATORS AND COMMITTEES

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SUPPLEMENTAL METHODS

ACCELEROMETER BASED ACTIVITY MEASUREMENT

Patients were supplied with an elastic, hip worn belt outfitted with two Kinetic Activity Monitors (KAMs, Kersh Health, Plano, Texas)containing high-sensitivity, tri-axis, silicon micro-machined accelerometers (model KXUD9-2050, Kionix, Ithaca, NY) (Figure S1 below). Acceleration sensing is based on the principle of differential capacitance. Differential capacitance results from acceleration-induced motion of a silicon sense element and is measured in three dimensions (x, y and z axes). When the patient wears the accelerometer, body movement causes the silicon sense element to shift in position, changing capacitance, which is measured as changes in voltage. The cumulative vector of the three capacitances in three dimensions for each body movement is expressed as arbitrary accelerometer units.

ACCELEROMETER ANALYTIC METHODS

The threshold for activity (15 minute cumulative vector magnitude value > 50) as defined in the primary manuscript equates to walking at 1.0 mph for one minute or 0.5 mph for four minutes interspersed with sedentary status over the 15-minute epoch. Even when wearers are sedentary, the effect of breathing and shifting in sitting/lying position is evident as low level accelerometer units (AU). In contrast, if the accelerometer is left on a surface (table, counter, chair, floor etc), the 15 minute cumulative vector magnitude values are zero unless the surface itself is moved. The threshold for not wearing the accelerometer was set at a 15 minute cumulative vector magnitude value < 5, present for at least four consecutive 15 minute periods. The accelerometer core laboratory (Mayo Clinic, Rochester, MN and Scottsdale, AZ) processed the data, prepared the devices, down-loaded and processed the raw data and supplied the cleaned raw data to the data coordinating center.

TABLE S1: COMPLETE INCLUSION AND EXCLUSION CRITERIA FOR THE NEAT-HFpEF STUDY

INCLUSION CRITERIA

1. Age ≥ 50 years
2. Symptoms of dyspnea (NYHA class II-IV) without evidence of a non-cardiac or ischemic explanation for dyspnea
3. EF ≥ 50% as determined on imaging study within 12 months of enrollment with no change in clinical status suggesting potential for deterioration in systolic function
4. Stable medical therapy for 30 days as defined by:
    - No addition or removal of ACE, ARB, beta-blockers, calcium channel blockers (CCBs) or aldosterone antagonists
    - No change in dosage of ACE, ARBs, beta-blockers, CCBs or aldosterone antagonists of more than 100%
5. One of the following within the last 12 months
    - Previous hospitalization for HF with radiographic evidence of pulmonary congestion (pulmonary venous hypertension, vascular congestion, interstitial edema, pleural effusion) ***or***
    - Catheterization documented elevated filling pressures at rest (LVEDP≥15 mmHg or PCWP≥20 mmHg) or with exercise (PCWP≥25 mmHg) ***or***
    - Elevated NT-proBNP (> 400 pg/ml) or BNP (> 200 pg/ml) ***or***
    - Echo evidence of diastolic dysfunction / elevated filling pressures (***at least two***)
        - E/A > 1.5 + decrease in E/A of > 0.5 with Valsalva maneuver
        - Deceleration time ≤ 140 ms
        - Pulmonary vein velocity in systole < diastole (PVs<PVd) (sinus rhythm)
        - E/e'≥15
        - Left atrial enlargement (≥ moderate)
        - Pulmonary artery systolic pressure > 40 mmHg
        - Evidence of left ventricular hypertrophy
            - LV mass/BSA ≥ 96 (♀) or ≥ 116 (♂) g/m^2
            - Relative wall thickness ≥ 0.43 (♂ or ♀)
            - Posterior wall thickness ≥ 0.9 (♀) or 1.0 (♂) cm
6. No chronic nitrate therapy or infrequent (≤ 1x week) use of intermittent sublingual nitroglycerin within last 3 months
7. Ambulatory (not wheelchair / scooter / walker / cane dependent)
8. HF is the primary factor limiting activity as indicated by answering # 2 to the following question:

    My ability to be active is <u>most</u> limited by:

    1. Joint, foot, leg, hip or back pain
    2. Shortness of breath and/or fatigue and/or chest pain
    3. Unsteadiness or dizziness
    4. Lifestyle, weather, or I just don't like to be active

9. Body size allows wearing of the accelerometer belt as confirmed by ability to comfortably fasten the test belt provided for the screening process (belt designed to fit persons with BMI 20-40 Kg/m^2 but belt may fit some persons outside this range)
10. Willingness to wear the accelerometer belt for the duration of the trial
11. Willingness to provide informed consent

EXCLUSION CRITERIA

1. Recent (< 3 months) hospitalization for HF
2. Hemoglobin < 8.0 g/dl
3. Glomerular filtration rate < 20 ml/min/1.73 m^2 on most recent clinical laboratories
4. SBP < 110 mmHg or > 180 mmHg at consent
5. Diastolic blood pressure < 40 mmHg or > 100 mmHg at consent
6. Resting HR > 110 bpm at consent
7. Previous adverse reaction to nitrates necessitating withdrawal of therapy
8. Chronic therapy with phosphodiesterase type-5 inhibitors (intermittent use of phosphodiesterase type-5 inhibitors for erectile dysfunction is allowable if the patient is willing to hold for the duration of the trial)
9. Regularly (> 1x per week) swims or does water aerobics
10. Significant COPD thought to contribute to dyspnea
11. Ischemia thought to contribute to dyspnea
12. Documentation of previous EF < 50%
13. Acute coronary syndrome within 3 months defined by electrocardiographic changes and biomarkers of myocardial necrosis (e.g. troponin) in an appropriate clinical setting (chest discomfort or anginal equivalent)
14. Percutaneous coronary intervention, coronary artery bypass grafting or new biventricular pacing within past 3 months
15. Primary hypertrophic cardiomyopathy
16. Infiltrative cardiomyopathy (amyloid)
17. Constrictive pericarditis or tamponade
18. Active myocarditis
19. Complex congenital heart disease
20. Active collagen vascular disease
21. More than mild aortic or mitral stenosis
22. Intrinsic (prolapse, rheumatic) valve disease with moderate to severe or severe mitral, tricuspid or aortic regurgitation
23. Acute or chronic severe liver disease as evidenced by any of the following: encephalopathy, variceal bleeding, INR > 1.7 in the absence of anticoagulation treatment
24. Terminal illness (other than HF) with expected survival of less than 1 year
25. Enrollment or planned enrollment in another therapeutic clinical trial in the next 3 months.
26. Inability to comply with planned study procedures
27. Pregnant women

TABLE S2: CHARACTERIZATION OF PATIENTS MEETING ENTRY CRITERIA

The NEAT-HFpEF case report forms did not collect data regarding which "objective evidence of heart failure in the last year" entry criteria were met. However, data on HF hospitalizations in the 12 months prior to enrollment, core laboratory NT-proBNP levels *at enrollment* and core laboratory echocardiographic data *at enrollment* are available. Of enrolled patients, 95 (86%) had a heart failure hospitalization in the last year, an elevated NT-proBNP level at enrollment or rigorous Doppler criteria indicative of elevated filling pressures at enrollment. Of note, four of the highest enrolling centers routinely obtain invasive assessment of hemodynamics at rest or with exercise in the evaluation of patients with heart failure with preserved ejection fraction and studies have shown that a significant subset of symptomatic patients with heart failure with preserved ejection fraction have normal NT-proBNP and/or resting Doppler diastolic indices but markedly abnormal filling pressures at rest or with exercise[1,2].

	N
HF hospitalization in last year AND Core Lab NT-proBNP ≥ 400 pg/ml at enrollment	11
HF hospitalization in last year AND Core Lab NT-proBNP < 400 pg/ml at enrollment	10
No HF hospitalization in last year AND Core Lab NT-proBNP ≥ 400 pg/ml at enrollment	24

No HF hospitalization in last year AND Core Lab NT-proBNP < 400 pg/ml at enrollment (n=65)			
Doppler variable	**Abnormal value**	**N with data**	**N with abnormal value at enrollment**
Medial E/e'	≥ 15	62	39
LA volume index (ml/m2)	≥ 42	55	30
PASP (mmHg)	≥ 40	28	10
E/A	≥ 1.5	62	10
Deceleration time (ms)	≤ 140	64	5
At least one abnormal value at enrollment		N=50	

TABLE S3: ENTRY CRITERIA OF NEAT-HFPEF AND RECENT TRIALS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

	NEAT-HFpEF (n=110)	ALDO DHF[3] (n=422)	RELAX[4] (n=216)	TOPCAT Americas Subset[5] (n=1767)	PARAMOUNT LCZ696 Subset[6] (n=152)
Primary Endpoint	Accelerometer assessed activity	Peak VO_2 E/e'	Peak VO_2	Outcomes (CV death, cardiac arrest or HF hospitalization)	Change in NT-proBNP at 12 weeks
Key Secondary Endpoints	Six Minute Walk KCCQ, MLHFQ NT-proBNP levels	Six Minute Walk MLHFQ NT-proBNP levels	Six Minute Walk MLHFQ NT-proBNP levels	All cause death and hospitalization	Quality of Life Echo Variables
Entry Criteria					
Clinical diagnosis of HF	NYHA II-IV	NYHA II-III	NYHA II-IV	NYHA II-IV	NYHA II-III
Ejection Fraction	≥ 50%	≥ 50%	≥ 50%	≥ 45%	≥ 45%
Objective evidence of HF	HF Hsp in last year *or* NT-proBNP (BNP) > 400(200) in last year *or* Invasive Hemodynamics* *or* Echo DD Grade ≥2‡	Echo DD Grade ≥1‡ *or* Atrial Fibrillation	HF Hsp in last year *or* Invasive Hemodynamics* *or* Left Atrial Enlargement + Loop Diuretic Use	HF Hsp in last year *or* NT-proBNP (BNP) > 360(100) in last 60 days	Signs or symptoms of HF (dyspnea, orthopnea, paroxysmal nocturnal dyspnea or edema)
Screening Criteria (Must be met at Study Entry)					
	Patient self identifies HF symptoms (rather than neurologic, orthopedic or behavioral factors) limit activity on screening questionnaire	Peak VO_2 < 25 mL/kg/min	Peak VO_2 < 60% predicted for age and sex *and* NT-proBNP(BNP) > 400(200)†	None	NTproBNP > 400 pg/ml *and* Diuretic therapy

***** At heart catheterization, elevated left ventricular end diastolic pressure (15 mmHg or greater) at rest or pulmonary capillary wedge pressure at rest (20 mmHg or greater) or with exercise (25 mmHg or greater)

†Patients with an NT-proBNP(BNP) < 400(200) on screening assessment could be enrolled if they had been previously documented to have elevated filling pressures* at the time an NT-proBNP(BNP) level was < 400(200).

‡ Grade I diastolic dysfunction (DD) requires evidence of impaired relaxation without evidence of elevated filling pressures; Grade II DD requires evidence of elevated filling pressures.

Abbreviations: HF, heart failure; Hsp, hospitalization; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; Peak VO2, peak oxygen consumption at cardiopulmonary exercise test; CV, cardiovascular; E/e', ratio of early transmitral filling velocity to early diastolic medial mitral annular tissue velocity on Doppler examination

TABLE S4: BASELINE CHARACTERISTICS OF PARTICIPANTS IN NEAT-HFpEF AND RECENT TRIALS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

	NEAT-HFpEF (n=110)	ALDO DHF[3] (n=422)	RELAX[4] (n=216)	TOPCAT Americas Subset[5] (n=1767)	PARAMOUNT LCZ696 Subset[6] (n=152)
Age-yr	69	67	69	72	71
Female sex – %	57%	52%	48%	50%	57%
Body Mass Index – kg/m^2	35	29	33	33	30
Functional measures					
NYHA class II	53%	86%	47%	59%	81%
NYHA class III	45%	14%	53%	35%	19%
KCCQ clinical score (higher better)	59	NA	NA	60	NA
MLHFQ total Score (lower better)	44	22	43	NA	NA
Six minute walk distance - meters	325	530	308	NA	NA
Peak VO_2	NA	16.4	11.7	NA	NA
Physical examination					
Systolic blood pressure - mmHg	128	135	126	129	136
Heart rate – beats/min	68	65	69	68	69
Elevated jugular venous pressure-%	34%	NA	45%	18%	NA
Edema – %	60%	39%	58%	72%	NA
Medical History and Medications					
Heart failure hospitalization	25%	37%	37%	55%	40%
Hypertension	90%	92%	85%	90%	95%
Prior myocardial infarction	10%	NA	12%	20%	21%
History of atrial fibrillation	35%	NA	51%	42%	40%
Atrial fibrillation on ECG	17%	5%	37%	34%	27%
Hyperlipidemia	62%	65%	74%	71%	NA
Diabetes mellitus	39%	17%	43%	45%	41%
Chronic obstructive lung disease	15%	3%	19%	16%	NA
Chronic kidney disease	49%	NA	55%	48%	38%
Loop diuretic	65%	NA	77%	75%	NA
Any diuretic	76%	54%	86%	89%	100%
ACE/ARB	64%	77%	70%	79%	93%
Beta blocker	70%	72%	76%	79%	79%
Aldosterone antagonist	25%	NA	11%	NA	19%
Calcium channel blocker	31%	25%	31%	39%	NA
Statin	55%	NA	64%	65%	NA
Laboratory and Echocardiographic variables					
NT-proBNP or BNP measured	All	All	All	Only if elevated*	All
NT-proBNP – pg/ml	227	158	700	900	828
BNP – pg/ml	NA	NA	NA	234	NA
Ejection fraction - %	64	67	60	58	58
Medial E/e' (Available in)	14 (95%)	13 (100%)	16 (87%)	15 (21%)	12 (NA)
LAVI – ml/m^2 (Available in)	37 (83%)	28 (100%)	44 (69%)	28 (33%)	35 (NA)

*NT-proBNP (BNP) levels were only available in the 56% of patients who entered the study due to an elevated NT-proBNP (BNP). NT-proBNP (BNP) were not recorded in those who qualified for the study on the basis of a heart failure hospitalization.

Data are percent or median (NEAT-DHF, RELAX, TOPCAT) or mean (ALDO-DHF, PARAMOUNT) as available from quoted references or supplied by RELAX or TOPCAT investigators.

Abbreviations: ACE/ARB; angiotensin converting enzyme inhibitor or angiotensin receptor antagonist; KCCQ, Kansas City Cardiomyopathy Questionnaire (range 1-100); MLHFQ, Minnesota Living with Heart Failure Questionnaire (range 0-105); NYHA, New York Heart Association; Peak VO2, peak oxygen consumption at cardiopulmonary exercise test; E/e', ratio of early transmitral filling velocity to early diastolic medial mitral annular tissue velocity on Doppler examination; LAVI, left atrial volume/body surface area.

FIGURE S1. THE NEAT-HFpEF ACCELEROMETER DEVICE

Patients were supplied with an elastic, hip worn belt outfitted with two Kinetic Activity Monitors (KAMs, Kersh Health, Plano, Texas)containing high-sensitivity, tri-axis, silicon micro-machined accelerometers (model KXUD9-2050, Kionix, Ithaca, NY).

FIGURE S2. CONSORT DIAGRAM AND STUDY DRUG ADMINISTRATION

110 patients were enrolled at 20 sites (enrollment rate 0.9 patients/site/month)

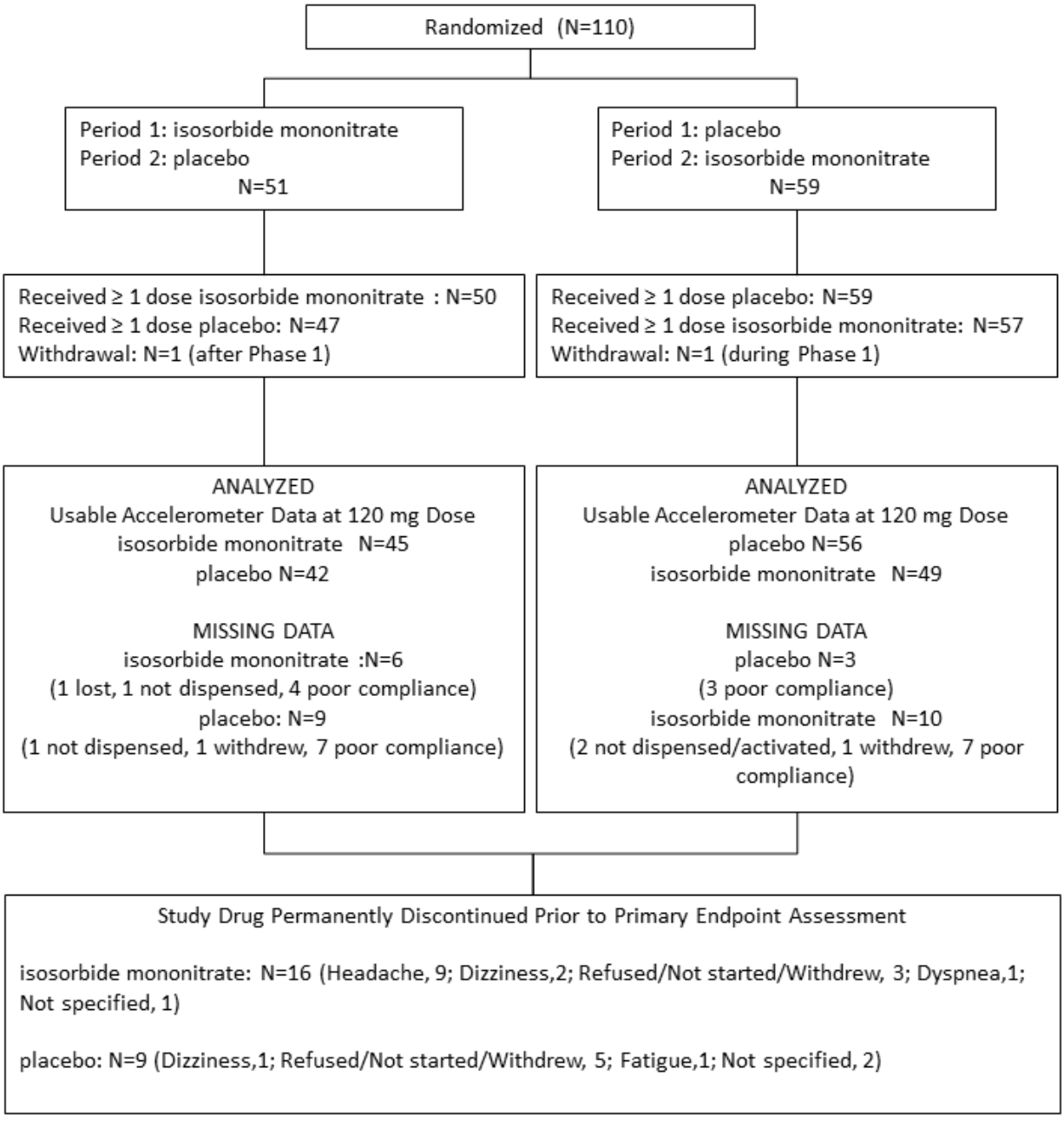
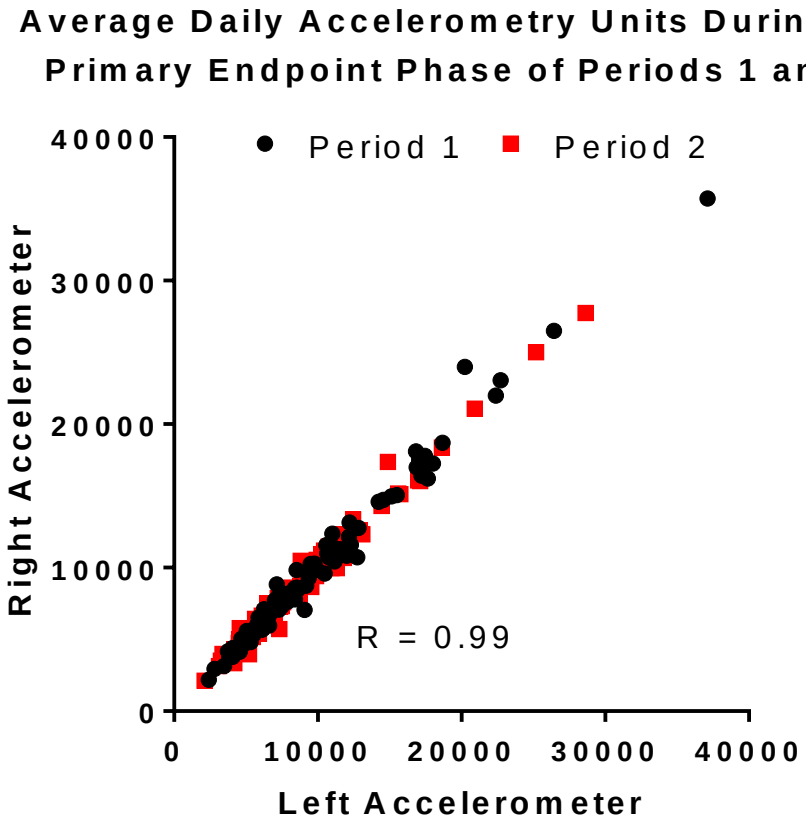


FIGURE S3. CORRELATION BETWEEN THE TWO ACTIVITY MONITORS USED IN THE NEAT-HFpEF

ACCELEROMETER DEVICE

Two accelerometers were used to provide reproducibility data and help insure primary endpoint data availability in the case of a single device failure. During the primary endpoint data periods, there was excellent correlation between the two devices for the primary endpoint of average daily accelerometer units. When data were available from both accelerometers, the average of the two was used. Of the 220 potential primary endpoint periods, 192 had usable accelerometry data with 13 of these using data from only one accelerometer.



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