HEART FAILURE NETWORK

Nitrate's **E**ffect on **A**ctivity **T**olerance in **H**eart **F**ailure with **p**reserved **E**jection **F**raction

NEAT-HFpEF: A Randomized Clinical Trial

Margaret M Redfield, MD on behalf of the

NHLBI Heart Failure Clinical Research Network

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute
People Science Health

Background

- Exercise intolerance is a cardinal feature of HFpEF and perpetuates sedentary behavior, deconditioning and frailty.
- Nitrates are commonly prescribed for symptom relief in HFpEF.
- Hemodynamic effects of nitrates may attenuate pulmonary congestion with exertion and improve exercise capacity in HFpEF.
- HFpEF pts may be at increased risk for nitrate induced hypotension or other side effects.

Background

- Intermittent coached exercise tests may not reflect the full effect of a HF therapy on patient's daily functional status.
- Patient-worn accelerometers provide continuous assessment of physical activity during daily life and may more accurately reflect the effect of a therapy on functional status.

Hypothesis

- As compared to placebo, isosorbide mononitrate (ISMN) will improve daily activity in HFpEF patients as assessed by averaged daily accelerometer units.

Study population

- NYHA class II-IV HF symptoms + EF ≥ 50%
- Objective evidence of HF (at least one)
  - *HF hospitalization*
  - *Elevated NT-proBNP or BNP*
  - *Elevated rest or exercise PAWP at RHC*
  - *Echo Doppler Diastolic Dysf (≥ 2 variables)*
- Identify HF symptoms as primary factor limiting ability to be active on screening questionnaire
  - *Versus neurologic, orthopedic or life-style factors*

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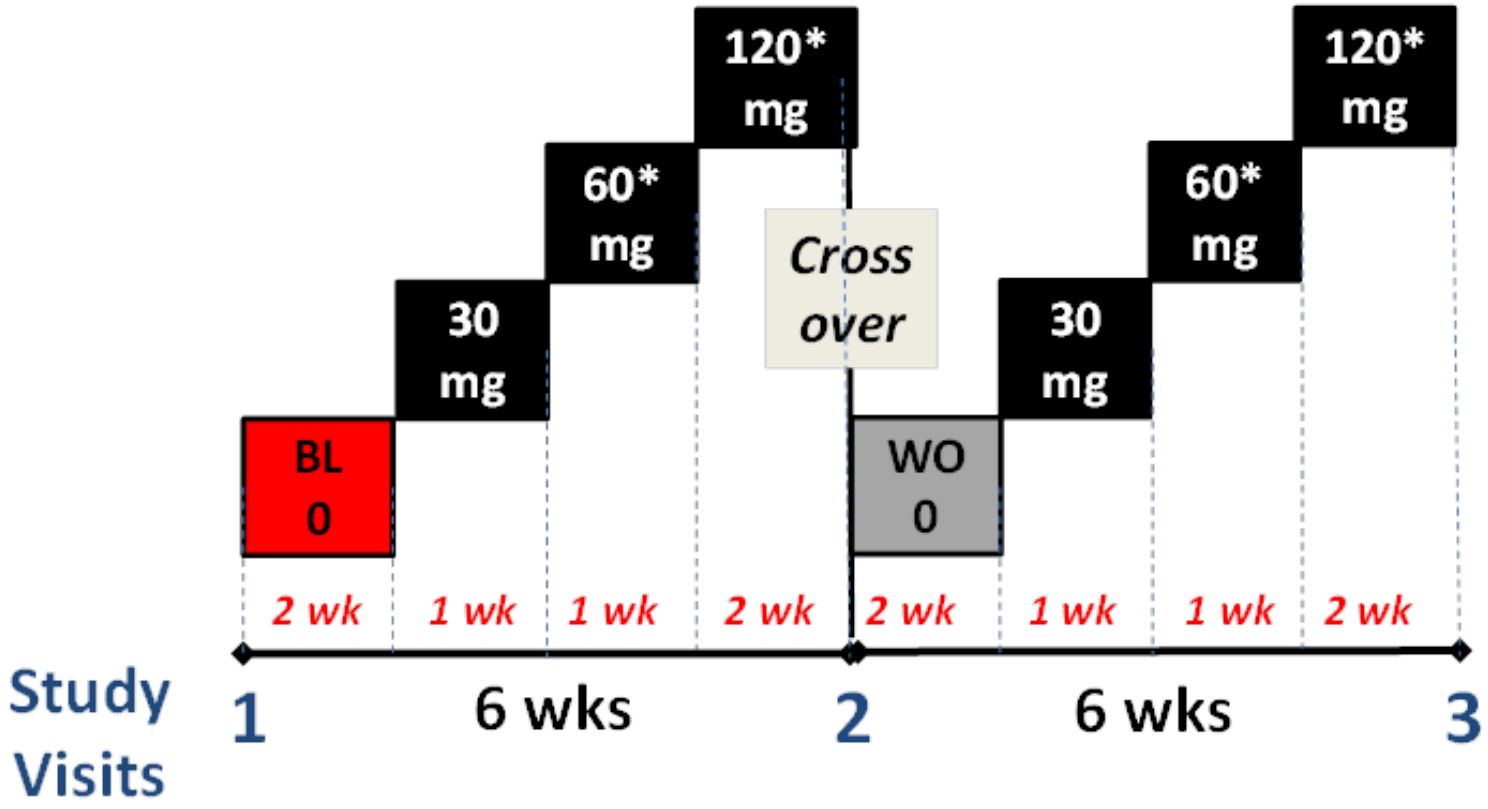
Study Design: *Randomized, double-blind, placebo-controlled crossover study*



BL, baseline; WO, washout; wk, week

** Or maximally tolerated dose*

NEAT-HFpEF Primary End-point

- Average daily arbitrary accelerometer units (AAU) during 14 days of the 120 mg (or maximally tolerated) dose
  - *Hip-worn, tri-axial accelerometers*
  - *Worn 24 hours per day (except bathing)*
  - *Throughout the entire study*

Secondary End-points

- Additional accelerometer endpoints
  - *Hours active per day*
  - *Area under the curve for time and daily accelerometer units during all doses of study drug (30 mg, 60 mg, 120 mg) / total days of dosing.*
- Standard HF endpoints
  - *Six minute walk distance and dyspnea score*
  - *HF specific quality of life (KCCQ, MLHFQ)*
  - *NT-proBNP levels*

Statistical Analysis

- Intention to treat
- Mixed Model: Treatment Effect (ISMN-Placebo)
  - *Sequence effect*
  - *Period effect*
  - *Random effect of each patient*
  - *Baseline value*
- 110 patients powered to detect:
  - *43 m difference in 6MWD (>90%)*
  - *5 pts difference in KCCQ (>80%)*
  - *2.5% change relative to baseline in AAU (>90%)*

Baseline Features

Characteristic	Placebo 1st (n=59)	ISMN 1st (N = 51)
Age (years)	69	68
Female	64%	49%
White race	92%	86%
BMI (kg/m^2)	35	36
HF hsp in past year	27%	24%
Hx hypertension	92%	88%
Hx of coronary disease	61%	63%
Diabetes	36%	43%
Hx of atrial fibrillation	34%	37%

Mean values or % shown

All p > 0.05

Baseline Features

Characteristic	Placebo 1st (n=59)	ISMN 1st (N = 51)
COPD	17%	12%
Sleep Apnea	50%	57%
CKD (≥ Stage 3)	54%	42%
Loop diuretic	61%	71%
Any diuretic	71%	83%
ACE/ARB	61%	67%
Beta Blocker	69%	71%
Aldosterone Antagonist	22%	27%
Lipid lowering agent	71%	63%

Mean values or % shown

All p > 0.05

Baseline Features

Characteristic	Placebo 1st (n=59)	ISMN 1st (N = 51)
Systolic BP	132	129
NYHA class II/III	56% / 41%	49% / 51%
6MWD (m)	321	300
KCCQ (higher better)	60	55
Ejection fraction (%)	65	62*
NT-proBNP (median, pg/ml)	248	210
E/e' - (normal ≤ 8)	15	15
LAVI (ml/m^2) - (normal < 29)	39	41
RWT ≥ 0.42	45%	50%

Mean values or % shown except as noted

****p < 0.05***

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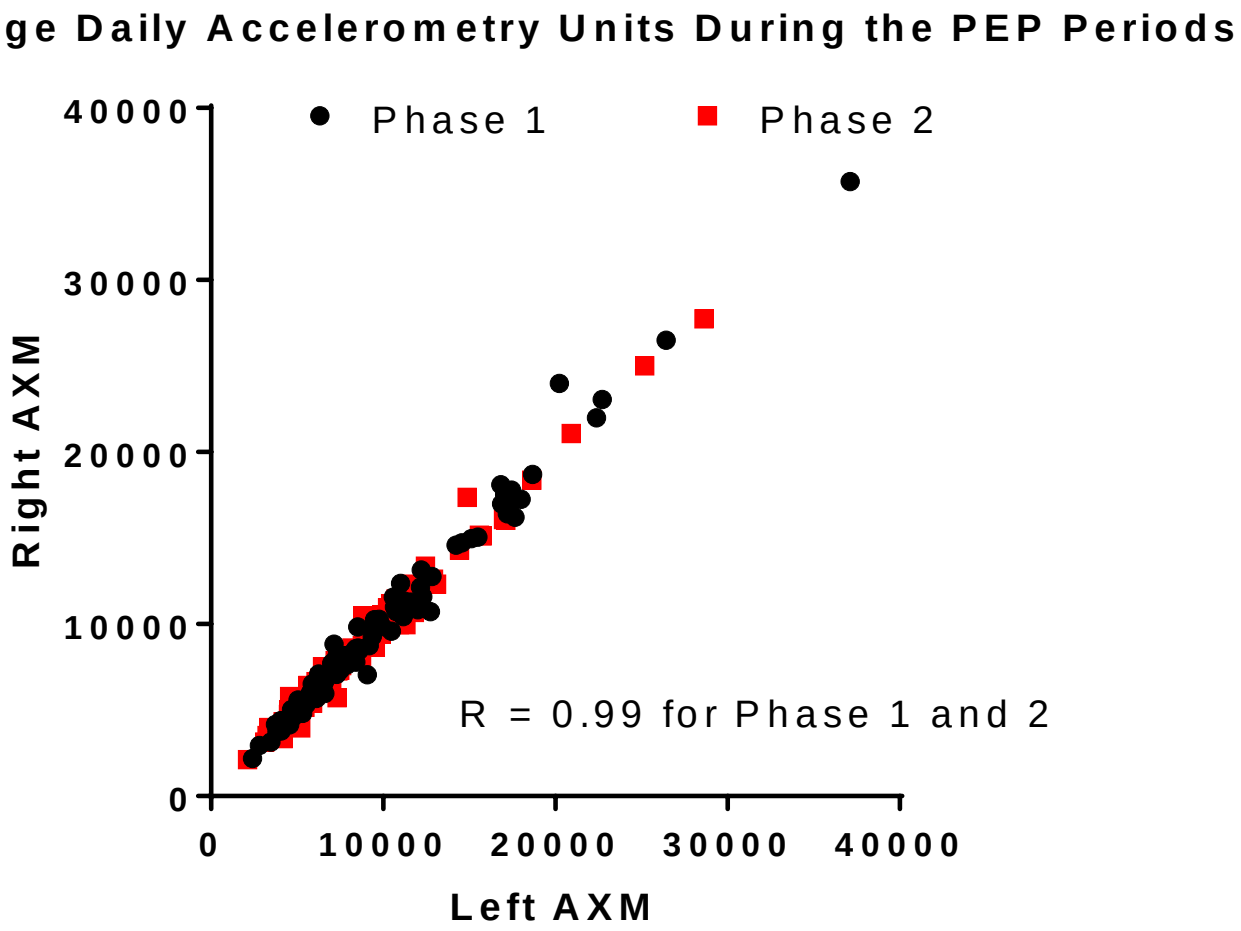
Results

Agreement between the two accelerometers



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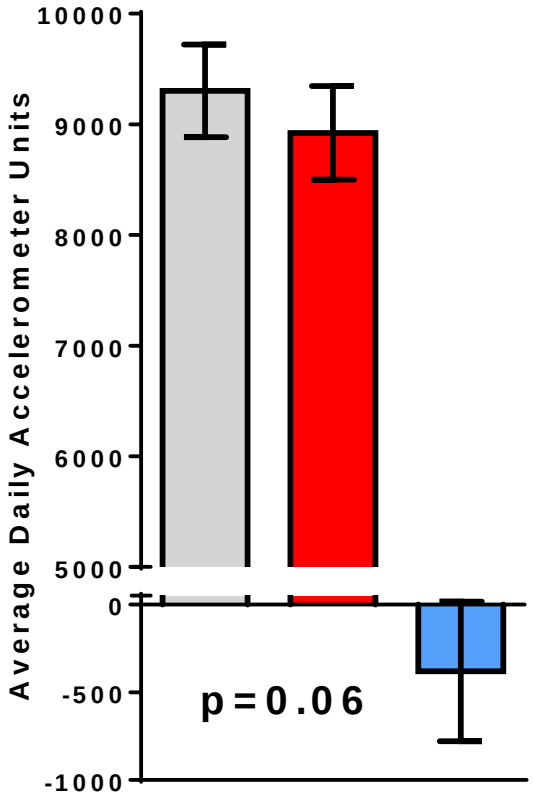
Primary Endpoint

Placebo Isosorbide mononitrate Treatment Difference

A



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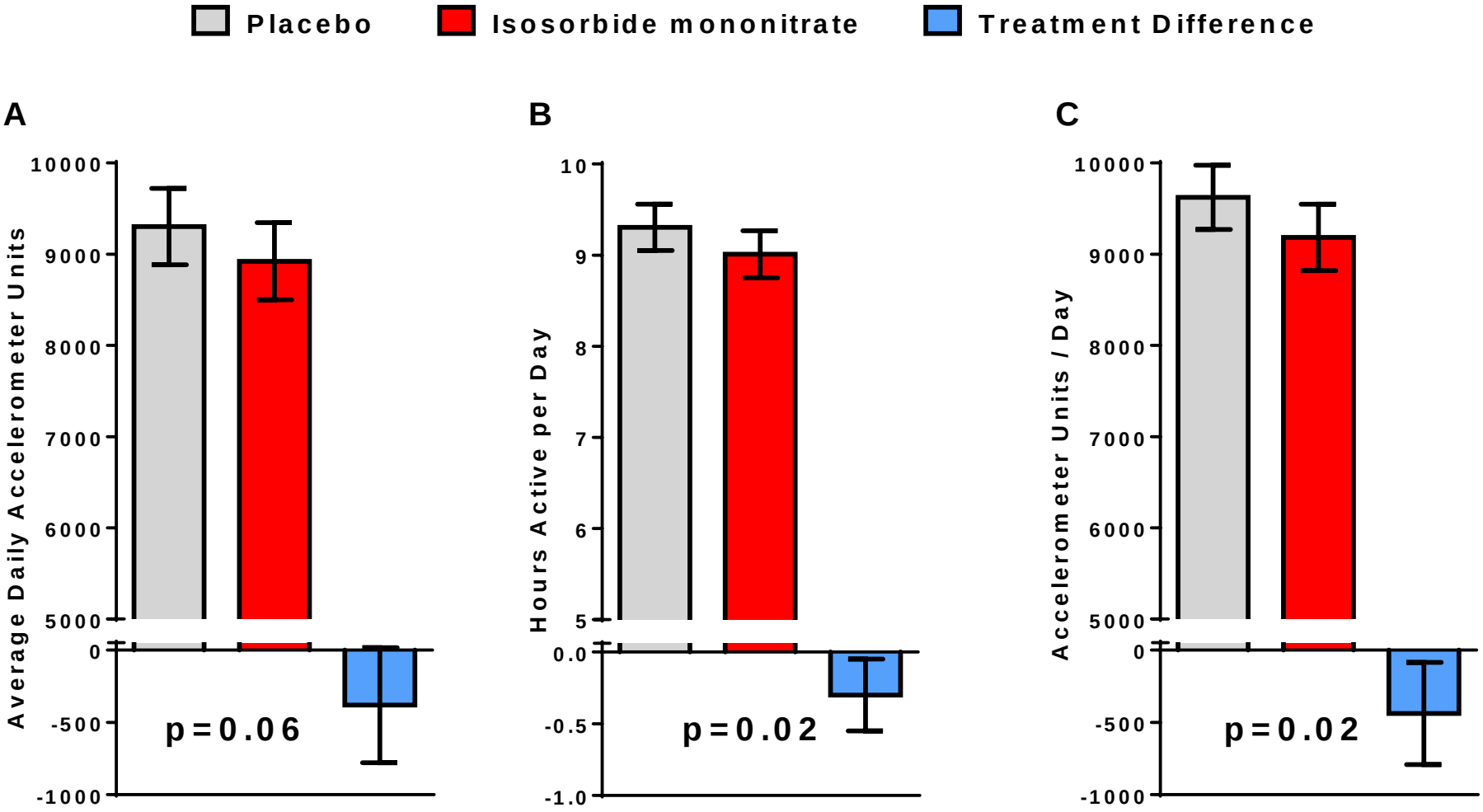
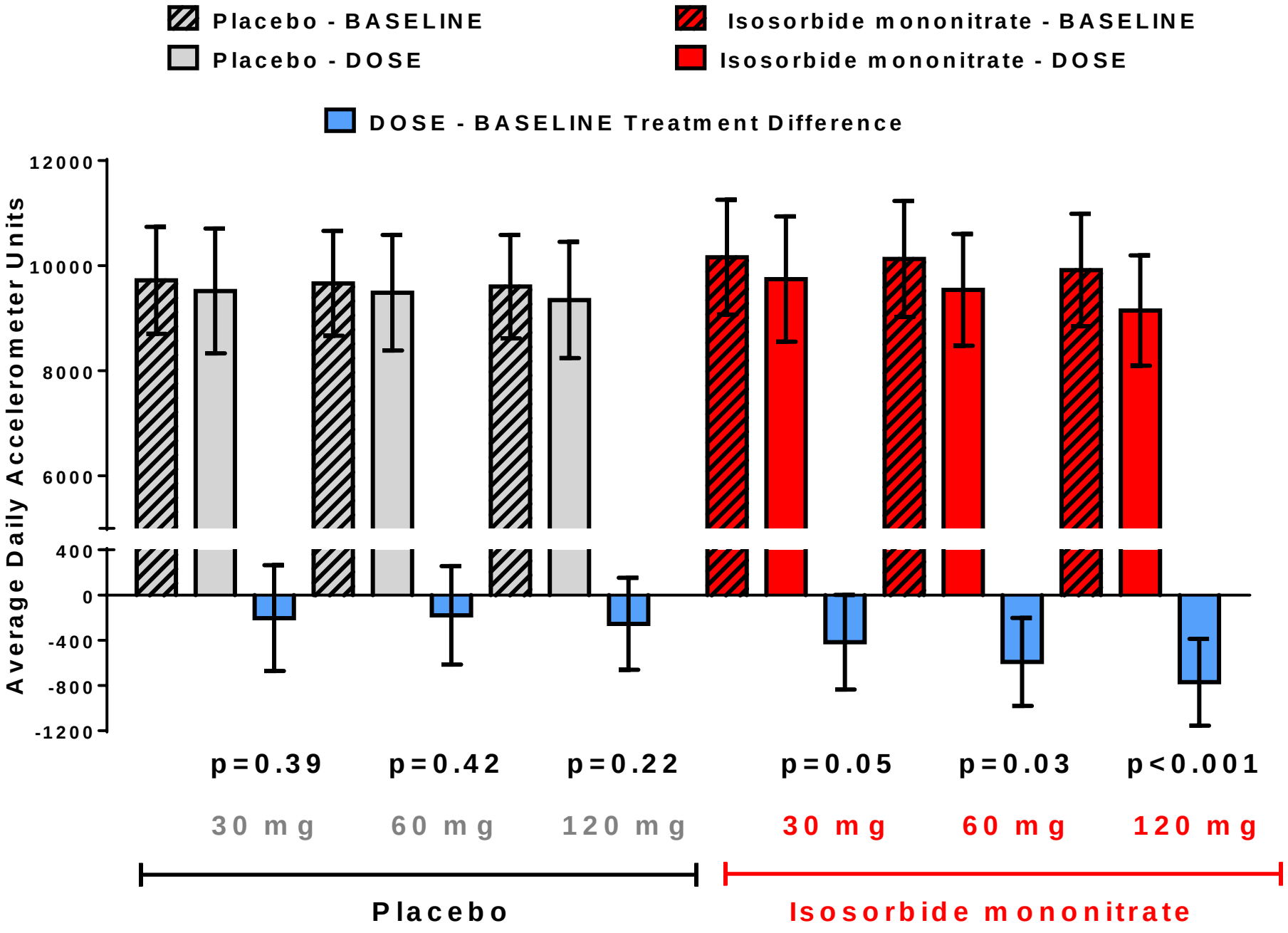
All Activity Endpoints




Placebo - BASELINE
Placebo - DOSE
Isosorbide mononitrate - BASELINE
Isosorbide mononitrate - DOSE
DOSE - BASELINE Treatment Difference
Average Daily Accelerometer Units
12000
10000
8000
6000
400
0
-400
-800
-1200
p=0.39
p=0.42
p=0.22
p=0.05
p=0.03
p<0.001
30 mg
60 mg
120 mg
30 mg
60 mg
120 mg
Placebo
Isosorbide mononitrate

Other Endpoints

	Placebo	ISMN	P value
6 Minute Walk			
Distance (m)	321	322	0.91
Dyspnea (1-10)	3.97	3.89	0.74
KCCQ (Higher better)	61.6	59.7	0.16
MLHFQ (Lower better)	35.4	37.0	0.37
NT-proBNP (pg/ml)	497	550	0.22
Systolic BP (mmHg)	129	125	0.04

Data are the model derived estimates of the mean treatment value

Safety / Tolerability Endpoints

Characteristic	Placebo	ISMN
Discontinued study drug	9	16
Any Event of Interest	6	14
Arrhythmia	2	2
Worsening HF	1	5
Stroke	0	1
Presyncope/Syncope	3	6
SAE - Death	0	0
SAE - Other	1	2

All p > 0.05

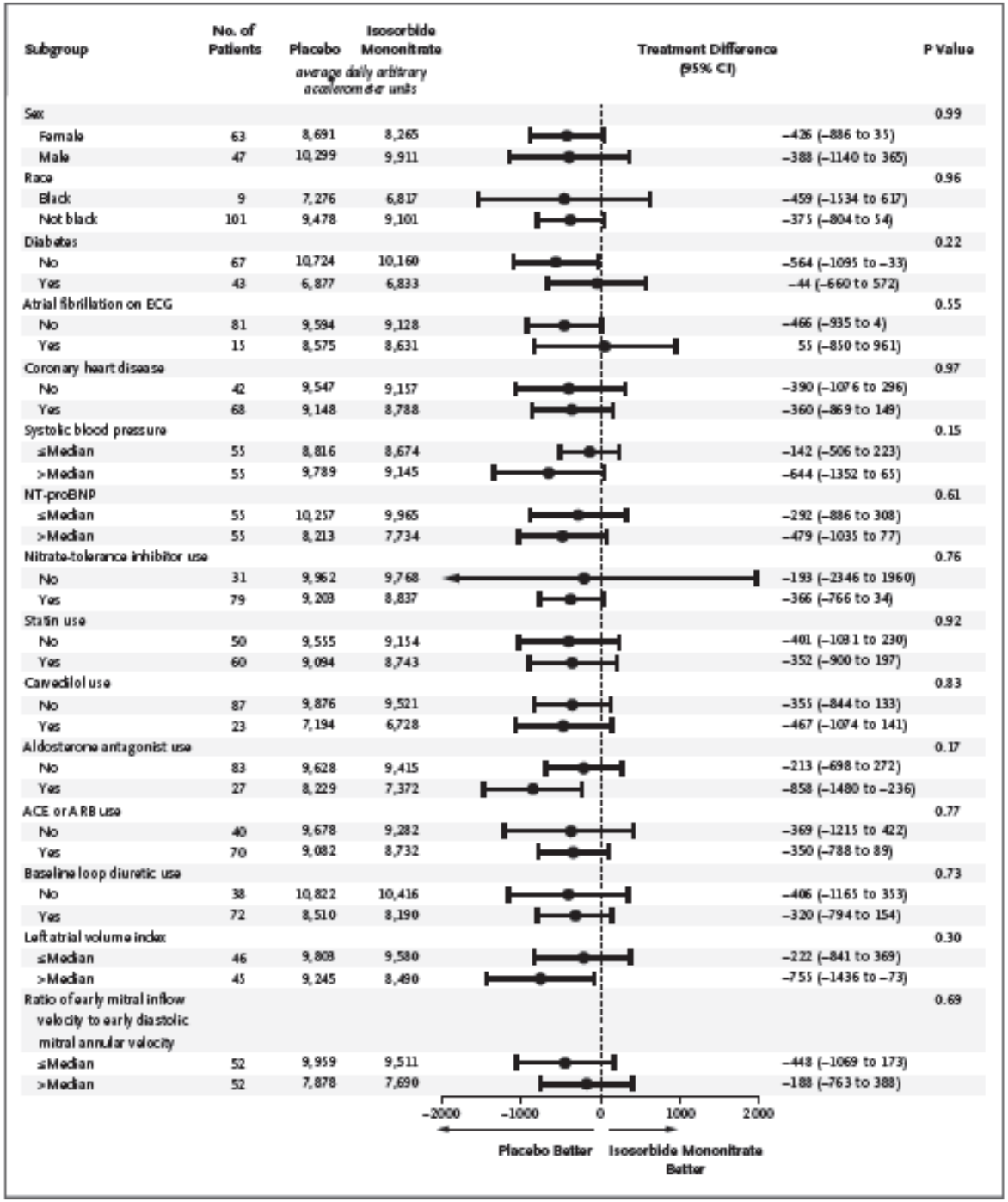
Summary

- In patients with HFpEF, as compared to placebo, isosorbide mononitrate decreased daily activity levels and did not improve submaximal exercise capacity, quality-of-life scores or NT-proBNP levels

Conclusions

- These data do not support use of long acting nitrates for symptom relief in HFpEF.
- Patient worn devices provide unique information about the impact of therapies on patients daily functional status

NEJM Galley Title Page


Subgroup
No. of Patients
Placebo
Isosorbide Mononitrate
average daily arbitrary accelerometer units
Treatment Difference (95% CI)
P Value
Sex 0.99
Female 63 8,691 8,265 −426 (−886 to 35)
Male 47 10,299 9,911 −388 (−1140 to 365)
Race 0.96
Black 9 7,276 6,817 −459 (−1534 to 617)
Not black 101 9,478 9,101 −375 (−804 to 54)
Diabetes 0.22
No 67 10,724 10,160 −564 (−1095 to −33)
Yes 43 6,877 6,833 −44 (−660 to 572)
Atrial fibrillation on ECG 0.55
No 81 9,594 9,128 −466 (−935 to 4)
Yes 15 8,575 8,631 55 (−850 to 961)
Coronary heart disease 0.97
No 42 9,547 9,157 −390 (−1076 to 296)
Yes 68 9,148 8,788 −360 (−869 to 149)
Systolic blood pressure 0.15
≤Median 55 8,816 8,674 −142 (−506 to 223)
>Median 55 9,789 9,145 −644 (−1352 to 65)
NT-proBNP 0.61
≤Median 55 10,257 9,965 −292 (−886 to 308)
>Median 55 8,213 7,734 −479 (−1035 to 77)
Nitrate-tolerance inhibitor use 0.76
No 31 9,962 9,768 −193 (−2346 to 1960)
Yes 79 9,208 8,837 −366 (−766 to 34)
Statin use 0.92
No 50 9,555 9,154 −401 (−1081 to 230)
Yes 60 9,094 8,743 −352 (−900 to 197)
Carvedilol use 0.83
No 87 9,876 9,521 −355 (−844 to 133)
Yes 23 7,194 6,728 −467 (−1074 to 141)
Aldosterone antagonist use 0.17
No 83 9,628 9,415 −213 (−698 to 272)
Yes 27 8,229 7,372 −858 (−1480 to −236)
ACE or ARB use 0.77
No 40 9,678 9,282 −369 (−1215 to 422)
Yes 70 9,082 8,732 −350 (−788 to 89)
Baseline loop diuretic use 0.73
No 38 10,822 10,416 −406 (−1165 to 353)
Yes 72 8,510 8,190 −320 (−794 to 154)
Left atrial volume index 0.30
≤Median 46 9,809 9,580 −222 (−841 to 369)
>Median 45 9,245 8,490 −755 (−1436 to −73)
Ratio of early mitral inflow velocity to early diastolic mitral annular velocity 0.69
≤Median 52 9,959 9,511 −448 (−1069 to 173)
>Median 52 7,878 7,690 −188 (−763 to 388)
−2000
−1000
0
1000
2000
Placebo Better
Isosorbide Mononitrate Better