Nitrate’s Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction Trial

Rationale and Design

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Heart Failure With Preserved Ejection Fraction

The prevalence of heart failure (HF) with preserved ejection fraction (HFpEF) is increasing. In patients with HFpEF, the burden of symptoms, functional decline, and mortality is high, and health-related quality of life is poor. Physicians caring for these patients currently have limited therapeutic options beyond diuresis and management of comorbid conditions. Hence there remains an immediate and critical need for therapies to alleviate symptoms and meaningfully improve quality of life for patients with HFpEF.

Role of Nitrate Therapy in HF

Long-acting nitrates are used as the cornerstone of antianginal therapy and have demonstrated beneficial effects for treatment of patients with HF and reduced EF (HFrEF). In randomized studies, sustained increases in treadmill exercise time and peak oxygen consumption have been observed at 3 months after initiation of nitrate therapy in patients with HFrEF, including those already treated with angiotensin converting enzyme inhibitors. Attenuation of pathological left ventricular (LV) remodeling and improved LV systolic function have also been reported. Although no study has directly examined the effects of nitrate monotherapy on survival in HF, symptom relief is a key management goal in patients with HFpEF, whose primary chronic symptom is often exercise limitation.

Practice guidelines for the management of chronic HF from the American College of Cardiology/American Heart Association and Heart Failure Society of America advocate a potential role for nitrates in diminishing symptoms in HFpEF but acknowledge the lack of supportive data and the risk of excessive nitrate–induced hypotension in elderly patients with HFpEF. Therefore, it is desirable that a randomized, controlled evaluation of the efficacy and tolerance of nitrate therapy in HFpEF is performed to support its therapeutic applications.

To address this lack of data and current clinical equipoise for nitrate therapy in HFpEF, the Nitrate’s Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction (NEAT-HFpEF) trial (clinicaltrials.gov, NCT02053493) is being conducted within the National Heart, Lung, and Blood Institute-sponsored HF clinical research network. Cognizant of the primary goal to reduce symptom burden and improve quality of life, NEAT-HFpEF will simultaneously assess a new paradigm of using patient-centric data, ie, data emanating from, and of immediate relevance to, patients’ daily living, as the primary efficacy end point. Thus, NEAT-HFpEF is expected to provide important information about nitrate’s safety and therapeutic benefit, as well as the feasibility of a novel end point, with potential for wider applications to future HF studies.

Rationale for Nitrate Therapy in HFpEF

Hemodynamic Effects

A fundamental hemodynamic derangement in HFpEF is pathological elevation in LV filling pressure, at rest or on exertion. Commonly used organic nitrates, isosorbide dinitrate, isosorbide-5-mononitrate (ISMN), and nitroglycerin, reduce ventricular preload by increasing peripheral venous capacitance, reducing LV filling pressure and wall stress. At higher doses, dilatation of pulmonary and systemic resistance vessels occurs, particularly in patients with high arterial pressures. Coronary artery disease is prevalent in HFpEF, and symptoms of angina may occur in patients without angiographically apparent coronary disease. Nitrate-induced coronary vasodilatation may improve subendocardial perfusion, which could benefit patients with HFpEF for whom ischemia is a contributory factor. Nitrate-induced preload reduction may also be beneficial in HFpEF where the steep diastolic pressure–volume relationship confers marked increases in LV filling pressures, even at low stroke volumes (SVs) and low work rate, prompting early cessation of exercise. Preload...
reduction may therefore be expected to improve exercise wave reflections in the arterial tree, which increase LV late systolic load and wall stress and impair diastolic relaxation.

However, nitrate-induced hemodynamic effects may also be blunted or deleterious in HFrEF. Although nitrates reduce arterial impedance and increase SV without causing hypertension in patients with HFrEF, a steeper end-systolic pressure volume relationship in HFrEF means SV increases less and systolic LV pressure decreases more in response to a decrease in preload or afterload. In fact, Schwartzenberg et al observed a reduction in SV among 35% of patients with HFpEF after infusion of sodium nitroprusside, suggesting greater vulnerability to excessive preload reduction. Because deficient SV reserve contributes to exercise limitation in patients with HFpEF, excessive venodilation from nitrates might offset any beneficial effects on filling pressures, coronary vasodilation, or relief of pericardial constraint. Moreover, patients with HFpEF are frequently elderly and may have autonomic dysfunction, chronotropic incompetence, and altered baroreflex sensitivity, all of which may exaggerate hypotension with load changes and thus heighten nitrate intolerance. Finally, whether the potentially favorable effects of nitrates on wave reflections reported in unselected hypertensive subjects also occur in patients with HFpEF is unknown.

Endothelial Effects of Nitrates
Nitrates vasorelaxant effects are thought to be mediated by the formation of nitric oxide (NO) or a closely related entity. NO activates soluble guanylyl cyclase in vascular smooth muscle, prompting the synthesis of the second messenger cyclic guanosine monophosphate (cGMP). Downstream activation of cGMP effector proteins, including cGMP-dependent protein kinase (PKG), leads to a reduction in intracellular calcium and thus to vasodilation. Endothelial-dependent vaso-dilation is impaired in patients with HFpEF, compared with healthy age-matched controls, and correlates with greater symptoms and poorer exercise capacity. Exogenous NO delivery or enhancement of endogenous NO biosynthesis may therefore improve endothelial function, as has been observed in HFrEF.

However, nitrates could also paradoxically worsen endothelial function. Studies in normal humans and experimental animals have shown endothelial dysfunction resulting from chronic nitrate therapy, attributed to the generation of reactive oxygen species and local endothelin activation.

Myocardial Effects of Nitrates
Increased NO bioavailability with nitrates, and thus cGMP/PKG signaling, may acutely improve LV diastolic function and ameliorate myocardial hypertrophic remodeling. Low PKG activity has been implicated in the development of myocardial hypertrophy, delayed relaxation, and increased passive stiffness. Van Heerebeek et al confirmed both low cGMP content and low PKG activity in myocardial tissue obtained from patients with HFrEF, compared with samples from patients with HFpEF and aortic stenosis. cGMP-phosphodiesterase expression, a mediator of cGMP hydrolysis, was similar between groups. This observation may provide insight into the lack of effect of phosphodiesterase-5 inhibition in HFpEF as enhanced cGMP hydrolysis does not seem to mediate the unique reduction in myocardial cGMP in HFpEF. Rather, the nitrotyrosine content (reflecting oxidative/nitrosative stress) was highest in HFpEF, suggesting that a reduction in NO-stimulated cGMP synthesis due to reactive oxygen species scavenging of NO and oxidation of the NO target, soluble guanylyl cyclase, underlies the low myocardial cGMP content and reduced PKG activity in HFpEF. Activation of PKG-PKG may also acutely improve diastolic function via phosphorylation of titin. Acute titin phosphorylation via exogenous administration of PKG results in dramatic reduction in cardiomyocyte stiffness in vitro. Although direct augmentation of PKG improves myocardial diastolic properties in vivo, whether chronic nitrate therapy will enhance cGMP, PKG activity, and myocardial diastolic function in HFpEF is unclear.

Nitrate Resistance
Therapeutic responses to nitrates are variable, and higher doses are needed to elicit hemodynamic and endothelial responses in patients with HFrEF compared with patients without HF (nitrate resistance). Furthermore, early systemic effects, including reflex neurohumoral activation and volume expansion, may lead to reversal of initial hemodynamic benefits (nitrate pseudotolerance).

Prolonged exposure is widely recognized to induce true nitrate tolerance. This is thought to involve vascular processes, such as impaired nitrate biotransformation, increased reactive oxygen species production with impaired clearance, soluble guanylyl cyclase desensitization to NO, enhanced sensitivity to endogenous vasoconstrictors, and increased cGMP phosphodiesterase activity, all of which inactivate nitrate vaso-dilator effects. The extent of tolerance is somewhat dose-related, and low doses or intermittent dosing regimens with low-nitrate or nitrate-free intervals may be sufficient to prevent its occurrence. Although a combination of hydralazine and nitrates is suggested to reduce nitrate tolerance and is used in HFrEF, the additional vasodilation and afterload reduction imparted by hydralazine may prove excessive in HFpEF because of the aforementioned differences in pressure–volume relationships and may mask a beneficial effect of lone nitrate therapy in HFpEF. Furthermore, tolerance differs between nitrate preparations because once daily ISMN was shown to be devoid of tolerance in patients with coronary artery disease. Therefore, once daily lone ISMN therapy has been selected for NEAT-HFpEF.

Assessment of Symptom Burden in HF
To determine whether nitrates are effective at reducing symptom burden, selection of an appropriate functional end point is preferable to conventional disease–related outcomes. Functional performance refers to the ability to perform day-to-day activities to: “meet basic needs, fulfill usual roles, and maintain health and wellbeing.” Such activities often require much less than maximal exertion and may not be accurately summarized by the peak exertional measures used in recent HF trials.
Likewise, intermittent evaluation of submaximal exercise capacity, such as the 6-minute walk distance (6MWD), provides low-density data that are subject to coaching effects and may underestimate the true burden of disease, for example, when patients voluntarily reduce activity to avoid symptoms. Accelerometer-assessed activity is a novel end point, which may circumvent these limitations by providing high-density, quantitative data from continuous assessment of physical activity during usual daily life.

Previous recent studies in patients with HFrEF have demonstrated correlations between accelerometer data and New York Heart Association functional class, oxygen consumption, and estimated (Seattle Heart Failure Model) or observed mortality risks. Studies have also shown increases in accelerometer-assessed activity after cardiac resynchronization therapy, confirming its ability to reflect therapeutic response. Validity, analytic issues, and compliance with externally worn accelerometer devices have been addressed in clinical trials for patients with chronic obstructive pulmonary disease, among whom age and activity level are likely comparable with elderly patients with HFP EF.

Notably, patients who may be too frail to undergo comprehensive cardiopulmonary exercise testing will still be eligible for a patient-centric method to detect a clinically relevant response (belt-attached) accelerometer devices (Figure 1). At each titration step, study staff will discuss tolerability and determine safety to proceed with uptitration. In the case of drug intolerance, participants will be instructed to downtitrate to the previously tolerated dose or discontinue as necessary. At the end of phase 1, repeat assessment is performed (blood sampling, 6MWD, and symptom questionnaires) and all participants receive a new accelerometer device and study drug supply and begin a 2-week drug-free washout phase. Dose titration is then performed as before. Participants are called weekly and encouraged to be active within the limitations imposed by their HF symptoms. After completion of phase 2, patients undergo a final in-person assessment as at the end of phase 1.

### Crossover Study Design Considerations

As per the crossover study design, each participant will serve as their own control. Avoiding between-participant variation in estimating the intervention effect enables a smaller sample size and timely completion. External social and behavioral related factors influencing exercise capacity would also be expected to vary little during the trial; thus, the within-subject comparisons will remain robust. The modest total treatment duration (4 weeks) was selected to minimize potential bias because of period effects or remodeling (carryover effect). In particular, nitrates have a rapid onset and offset of action, and the 2-week washout phase was determined based on nitrate pharmacokinetics and literature review. The key hypothesis to be tested in NEAT-HFP EF is that nitrate hemodynamic effects provide acute symptom relief in HFP EF and that symptom relief will translate into an increase in activity levels. Importantly, NEAT-HFP EF is not designed to evaluate chronic remodeling effects associated with nitrate therapy and, in the event of a negative outcome, should not preclude further investigation into these.

## End Points

### Primary End Point

As outlined above, the primary end point for NEAT-HFP EF will be a within-participant comparison of accelerometer-assessed physical activity averaged over 14 days between the ISMN and placebo phases.

### Technical Details

#### Patient Factors

Each patient will wear 2 external, hip-worn (belt-attached) accelerometer devices (Figure 2) throughout the

## Rationale and Design of NEAT-HFP EF

NEAT-HFP EF is a multicenter, randomized (1:1), double-blind, placebo-controlled, crossover study designed to test the hypothesis that once daily extended-release ISMN, at a maximally tolerated dose (30–120 mg), improves daily physical activity in patients with HFP EF. Daily activity will be assessed by 2 hip-worn triaxial accelerometers and the primary end point will be a within-patient comparison of 14-day averaged arbitrary accelerometer units (AAU14) achieved during the ISMN treatment phase, compared with placebo. Because the ability to carry out usual daily activities is a pervasive marker of symptom burden and yet may be highly variable between patients, the novel end point and crossover design used in NEAT-HFP EF are uniquely suited to address the primary hypothesis while taking heed of nitrate pharmacology and pragmatic sample size.

### Study Protocol and Dose-Titration Schedule

Approximately 110 patients with chronic stable HF and preserved EF (≥50%) will be enrolled. Specific entry criteria stipulate that activity limitation is primarily because of HF symptoms (Table). Eligible participants undergo baseline assessment (echocardiography, blood sampling for biomarkers, including cGMP and N-terminal pro-brain type natriuretic peptide, 6MWD, and symptom questionnaires: Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire [KCCQ]) followed by training in accelerometer use. Participants are subsequently randomized to 1 of 2 treatment groups, placebo first with crossover to ISMN or ISMN first with crossover to placebo, stratified by the clinical site (permuted block randomization) to ensure equal distribution of participants per arm per site.

All participants enter a 2-week run-in phase during which accelerometer data obtained reflect baseline physical activity off nitrates. Thereafter, participants commence once daily placebo or oral ISMN according to the dose-titration schedule in Figure 1. At each titration step, study staff will discuss tolerability and determine safety to proceed with uptitration. In the case of drug intolerance, participants will be instructed to downtitrate to the previously tolerated dose or discontinue as necessary. At the end of phase 1, repeat assessment is performed (blood sampling, 6MWD, and symptom questionnaires) and all participants receive a new accelerometer device and study drug supply and begin a 2-week drug-free washout phase. Dose titration is then performed as before. Participants are called weekly and encouraged to be active within the limitations imposed by their HF symptoms. After completion of phase 2, patients undergo a final in-person assessment as at the end of phase 1.
The triaxial accelerometer (piezoelectric) sensor measures physical activity in terms of acceleration (movement) values along the vertical (z), anteroposterior (y), and mediolateral (x) axes over time. The accelerometer unit samples these measurements 16x per second, and the raw output generated, ie, the change in voltage vector from 1 sample to the next is converted into a digital series of numbers known as Kionix-based AAUs (Kionix is the integrated circuit accelerometer supplier) according to the formula:

\[
\sqrt{x_1^2 + y_1^2 + z_1^2} \approx 1.5 \text{ miles per hour and would, therefore, be unsuitable for sedentary individuals with HFpEF.}
\]

At present, there are no consistent cutoffs for classifying accelerometer-assessed activity units into recognized intensity levels for direct clinical interpretation.\(^*\) Furthermore, NEAT-HFpEF represents the first study within a dedicated HFpEF population to use accelerometer-assessed physical activity as a primary end point. Therefore, in addition to within-patient comparisons with and without nitrate therapy, NEAT-HFpEF will also define the typical AAU\(_{14}\), reflecting the average accelerometer-assessed physical activity during habitual free-living conditions, for each individual, for each phase. All raw data collected will be available for analysis, irrespective of activity level. This is important as some commercially available devices eliminate data corresponding to walking speeds of less than \(=1.5\) miles per hour and would, therefore, be unsuitable for sedentary individuals with HFpEF.

### Table. NEAT-HFpEF Eligibility Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Age, (\geq 50) yrs.</td>
<td>Symptoms of dyspnea (II–IV) without noncardiac or ischemic cause</td>
</tr>
<tr>
<td>EF, (\geq 50%)</td>
<td>Previous hospitalization for HF or</td>
</tr>
<tr>
<td>One of the following within the last 12 mo</td>
<td>Catheterization documented elevated filling pressures at rest (LVEDP (\geq 15)</td>
</tr>
<tr>
<td>Previous hospitalization for HF or</td>
<td>or PCWP (\geq 20)) with exercise (PCWP (\geq 25)) or</td>
</tr>
<tr>
<td>Elevated NT-proBNP ((\geq 400 \text{ pg/mL})) or BNP ((\geq 200 \text{ pg/mL}))</td>
<td>Echocardiographic evidence of diastolic dysfunction or elevated filling pressures</td>
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<tr>
<td>Echocardiographic evidence of diastolic dysfunction/elevated filling pressures (at least two)</td>
<td>Evidence of LVH</td>
</tr>
<tr>
<td>Deceleration time (\leq 140) ms</td>
<td>LV mass/BSA (\geq 96) (♂) or (\geq 116) (♀) g/m(^2)</td>
</tr>
<tr>
<td>LA enlargement (\geq 3.5) moderate</td>
<td>RWT (\geq 0.43) (♂) or (♀)</td>
</tr>
<tr>
<td>PASP (\geq 35) mm Hg</td>
<td>Posterior wall thickness (\geq 0.9) (♂) or 1.0 (♀) cm</td>
</tr>
<tr>
<td>Evidence of LVH</td>
<td>No chronic nitrate therapy or not using ((\leq 1\times \text{ wk})) intermittent sublingual GTN</td>
</tr>
<tr>
<td>No chronic nitrate therapy or not using ((\leq 1\times \text{ wk})) intermittent sublingual GTN</td>
<td>Ambulatory (not wheelchair/scooter dependent)</td>
</tr>
<tr>
<td>Heart failure is primary factor limiting activity as indicated by answering number 2 to the following question:</td>
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</tr>
<tr>
<td><strong>My ability to be active is most limited by:</strong></td>
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<tr>
<td>(3) Unsteadiness or dizziness</td>
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<tr>
<td>(4) Lifestyle, weather, or I just do not like to be active</td>
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<tr>
<td>Does not regularly swim or do water aerobics as primary form of exercise</td>
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</table>

### Secondary End Points

NEAT-HFpEF is powered to detect a clinically meaningful change in the 6MWD, the KCCQ score, and the Minnesota Living with Heart Failure Questionnaire score. Perceived period to minimize patient handling. Baseline training and weekly study calls will address participant-specific strategies to enhance steadfast use, including during sleep. Participants will be advised to remove the belt only during bathing or swimming.

#### Figure 1. Study protocol and dose-titration schedule for NEAT-HFpEF.

- \(120^*\) mg: Cross-over to second arm
- \(60^*\) mg: Baseline
- \(30^*\) mg: Wash-out
- \(120^*\) mg: Cross-over
- \(60^*\) mg: Baseline
- \(30^*\) mg: Wash-out
- \(120^*\) mg: Cross-over
- \(60^*\) mg: Baseline
- \(30^*\) mg: Wash-out

#### Study Visits

1. 6 wks
2. 6 wks
3. 6 wks

- BL: Baseline
- WO: Washout
- C: Cross-over

- Wk: Week
dyspnea and effort (Borg) scores during 6MWD and changes in plasma N-terminal pro-brain type natriuretic peptide concentration will also be assessed. Additional accelerometer end points will include hours active, the slope of daily-averaged AAU during study drug administration, and area under the curve for daily-averaged AAU during study drug administration. Patient preference for study phase will also be assessed via a standardized questionnaire.

Tertiary End Points
Tertiary end points will include the quotients of 6MWD and associated Borg score (integrated measure of performance and symptoms), plasma cGMP concentration and, where available, accelerometer-assessed dose–response to nitrate therapy.

Subgroup Analysis
Prespecified subgroup exploratory analyses include comparison of nitrate efficacy according to treatment (or absence of treatment) with agents reported to reduce nitrate tolerance (renin–angiotensin–aldosterone antagonists, statins,59 or hydralazine),35,60 plasma N-terminal pro-brain type natriuretic peptide level, systolic blood pressure, and presence or absence of coronary artery disease. An analysis confined to on-drug patients will also be performed.

Statistical Considerations
Analyses will be conducted on a modified intention-to-treat basis and include all randomized participants who complete both phases. The primary end point is based on the within-patient comparison of AAU\textsubscript{14} achieved during the maximally tolerated dose period of ISMN versus placebo, ie, using accelerometer data obtained during weeks 5 to 6 versus weeks 11 to 12. For missing data corresponding to periods when the device belt is not worn (bathing or water activities), the imputation approach of Catellier et al\textsuperscript{61} will be used to create a pseudocomplete data set. The imputation plan will also account for potential differences in activity between weekdays and weekends. The primary analysis will involve a mixed model with fixed effect terms for the sequence, study phase, and treatment.\textsuperscript{62} A random effect term will be included to account for the correlated measurement within each participant.\textsuperscript{63} Baseline characteristics (demographics, echocardiographic data, biomarkers, and questionnaire scores) will be used for adjusted and subgroup analyses. Data from the first phase (baseline to maximum tolerated dose) and second phase (washout to maximum tolerated dose) will be presented separately in a sensitivity analysis, thereby including any patients who may have completed only 1 phase. For secondary and tertiary end points, continuous outcomes will be assessed using mixed models, as for the primary analysis; binary outcomes will be assessed using \( \chi^2 \) tests and Fisher exact test, for unadjusted comparisons.

Sample Size and Power
Because the primary end point has not previously been examined in the proposed study population, the justification for sample size is based on 2 key secondary end points: the overall summary score from KCCQ and the 6MWD.

Data from the recently completed Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) trial\textsuperscript{64} suggest that the within-patient SD for the KCCQ overall summary score is \( \approx \)17 points. A clinically significant difference is considered to be 5 points and a moderately large clinical difference is 10 points.\textsuperscript{55,66} Assuming a 2-sided type I error (\( \alpha \)) of 0.05, based on a crossover ANOVA\textsuperscript{63} and a 17-point SD in the KCCQ summary score, a total of 94 participants (47 per sequence) would have 80% power to detect a difference of 5 points in the KCCQ summary score. 6MWD data from the RELAX (Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction) trial\textsuperscript{62} suggest that the within-patient SD is \( \approx \)90 m. Based on a clinically meaningful difference of 43 m,\textsuperscript{67} a sample size of \( \geq \)60 participants (30 per sequence) would have \( \geq \)90% power to detect this difference in this 2x2 crossover design. The NEAT-HFpEF sample size is larger than that used in previous crossover studies, which established nitrate efficacy for HFrEF and angina.\textsuperscript{5,53–55,68–70}

We have also previously measured accelerometer-assessed activity as the AAU\textsubscript{14} at baseline, 3 months, and 6 months in 49 elderly sedentary volunteers receiving no intervention.\textsuperscript{71} The average within-patient SD between the baseline (mean, 4462 AAU) and 3 months (mean, 4496 AAU) was 337 AAU. If the baseline AAU\textsubscript{14} and the within-patient variability in patients with HFrEF are similar to those observed in healthy elderly sedentary individuals, NEAT-HFpEF would have 90% power to detect a difference between the intervention and placebo phases of 114 AAU (\( \approx \)2.5% of the baseline measurement).

Safety
Potential inadvertent unblinding of treatment because of nitrate-related side effects, including headache, and rarely, lightheadedness, and syncope, is recognized. Once daily extended–release ISMN has been chosen as the study drug for NEAT-HFpEF, with gradual uptitration from a low dose at weekly intervals to minimize the risk of severe side effects and enhance tolerability. ISMN is the active metabolite of isosorbidinitrate, and at doses of 60 or 120 mg, it has a plasma elimination half-life of \( \approx \)6 hours,\textsuperscript{72} and thus, the dosing regimen in NEAT-HFpEF will provide a low-nitrate interval per 24 hours. Coadministration of phosphodiesterase-5 inhibitors will be prohibited because of the risk of excessive hypotension.

Conclusions
Although expert consensus guidelines recommend consideration of nitrates in HFrEF, there are currently no data supporting this recommendation. The NEAT-HFpEF trial will address this
critical question and determine whether nitrate pharmacodynamic effects may be leveraged for acute symptom relief among ambulatory patients with HFpEF. Moreover, in using accelerometer-assessed activity as the primary end point, NEAT-HFpEF will ascertain the true effect of nitrate therapy on patients’ physical activity during daily living and establish the clinical use of this novel and patient-centric end point for future HF trials.

Sources of Funding
This work was supported by grants from the National Heart, Lung and Blood Institute (co-coordinating center: U10 HL084904 and regional clinical centers: U10 HL110312, U10 HL110337, U10 HL110342, U10 HL110348, U10 HL110352, U10 HL110361, and U10 HL110366).

Disclosures
None.

References


Key Words: accelerometry ■ clinical trial ■ heart failure, diastolic
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_Circ Heart Fail._ 2015;8:221-228
doi: 10.1161/CIRCHEARTFAILURE.114.001598
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/8/1/221