# 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.[1] In patients with HFpEF, the burden of symptoms, functional decline, and mortality is high,[2] and health-related quality of life is poor.[3] 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[4,5] and peak oxygen consumption[6] have been observed at 3 months after initiation of nitrate therapy in patients with HFrEF, including those already treated with angiotensin converting enzyme inhibitors.[5] Attenuation of pathological left ventricular (LV) remodeling and improved LV systolic function have also been reported.[5] 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.[7]

Practice guidelines for the management of chronic HF from the American College of Cardiology/American Heart Association[8] and Heart Failure Society of America[9] 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.[7,10] 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.[11,12] At higher doses, dilatation of pulmonary and systemic resistance vessels occurs,[13] particularly in patients with high arterial pressures.[14] Coronary artery disease is prevalent in HFpEF, and symptoms of angina may occur in patients without angiographically apparent coronary disease.[15] 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.[7] Preload

reduction may therefore be expected to improve exercise capacity in HFpEF. Furthermore, nitrates may reduce wave reflections in the arterial tree,[16,17] which increase LV late systolic load and wall stress[18] and impair diastolic relaxation.[19]

However, nitrate-induced hemodynamic effects may also be blunted or deleterious in HFpEF. Although nitrates reduce arterial impedance and increase SV without causing hypotension in patients with HFrEF, a steeper end-systolic pressure volume relationship in HFpEF means SV increases less and systolic LV pressure decreases more in response to a decrease in preload or afterload.[20–22] In fact, Schwartzenberg et al[22] 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,[23] excessive venodilation from nitrates might offset any beneficial effects on filling pressures, coronary vasodilation, or relief of pericardial constraint.[24] 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.[25] 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

Nitrate vasorelaxant responses are thought to be mediated by the formation of nitric oxide (NO) or a closely related entity.[26] 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 vasodilation is impaired in patients with HFpEF, compared with healthy age–matched controls, and correlates with greater symptoms and poorer exercise capacity.[23] Exogenous NO delivery or enhancement of endogenous NO biosynthesis may therefore improve endothelial function, as has been observed in HFrEF.[27]

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.[28,29]

### 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.[30] Van Heerebeek et al[31] confirmed both low cGMP content and low PKG activity in myocardial tissue obtained from patients with HFpEF, compared with samples from patients with HFrEF 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[32] as enhanced cGMP hydrolysis does not seem to mediate the unique reduction in myocardial cGMP in HFpEF.[31] Rather, the nitrotyrosine content (reflecting oxidative/nitrosative stress) was highest in HFpEF,[31] 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 cGMP-PKG may also acutely improve diastolic function via phosphorylation of titin.[33] Acute titin phosphorylation via exogenous administration of PKG results in dramatic reduction in cardiomyocyte stiffness in vitro.[31] 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).[34] Furthermore, early systemic effects, including reflex neurohumoral activation and volume expansion, may lead to reversal of initial hemodynamic benefits (nitrate pseudotolerance).[34]

Prolonged exposure is widely recognized to induce true nitrate tolerance.[34,35] 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 phophodiesterase activity, all of which inactivate nitrate vasodilator effects.[34] 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.[35,36] 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.[37,38] 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."[39] 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,[40] 6MWD,[41,42] peak oxygen consumption,[40,43] and estimated (Seattle Heart Failure Model) or observed mortality risks.[44,45] Studies have also shown increases in accelerometer-assessed activity after cardiac resynchronization therapy, confirming its ability to reflect therapeutic response.[41,46,47] 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 HFpEF.[48–51] Notably, patients who may be too frail to undergo comprehensive cardiopulmonary exercise testing will still be eligible for a study using accelerometry, thereby addressing concerns about the spectrum of disease severity in recent HFpEF trials.[32,52]

Importantly, cardiopulmonary diseases, or even therapy, are not the only determinants of physical activity. Behavioral and psychological factors, as well as the patient's immediate environment and social support, may have an effect on habitual physical activity. Thus, although accelerometer-assessed physical activity represents a novel, feasible, and patient-centric method to detect a clinically relevant response to nitrate therapy in ambulatory patients with HFpEF, whether enhanced exercise capacity will translate into increased daily physical activity in patients with HFpEF remains uncertain.

## Rationale and Design of NEAT-HFpEF

NEAT-HFpEF 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 HFpEF. 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 ($AAU_{14}$) 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-HFpEF 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.

### 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.[17,38,53–55] The key hypothesis to be tested in NEAT-HFpEF is that nitrate hemodynamic effects provide acute symptom relief in HFpEF and that symptom relief will translate into an increase in activity levels. Importantly, NEAT-HFpEF 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-HFpEF will be a within-patient 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

**Table.    NEAT-HFpEF Eligibility Criteria**

Inclusion criteria

Age, ≥50 y

Symptoms of dyspnea (II–IV) without noncardiac or ischemic cause

EF, ≥ 50%

One of the following within the last 12 mo

Previous hospitalization for HF or

Catheterization documented elevated filling pressures at rest (LVEDP≥15 or PCWP≥20) or with exercise (PCWP≥25) 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

Deceleration time ≤140 ms

PVs<PVd (sinus rhythm)

E/e' ≥15

LA enlargement (≥moderate)

PASP >35 mm Hg

Evidence of LVH

LV mass/BSA ≥96 (♀) or ≥116 (♂) g/m²

RWT ≥0.43 (♂ or ♀)

Posterior wall thickness ≥0.9 (♀) or 1.0 (♂) cm

No chronic nitrate therapy or not using (≤1× wk) intermittent sublingual GTN

Ambulatory (not wheelchair/scooter dependent)

Heart failure is primary factor limiting activity as indicated by answering number 2 to the following question:

My ability to be active is most limited by:

(1) Joint, foot, leg, hip, or back pain

(2) Shortness of breath or fatigue or chest pain

(3) Unsteadiness or dizziness

(4) Lifestyle, weather, or I just do not like to be active

Does not regularly swim or do water aerobics as primary form of exercise

Primary exclusion criteria

Recent (<3 mo) hospitalization for heart failure or acute coronary syndrome

Previous adverse reaction to the nitrates which necessitated withdrawal of therapy

Therapy with phosphodiesterase type 5 inhibitors

Documentation of previous EF <50%

Hemodynamic instability, rare causes of HFpEF, significant primary valve disease, or severe hematologic, liver or kidney disease

BNP indicates brain-type natriuretic peptide; BSA, bovine serum albumin; E/A, ratio of early (E) to late (A) Doppler mitral inflow velocity; E/e', ratio of early Doppler mitral inflow velocity (E) to early mitral annular tissue Doppler velocity (e'); EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; GTN, glyceryl trinitrate; LA, left atrial; LVEDP, left ventricular end diastolic pressure; LVH, left ventricular hypertrophy; NEAT-HFpEF, Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction; NT-proBNP, N-terminal probrain type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PSAP, pulmonary artery systolic pressure; PVd, pulmonary venous diastolic wave; PVs, pulmonary venous systolic wave; and RWT, relative wall thickness.

study duration, which will also provide variability data. The devices will not display activity or step counts to the patient. Device settings are preprogrammed, and the accelerometers will remain switched on throughout the entire measurement 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.

*Accelerometer Measures.*    The triaxial accelerometer (piezo-electric) sensor measures physical activity in terms of acceleration (movement) values along the vertical ($x$), anteroposterior ($y$), and mediolateral ($z$) axes over time. The accelerometer unit samples these measurements 16× 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:

$$\sqrt{\left(x_1 - x_2\right)^2 + \left(y_1 - y_2\right)^2 + \left(z_1 - z_2\right)^2}$$

where subscript 1=time point 1, subscript 2=time point 2, and time points 1 and 2 are 1/16th of a second apart. Data are continuously recorded, and cumulative AAUs are stored in 15-minute epochs (assigned recording periods), providing a total of 96 data points per day. In NEAT-HFpEF, these AAU data points will be averaged for a period of 14 days (area under the curve integration) to provide a single measure of $AAU_{14}$, 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.

At present, there are no consistent cutoffs for classifying accelerometer-assessed activity units into recognized intensity levels for direct clinical interpretation.[56] 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 $AAU_{14}$ value and SD relevant for an HFpEF population and future studies.

## 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
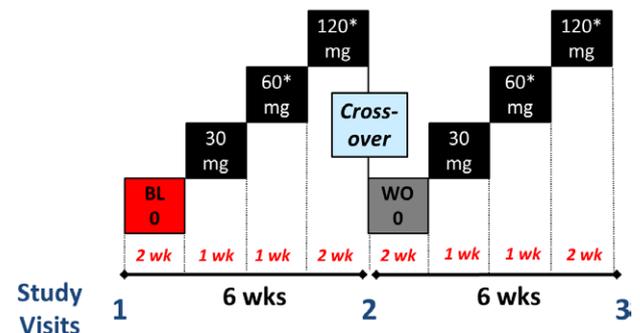
**Figure 1.** Study protocol and dose-titration schedule for NEAT-HFpEF. * indicates or maximally tolerated dose; BL, baseline; and WO, washout; wk, week.

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,[35,57] carvedilol,[58] 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 $AAU_{14}$ 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[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, period (study phase), and treatment.[62] A random effect term will be included to account for the correlated measurement within each participant.[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.



**Figure 2.** The NEAT-HFpEF accelerometer device.

Data from the recently completed Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF) trial[64] suggest that the within-patient SD for the KCCQ overall summary score is ≈17 points. A clinically significant difference is considered to be 5 points and a moderately large clinical difference is 10 points.[65,66] Assuming a 2-sided type I error ($\alpha$) of 0.05, based on a crossover ANOVA[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[32] suggest that the within-patient SD is ≈90 m. Based on a clinically meaningful difference of 43 m,[67] a sample size of >60 participants (30 per sequence) would have >90% power to detect this difference in this 2×2 crossover design. The NEAT-HFpEF sample size is larger than that used in previous crossover studies, which established nitrate efficacy for HFrEF and angina.[5,53–55,68–70]

We have also previously measured accelerometer-assessed activity as the $AAU_{14}$ at baseline, 3 months, and 6 months in 49 elderly sedentary volunteers receiving no intervention.[71] The average within-patient SD between the baseline (mean, 4462 AAU) and 3 months (mean, 4496 AAU) was 337 AAU. If the baseline $AAU_{14}$ and the within-patient variability in patients with HFpEF 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 (≈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 isosorbide dinitrate, and at doses of 60 or 120 mg, it has a plasma elimination half-life of ≈6 hours,[38] 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 HFpEF, 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

## Disclosures

None.

## References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259. doi: 10.1056/NEJMoa052256.

2. Smith GL, Masoudi FA, Vaccarino V, Radford MJ, Krumholz HM. Outcomes in heart failure patients with preserved ejection fraction: mortality, readmission, and functional decline. *J Am Coll Cardiol*. 2003;41:1510–1518.

3. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. *Eur J Heart Fail*. 2011;13:1013–1018. doi: 10.1093/eurjhf/hfr072.

4. Leier CV, Huss P, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. *Circulation*. 1983;67:817–822.

5. Elkayam U, Johnson JV, Shotan A, Bokhari S, Solodky A, Canetti M, Wani OR, Karaalp IS. Double-blind, placebo-controlled study to evaluate the effect of organic nitrates in patients with chronic heart failure treated with angiotensin-converting enzyme inhibition. *Circulation*. 1999;99:2652–2657.

6. Franciosa JA, Goldsmith SR, Cohn JN. Contrasting immediate and long-term effects of isosorbide dinitrate on exercise capacity in congestive heart failure. *Am J Med*. 1980;69:559–566.

7. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588–595. doi: 10.1161/CIRCHEARTFAILURE.109.930701.

8. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065.

9. Heart Failure Society of America. Evaluation and management of patients with heart failure and preserved left ventricular ejection fraction. *J Card Fail*. 2006;12:e80–85.

10. Penicka M, Bartunek J, Trakalova H, Hrabakova H, Maruskova M, Karasek J, Kocka V. Heart failure with preserved ejection fraction in outpatients with unexplained dyspnea: a pressure-volume loop analysis. *J Am Coll Cardiol*. 2010;55:1701–1710. doi: 10.1016/j.jacc.2009.11.076.

11. Battock DJ, Levitt PW, Steele PP. Effects of isosorbide dinitrate and nitroglycerin on central circulatory dynamics in coronary artery disease. *Am Heart J*. 1976;92:455–458.

12. Elkayam U. Nitrates in the treatment of congestive heart failure. *Am J Cardiol*. 1996;77:41C–51C.

13. Packer M, Medina N, Yushak M, Lee WH. Comparative effects of captopril and isosorbide dinitrate on pulmonary arteriolar resistance and right ventricular function in patients with severe left ventricular failure: results of a randomized crossover study. *Am Heart J*. 1985;109:1293–1299.

14. Haber HL, Simek CL, Bergin JD, Sadun A, Gimple LW, Powers ER, Feldman MD. Bolus intravenous nitroglycerin predominantly reduces afterload in patients with excessive arterial elastance. *J Am Coll Cardiol*. 1993;22:251–257.

15. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63:2817–2827.

16. Yaginuma T, Avolio A, O'Rourke M, Nichols W, Morgan JJ, Roy P, Baron D, Branson J, Feneley M. Effect of glyceryl trinitrate on peripheral arteries alters left ventricular hydraulic load in man. *Cardiovasc Res*. 1986;20:153–160.

17. Stokes GS, Barin ES, Gilfillan KL. Effects of isosorbide mononitrate and AII inhibition on pulse wave reflection in hypertension. *Hypertension*. 2003;41:297–301.

18. Chirinos JA, Segers P, Gillebert TC, Gupta AK, De Buyzere ML, De Bacquer D, St John-Sutton M, Rietzschel ER; Asklepios Investigators. Arterial properties as determinants of time-varying myocardial stress in humans. *Hypertension*. 2012;60:64–70. doi: 10.1161/HYPERTENSIONAHA.112.190710.

19. Gillebert TC, Lew WY. Influence of systolic pressure profile on rate of left ventricular pressure fall. *Am J Physiol*. 1991;261:H805–H813.

20. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol*. 1998;32:1221–1227.

21. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003;107:714–720.

22. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol*. 2012;59:442–451. doi: 10.1016/j.jacc.2011.09.062.

23. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56:845–854. doi: 10.1016/j.jacc.2010.03.077.

24. Ludbrook PA, Byrne JD, Kurnik PB, McKnight RC. Influence of reduction of preload and afterload by nitroglycerin on left ventricular diastolic pressure-volume relations and relaxation in man. *Circulation*. 1977;56:937–943.

25. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation*. 2011;123:2006–2013. doi: 10.1161/CIRCULATIONAHA.110.954388.

26. Ignarro LJ, Lippton H, Edwards JC, Baricos WH, Hyman AL, Kadowitz PJ, Gruetter CA. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther*. 1981;218:739–749.

27. Schwarz M, Katz SD, Demopoulos L, Hirsch H, Yuen JL, Jondeau G, LeJemtel TH. Enhancement of endothelium-dependent vasodilation by low-dose nitroglycerin in patients with congestive heart failure. *Circulation*. 1994;89:1609–1614.

28. Thomas GR, DiFabio JM, Gori T, Parker JD. Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans: evidence of a free-radical-mediated mechanism. *J Am Coll Cardiol*. 2007;49:1289–1295. doi: 10.1016/j.jacc.2006.10.074.

29. Oelze M, Knorr M, Kröller-Schön S, Kossmann S, Gottschlich A, Rümmler R, Schuff A, Daub S, Doppler C, Kleinert H, Gori T, Daiber A, Münzel T. Chronic therapy with isosorbide-5-mononitrate causes endothelial dysfunction, oxidative stress, and a marked increase in vascular endothelin-1 expression. *Eur Heart J*. 2013;34:3206–3216. doi: 10.1093/eurheartj/ehs100.

30. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263–271. doi: 10.1016/j.jacc.2013.02.092.

31. van Heerebeek L, Hamdani N, Falcão-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ. Low myocardial protein kinase G activity in heart failure with preserved

ejection fraction. *Circulation*. 2012;126:830–839. doi: 10.1161/CIRCULATIONAHA.111.076075.

32. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268–1277. doi: 10.1001/jama.2013.2024.

33. Krüger M, Kötter S, Grützner A, Lang P, Andresen C, Redfield MM, Butt E, dos Remedios CG, Linke WA. Protein kinase G modulates human myocardial passive stiffness by phosphorylation of the titin springs. *Circ Res*. 2009;104:87–94. doi: 10.1161/CIRCRESAHA.108.184408.

34. Münzel T, Daiber A, Gori T. Nitrate therapy: new aspects concerning molecular action and tolerance. *Circulation*. 2011;123:2132–2144. doi: 10.1161/CIRCULATIONAHA.110.981407.

35. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, Marti CN, Yancy CW, Gheorghiade M, Fonarow GC, Konstam MA, Butler J. Nitrate therapy for heart failure: benefits and strategies to overcome tolerance. *JACC Heart Fail*. 2013;1:183–191. doi: 10.1016/j.jchf.2013.03.003.

36. Elkayam U, Roth A, Mehra A, Ostrzega E, Shotan A, Kulick D, Jamison M, Johnston JV, Rahimtoola SH. Randomized study to evaluate the relation between oral isosorbide dinitrate dosing interval and the development of early tolerance to its effect on left ventricular filling pressure in patients with chronic heart failure. *Circulation*. 1991;84:2040–2048.

37. Chrysant SG, Glasser SP, Bittar N, Shahidi FE, Danisa K, Ibrahim R, Watts LE, Garutti RJ, Ferraresi R, Casareto R. Efficacy and safety of extended-release isosorbide mononitrate for stable effort angina pectoris. *Am J Cardiol*. 1993;72:1249–1256.

38. Gunasekara NS, Noble S. Isosorbide 5-mononitrate: a review of a sustained-release formulation (Imdur) in stable angina pectoris. *Drugs*. 1999;57:261–277.

39. Coyne KS, Allen JK. Assessment of functional status in patients with cardiac disease. *Heart Lung*. 1998;27:263–273.

40. Jehn M, Schmidt-Trucksäss A, Hanssen H, Schuster T, Halle M, Koehler F. Association of physical activity and prognostic parameters in elderly patients with heart failure. *J Aging Phys Act*. 2011;19:1–15.

41. Kadhiresan VA, Pastore J, Auricchio A, Sack S, Doelger A, Girouard S, Spinelli JC; PATH-CHF Study Group. Pacing therapies in congestive heart failure. A novel method–the activity log index–for monitoring physical activity of patients with heart failure. *Am J Cardiol*. 2002;89:1435–1437.

42. Jehn M, Schmidt-Trucksäess A, Schuster T, Hanssen H, Weis M, Halle M, Koehler F. Accelerometer-based quantification of 6-minute walk test performance in patients with chronic heart failure: applicability in telemedicine. *J Card Fail*. 2009;15:334–340. doi: 10.1016/j.cardfail.2008.11.011.

43. van den Berg-Emons R, Balk A, Bussmann H, Stam H. Does aerobic training lead to a more active lifestyle and improved quality of life in patients with chronic heart failure? *Eur J Heart Fail*. 2004;6:95–100. doi: 10.1016/j.ejheart.2003.10.005.

44. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG, Paul R. Analysis of daily activity data from implanted cardiac defibrillators: the minimum clinically important difference and relationship to mortality/life expectancy. *World J Cardiovasc Dis*. 2012;2:129–135.

45. Conraads VM, Spruit MA, Braunschweig F, Cowie MR, Tavazzi L, Borggrefe M, Hill MR, Jacobs S, Gerritse B, van Veldhuisen DJ. Physical activity measured with implanted devices predicts patient outcome in chronic heart failure. *Circ Heart Fail*. 2014;7:279–287. doi: 10.1161/CIRCHEARTFAILURE.113.000883.

46. Kawabata M, Fantoni C, Regoli F, Raffa S, Pastori F, Fratini S, Prentice J, Klein HU, Auricchio A. Activity monitoring in heart failure patients with cardiac resynchronization therapy. *Circ J*. 2007;71:1885–1892.

47. Gilliam FR 3rd, Kaplan AJ, Black J, Chase KJ, Mullin CM. Changes in heart rate variability, quality of life, and activity in cardiac resynchronization therapy patients: results of the HF-HRV registry. *Pacing Clin Electrophysiol*. 2007;30:56–64. doi: 10.1111/j.1540-8159.2007.00582.x.

48. Lores V, García-Río F, Rojo B, Alcolea S, Mediano O. Recording the daily physical activity of COPD patients with an accelerometer: an analysis of agreement and repeatability. *Arch Bronconeumol*. 2006;42:627–632.

49. Hecht A, Ma S, Porszasz J, Casaburi R; COPD Clinical Research Network. Methodology for using long-term accelerometry monitoring to describe daily activity patterns in COPD. *COPD*. 2009;6:121–129. doi: 10.1080/15412550902755044.

50. Jehn M, Schmidt-Trucksäss A, Meyer A, Schindler C, Tamm M, Stolz D. Association of daily physical activity volume and intensity with COPD severity. *Respir Med*. 2011;105:1846–1852. doi: 10.1016/j.rmed.2011.07.003.

51. Waschki B, Spruit MA, Watz H, Albert PS, Shrikrishna D, Groenen M, Smith C, Man WD, Tal-Singer R, Edwards LD, Calverley PM, Magnussen H, Polkey MI, Wouters EF. Physical activity monitoring in COPD: compliance and associations with clinical characteristics in a multicenter study. *Respir Med*. 2012;106:522–530. doi: 10.1016/j.rmed.2011.10.022.

52. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309:781–791. doi: 10.1001/jama.2013.905.

53. Wisenberg G, Roks C, Nichol P, Goddard MD. Sustained effect of and lack of development of tolerance to controlled-release isosorbide-5-mononitrate in chronic stable angina pectoris. *Am J Cardiol*. 1989;64:569–576.

54. Svendsen JH, Aldershvile J, Abildgaard U, Amtorp O. Efficacy of controlled-release isosorbide-5-mononitrate as adjunctive treatment to beta-blocking agents in patients with stable angina pectoris. *J Cardiovasc Pharmacol*. 1989;14:358–363.

55. Rinaldi CA, Linka AZ, Masani ND, Avery PG, Jones E, Saunders H, Hall RJ. Randomized, double-blind crossover study to investigate the effects of amlodipine and isosorbide mononitrate on the time course and severity of exercise-induced myocardial stunning. *Circulation*. 1998;98:749–756.

56. Matthew CE. Calibration of accelerometer output for adults. *Med Sci Sports Exerc*. 2005;37:S512–S522.

57. Pizzulli L, Hagendorff A, Zirbes M, Fehske W, Ewig S, Jung W, Lüderitz B. Influence of captopril on nitroglycerin-mediated vasodilation and development of nitrate tolerance in arterial and venous circulation. *Am Heart J*. 1996;131:342–349.

58. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of carvedilol on the prevention of nitrate tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 1998;32:1194–1200.

59. Liuni A, Luca MC, Di Stolfo G, Uxa A, Mariani JA, Gori T, Parker JD. Coadministration of atorvastatin prevents nitroglycerin-induced endothelial dysfunction and nitrate tolerance in healthy humans. *J Am Coll Cardiol*. 2011;57:93–98. doi: 10.1016/j.jacc.2010.07.037.

60. Münzel T, Kurz S, Rajagopalan S, Thoenes M, Berrington WR, Thompson JA, Freeman BA, Harrison DG. Hydralazine prevents nitroglycerin tolerance by inhibiting activation of a membrane-bound NADH oxidase. A new action for an old drug. *J Clin Invest*. 1996;98:1465–1470. doi: 10.1172/JCI118935.

61. Catellier DJ, Hannan PJ, Murray DM, Addy CL, Conway TL, Yang S, Rice JC. Imputation of missing data when measuring physical activity by accelerometry. *Med Sci Sports Exerc*. 2005;37:S555–562.

62. Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. Design, analysis, and presentation of crossover trials. *Trials*. 2009;10:27. doi: 10.1186/1745-6215-10-27.

63. Senn S. *Cross-Over Trials in Clinical Research*, 2nd ed. Chichester, West Sussex, England: John Wiley & Sons Ltd; 2002.

64. Givertz MM, Mann DL, Lee KL, Ibarra JC, Velazquez EJ, Hernandez AF, Mascette AM, Braunwald E. Xanthine oxidase inhibition for hyperuricemic heart failure patients: design and rationale of the EXACT-HF study. *Circ Heart Fail*. 2013;6:862–868. doi: 10.1161/CIRCHEARTFAILURE.113.000394.

65. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS; Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J*. 2005;150:707–715. doi: 10.1016/j.ahj.2004.12.010.

66. Flynn KE, Lin L, Moe GW, Howlett JG, Fine LJ, Spertus JA, McConnell TR, Piña IL, Weinfurt KP. Relationships between changes in patient-reported health status and functional capacity in outpatients with heart failure. *Am Heart J*. 2012;163:88–94.e3. doi: 10.1016/j.ahj.2011.09.027.

67. O'Keeffe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart*. 1998;80:377–382.
68. Handler CE, Sullivan ID. Double-blind randomised crossover trial comparing isosorbide dinitrate cream and oral sustained-release tablets in patients with angina pectoris. *Int J Cardiol*. 1985;7:149–157.
69. Uusitalo A. Long term efficacy of a controlled-release formulation of isosorbide 5-mononitrate (Imdur) in angina patients receiving beta-blockers. *Drugs*. 1987;33(suppl 4):111–117.
70. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med*. 1998;338:520–531. doi: 10.1056/NEJM199802193380807.
71. Thompson WG, Kuhle CL, Koepp GA, McCrady-Spitzer SK, Levine JA. "Go4Life" exercise counseling, accelerometer feedback, and activity levels in older people. *Arch Gerontol Geriatr*. 2014;58:314–319. doi: 10.1016/j.archger.2014.01.004.

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## Heart Failure

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