Supplementary Online Content

Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction. *JAMA*. 2013;309(12):1268-1277.

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

1. E-Table 1.0: RELAX Trial Entry Criteria

Inclusion criteria

1. Age > 18 years
2. Previous clinical diagnosis of HF (see Appendix 22.2) with current NYHA Class II-IV symptoms
3. Must have had at least one of the following within the 12 months prior to consent
    a. Hospitalization for decompensated HF
    b. Acute treatment for HF with intravenous loop diuretic or hemofiltration
    c. Chronic treatment with a loop diuretic for control of HF symptoms + chronic diastolic dysfunction on echocardiography as evidenced by left atrial enlargement
    d. Mean pulmonary capillary wedge pressure > 15 mmHg or LV end diastolic pressure (LVEDP)>18 mmHg at catheterization for dyspnea
4. EF $\geq$ 50% on a clinically indicated echocardiogram or ventriculogram *within 12 months* prior to consent, in the absence of a change in cardiovascular status.
5. Stable medical therapy for 30 days as defined by:
    a. No addition or removal of ACE, ARB, beta-blockers, or calcium channel blockers (CCBs)
    b. No change in dosage of ACE, ARBs, beta-blockers or CCBs of more than 100%
6. Meet screening criteria
    a. VO_2 peak $\leq$ 60% normal value (see section 11: Screening Procedures) *with respiratory exchange ratio (RER) $\geq$ 1.0.*
    b. One of the following:
        i. NT-proBNP $\geq$ 400 pg/ml
        ii. NT-proBNP < 400 with mean pulmonary capillary wedge pressure (PCWP) > 20 mmHg at rest or > 25 mmHg with exercise.measured in proximity (within 2 weeks before or after) to the NT-proBNP level

Exclusion criteria

1. Have a neuromuscular, orthopedic or other non-cardiac condition that prevents patient from exercise testing on a bicycle ergometer or from walking in a hallway
2. Non-cardiac condition limiting life expectancy to less than one year, per physician judgment
3. Current or anticipated future need for nitrate therapy
4. Valve disease (> mild aortic or mitral stenosis; > moderate aortic or mitral regurgitation)
5. Hypertrophic cardiomyopathy
6. Infiltrative or inflammatory myocardial disease (amyloid, sarcoid)
7. Pericardial disease
8. Primary pulmonary arteriopathy
9. Have experienced a myocardial infarction or unstable angina, or have undergone percutaneous transluminal coronary angiography (PTCA) or coronary artery bypass grafting (CABG) within *60 days* prior to consent, or requires either PTCA or CABG at the time of consent
10. Other clinically important causes of dyspnea such as morbid obesity or significant lung disease defined by clinical judgment or use of steroids or oxygen for lung disease
11. Systolic blood pressure < 110 mmHg or > 180 mm Hg
12. Diastolic blood pressure < 40 mmHg or > 100 mmHg
13. Resting heart rate (HR) > 100 bpm
14. A history of reduced ejection fraction (EF<50%)
15. Implanted metallic device which will interfere with MRI examination (in patients without atrial fibrillation)
16. Severe renal dysfunction (estimated GFR < 20 ml/min/1.73m^2 by modified MDRD equation)
    GFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if African American) (conventional units)
17. Women of child bearing potential who do not have a negative pregnancy test at study entry and who are not using effective contraception

18. Hemoglobin <10 g/dL
19. Patients taking alpha antagonists or cytochrome P450 3A4 inhibitors (ketoconazole, itraconazole, erythromycin, saquinavir, cimetidine or serum protesase inhibitors for HIV).
20. Patients with retinitis pigmentosa, previous diagnosis of nonischemic optic neuropathy, untreated proliferative retinopathy or unexplained visual disturbance
21. Patients with sickle cell anemia, multiple myeloma, leukemia or penile deformities placing them at risk for priapism (angulation, cavernosal fibrosis or Peyronie's disease)
22. Patients with severe liver disease (AST > 3x normal, alkaline phosphatase or bilirubin > 2x normal)
23. Consistent with ACC/AHA guidelines, persons with dyspnea and risk factors for coronary artery disease, should have had a stress test and those patients with a clinically indicated stress test demonstrating significant ischemia within a year prior to enrollment would be excluded
24. Listed for cardiac transplantation

Up to 58 patients with chronic atrial fibrillation will be enrolled in the study. Once 58 patients with chronic atrial fibrillation have been enrolled, the DCC and DSMB will review the characteristics (atrial fibrillation versus sinus rhythm) of all patients enrolled, and will increase this limit (if needed) to insure adequate enrollment to address the primary endpoint.

2. e-Methods

The % predicted peak VO_2 used for entry criteria was calculated based on published age and sex specific normative values.[1] The % predicted 6MWD was calculated using an age, sex and body size specific formula.[2] The presence of chronotropic incompetence (CI) was ascertained using standard predicted maximal heart rate (220-age) and beta blocker adjusted criteria for CI ($HR_{peak} - HR_{rest}$)/(predicted maximal HR – Rest HR)) < 0.80 and < 0.63 if on beta blocker.[3]

Partition values for LV hypertrophy based on LV mass/ body surface area can underestimate the prevalence of LV hypertrophy in patients with obesity.[4] Given the high prevalence of obesity in the study population, the presence of LV hypertrophy (LV mass/height$^{1.7}$ > 95th percentile) was determined from published sex specific normal values for LV mass allometrically scaled to height as measured by echocardiography or CMR.[4]

Sildenafil drug levels were measured by liquid-liquid extraction, LC-MS/MS, (High Standards Products, North Wales, PA).

3. e-Table 2: Biomarker Reference Ranges

Biomarker	Reference Range in Normals
Creatinine (Roche Diagnostics)	0.51-1.17 mg/dL
Cystatin-C (Seimens)	0.53 - 0.95 mg/L
NT-proBNP (Roche Diagnostics)	125 - 450 pg/mL
Aldosterone (Diasorin)	7.5 - 150 pg/mL
Endothelin-1 (R&D)	0.4 – 2.0 pg/mL
NT-procollagen III peptide (Orion Diagnostics)	2.3 – 6.4 ug/L
Uric acid (Roche Diagnostics)	2.4 – 7.0 mg/dL

4. e-Table 3: Pre-specified subgroup analysis of change in peak VO2 (ml/kg/min) at 24 weeks according to baseline characteristics or study drug use at 24 weeks. Data are shown as median (Interquartile range).

	Placebo	Sildenafil	P value
On study drug at week 24[†]	n=92	n=86	
	-0.20 (-0.70,1.05)	-0.05 (-1.70,1.11)	0.92
LV hypertrophy by CMR			
No	n=40	n=39	
	-0.13 (-0.77,1.15)	-0.20 (-2.12,1.20)	0.85
Yes	n=13	n=13	
	-0.45 (-1.05, 0.23)	-0.40 (-0.63, 1.20)	0.29
PASP			
< 40 mmHg	n=32	n=22	
	-0.25 (-1.38, 1.00)	0.53 (-1.50, 2.40)	0.39
≥ 40 mmHg	n=35	n=27	
	-0.30 (-0.54, 0.60)	-0.20 (-2.25, 0.70)	0.40
NT-proBNP			
< 400 pg/ml	n=31	n=31	
	0.35 (-1.30, 1.20)	-1.50 (-1.90, 1.05)	0.64
≥ 400 pg/ml	n=61	n=60	
	-0.25 (-0.65, 1.00)	0.28 (-1.03, 1.16)	0.84
Atrial fibrillation at entry			
Yes	n=29	n=32	
	-0.20 (-0.50, 1.30)	-0.15 (-1.70, 0.83)	0.32
No	n=65	n=59	
	-0.20 (-0.83, 0.75)	-0.20 (-1.70, 1.25)	0.69
Beta blocker therapy			
Yes	n=69	n=70	
	-0.25 (-0.65, 1.00)	0.08 (-1.80, 1.20)	0.78
No	n=25	n=21	
	0.23 (-1.05, 1.00)	-0.70 (-0.65, 1.00)	0.99
ACE or ARB therapy			
Yes	n=76	n=60	
	-0.23(-0.77, 1.05)	-0.05(-1.50, 1.20)	0.59
No	n=18	n=31	
	-0.04 (-0.60, 1.00)	-0.50 (-2.30, 1.00)	0.29

Statin Therapy			
Yes	n=61	n=54	
	-0.20 (-0.60, 1.00)	-0.05 (-1.60, 1.00)	0.81
No	n=33	n=37	
	-0.35 (-0.70, 0.75)	-0.45 (-2.12, 1.20)	0.87
Gender			
Female	n=52	n=51	
	-0.33 (-0.77, 1.00)	-0.55 (-1.85, 1.11)	0.89
Male	n=42	n=40	
	-0.15 (-0.65, 1.20)	0.20 (-1.45, 1.25)	0.75

[†]Of patients alive and still in the study at 24 weeks, some patients still on study drug did not have primary endpoint data because they were either too sick to perform CPXT, were able but unwilling to perform CPXT or had inadequate peak VO_2 data for core lab interpretation.

5. e-table 4: Adverse events occurring in at least 5% of patients in either treatment group: Patients may have had more than one adverse event. Data shown as % (n)

	Placebo (n=103)	Sildenafil (n=113)	P value
Cardiac	19% (20)	23% (26)	0.62
Heart Failure	8% (8)	12% (14)	0.37
Acute Heart Failure	3% (3)	4% (4)	1.00
Ear, nose, throat	5% (5)	5% (6)	1.00
Eye	9% (9)	13% (15)	0.39
Gastrointestinal	15% (15)	23% (23)	0.29
Infection	14% (14)	20% (23)	0.21
Injury	7% (7)	8% (9)	0.80
Laboratory or exam abnormality	8% (8)	12% (14)	0.37
Metabolic or nutritional abnormality	8% (8)	7% (8)	1.00
Musculoskeletal	14% (14)	12% (12)	0.54
Central nervous system	28% (29)	32% (36)	0.66
dizziness	11% (11)	8% (9)	0.64
headache	16% (16)	24% (27)	0.13
Respiratory	10% (10)	13% (15)	0.52
Dermatologic	11% (11)	10% (11)	0.83
Vascular	8% (8)	20% (23)	0.011
flushing	3% (3)	8% (9)	0.14
hypotension	1% (1)	8% (9)	0.020
Genitourinary	2% (2)	5% (6)	0.28

6. e-Table 5: Serious adverse events exclusive of death and cardiovascular or cardiorenal hospitalization: Patients may have had more than one serious adverse event. Data shown as % (n)

	Placebo (n=103)	Sildenafil (n=113)	P value
Anemia	0% (0)	1% (1)	1.00
Cardiac	13% (13)	14% (16)	0.84
Heart Failure	7% (7)	8% (9)	0.80
Acute Heart Failure	3% (3)	2% (2)	0.67
Hereditary Hemorrhagic Telangiectasia	0% (0)	1% (1)	1.00
Non-cardiac chest pain	0% (0)	1% (1)	1.00
Visual impairment	0% (0)	2% (2)	0.50
Gastrointestinal bleeding	0% (0)	3% (3)	0.25
Hernia	1% (1)	0% (0)	0.48
Cholecystitis	1% (1)	0% (0)	0.48
Infection	1% (1)	5% (6)	0.12
Toxicity	0% (0)	1% (1)	1.00
Toxicity	0% (0)	1% (1)	1.00
Increased International Normalized Ratio	0% (0)	1% (1)	1.00
Weight gain	0% (0)	1% (1)	1.00
Metabolic or nutritional abnormality	2% (2)	4% (4)	0.69
Cancer	1% (1)	1% (1)	1.00
Central nervous system	2% (2)	3% (3)	1.00
syncope	0% (0)	2% (2)	0.50
Respiratory	1% (1)	2% (2)	1.00
Vascular	3% (3)	1% (1)	0.35
hypotension	0% (0)	1% (1)	1.00
Genitourinary	0% (0)	1% (1)	1.00

7. e-Table 6: Characteristics of patients with and without primary endpoint data at 24 weeks

Variable [median (IQR)] or count (%)	Included in the complete-case primary analysis N=185	Not included in the complete-case primary analysis N=31	P-value†
Age*	68 (62, 76)	76 (64, 81)	0.12
Minnesota Living with Heart Failure*	43 (29, 63)	44 (30, 58)	0.58
Systolic Blood Pressure*	126 (113, 138)	124 (112, 138)	0.85
GFR*	58 (42, 76)	56 (45, 65)	0.39
NT-proBNP*	633 (221, 1528)	1207 (633, 2059)	0.028
Female	92 (49.7)	12 (38.7)	0.25
NHYA Class III	100 (54.1)	15 (48.4)	0.56
1+ HF hospitalizations in prior year	68 (36.8)	11 (35.5)	0.89
Hypertension	155 (83.8)	28 (90.3)	0.43
Non-ischemic etiology	115 (62.6)	17 (54.8)	0.44
Afib / Aflutter on ECG	124 (67.0)	13 (41.9)	0.009
Diabetes	79 (42.7)	14 (45.2)	0.80
COPD	36 (19.5)	6 (19.4)	0.99
Anemia	63 (34.2)	13 (41.9)	0.41
† Wilcoxon rank-sum test for continuous and Chi-square test for categorical			

8. References

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