

## Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction in Patients With Preserved Ejection Fraction

### The Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction (SIDAMI) Trial

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**Background**—Diastolic dysfunction is frequently seen after myocardial infarction and is characterized by a disproportionate increase in filling pressure during exercise to maintain stroke volume. We hypothesized that sildenafil would reduce filling pressure during exercise in patients with diastolic dysfunction after myocardial infarction.

**Methods and Results**—Seventy patients with diastolic dysfunction and near normal left ventricular ejection fraction on echocardiography were randomly assigned sildenafil 40 mg thrice daily or matching placebo for 9 weeks. Before randomization and after 9 weeks of treatment patients underwent simultaneous echocardiography and right heart catheterization at rest and during exercise. Primary end point was pulmonary capillary wedge pressure, and secondary end points comprised cardiac index and pulmonary arterial pressure at rest and during exercise after 9 weeks. After 9 weeks there were no differences in pulmonary capillary wedge pressure at rest ( $13\pm 4$  versus  $13\pm 3$  mmHg,  $P=0.25$ ) or at peak exercise ( $35\pm 8$  mmHg versus  $31\pm 7$  mmHg,  $P=0.07$ ). However, with treatment cardiac index increased at rest ( $P=0.006$ ) and peak exercise ( $P=0.02$ ) in the sildenafil group, and systemic vascular resistance index (resting,  $P=0.0002$ ; peak exercise,  $P=0.007$ ) and diastolic blood pressure (resting,  $P=0.005$ ; peak exercise,  $P=0.02$ ) were lower in the sildenafil group. Resting left ventricular end-diastolic volume index increased ( $P=0.001$ ) within the sildenafil group but was unchanged in the placebo group.

**Conclusions**—Sildenafil did not decrease filling pressure at rest or during exercise in post-myocardial infarction patients with diastolic dysfunction. However, there were effects on secondary end points, which require further studies.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov/ct2/show/NCT01046838>. Unique identifier: NCT01046838. (*Circulation*. 2013;127:1200-1208.)

**Key Words:** cardiac catheterization ■ echocardiography ■ exercise ■ myocardial infarction

Clinical evidence of heart failure (HF) is a consistent and powerful predictor of outcome in patients after myocardial infarction (MI).<sup>1</sup> HF after MI reflects elevated left ventricular (LV) filling pressures, which are frequently observed despite apparently minor myocardial damage, with little overall effect on LV ejection fraction (LVEF). The pathophysiological mechanisms are incompletely understood but involve impaired relaxation and decreased LV chamber compliance, hence, abnormalities in diastolic function. Observational studies suggest that patients with preserved LVEF and diastolic dysfunction post MI has a worse prognosis than patients with infarcts of similar size but no diastolic dysfunction.<sup>2</sup> Abnormal LV diastolic

function is characterized by a disproportionate increase in filling pressure with exercise,<sup>3-5</sup> especially when chamber compliance is decreased. In case of increased LV filling pressures, left atrial (LA) pressure is elevated, exposing the pulmonary vascular bed to the increased pressure. In accordance, pulmonary arterial pressure (PAP) is frequently increased after MI,<sup>4</sup> and also associated with increased mortality and morbidity after MI, independent of LVEF.<sup>2</sup> Although there are robust data to support specific therapies for systolic dysfunction after MI,<sup>6</sup> the optimal management of patients with presumed diastolic dysfunction and especially those with preserved LVEF is unknown. Because hemodynamic abnormalities caused by diastolic dysfunction

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are believed to drive the progression from an asymptomatic stage to symptomatic heart failure, therapies that lower LV filling pressure or increase LV chamber compliance might attenuate this evolution and reduce the incidence of overt heart failure after MI.

**Clinical Perspective on p 1208**

Sildenafil is a potent and selective phosphodiesterase-5 (PDE-5) inhibitor that suppresses degradation of cyclic guanosine monophosphate. Sildenafil attenuates myocardial maladaptive remodelling in pressure overload states,<sup>7,8</sup> improves endothelium dependent vasodilation,<sup>9,10</sup> and has positive hemodynamic effects without causing systemic hypotension in a wide variety of patient populations.<sup>8,10-15</sup> These effects could likely be beneficial after MI, and thus we hypothesized that PDE-5 inhibition would improve central hemodynamics (reduce pulmonary capillary wedge pressure [PCWP]), increase cardiac index (CI), and reduce PAP at rest and during exercise in patients with diastolic dysfunction after MI.

**Methods**

**Study Design**

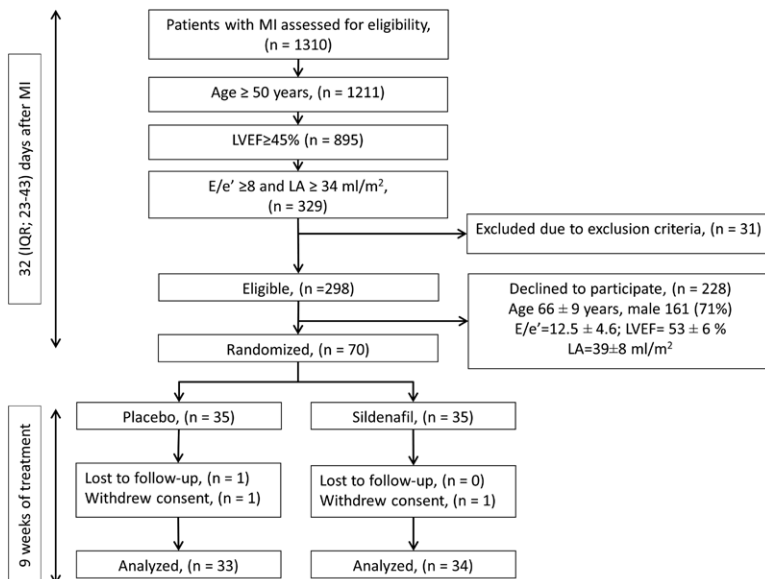
In a randomized, double-blind, placebo-controlled study, male or non-pregnant females aged ≥50 years with a recent documented MI, diastolic dysfunction, and LVEF ≥45% on echocardiography performed within 48 hours of the MI were enrolled. Diastolic dysfunction was defined as the ratio of early diastolic peak mitral inflow velocity (E) to early mitral annulus diastolic velocity (e') ratio > 8 and at least moderate LA dilatation (LA volume index >34 mL/m<sup>2</sup>).<sup>16,17</sup> Patients with permanent atrial fibrillation, known history of cardiomyopathy, more than mild valvular heart disease, obstructive or restrictive pulmonary disease, inability to perform exercise testing, and those with inadequate acoustic windows were excluded (Figure 1). As part of standard management of MI an urgent coronary angiogram was performed in all patients, which was performed before echocardiography in all patients. Revascularization was performed at the discretion of the attending invasive cardiologist. Patients with residual stenosis >60% in any epicardial coronary arteries and those referred for coronary bypass surgery were not eligible.

Subjects were randomized in a 1:1 double-blind fashion to receive sildenafil or matching placebo using a computer-generated randomization schedule prepared before study start. Compliance was assessed by pill count, and adequate compliance was defined as adherence to medication >80%.<sup>18</sup> The ethics Committee for the Capital Region Copenhagen approved the trial protocol (ID: H-A-2009-023). All patients provided written informed consent, and the study was registered with ClinicalTrials.gov (ID: NCT 01046838). The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and was monitored externally by the Copenhagen GCP unit.

Before randomization (baseline), spirometry, blood testing, comprehensive resting Doppler echocardiography, resting right heart catheterization, 6-minute walk test, and symptom-limited supine cycle exercise test with simultaneous echocardiography and right heart catheterization were performed. Estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease formula.<sup>19</sup> After randomization subjects were given 20 mg sildenafil thrice daily or matching placebo. After 1 week of treatment, the dose of sildenafil was increased to the target dose of 40 mg thrice daily or matching placebo. After 9 weeks treatment, echocardiography, right heart catheterization, and exercise test were repeated.

**Echocardiography**

Resting and exercise echocardiography was performed by an experienced echocardiographer using a Philips iE33 (Philips Healthcare, Best, The Netherlands) cardiac ultrasound system. Images were stored digitally for offline analysis using Philips Xcelera analysis software version 3.1 (Philips Healthcare). LV volumes and LVEF were assessed using the Simpson modified rule from the apical 4 and 2 chamber views. LA maximal volume was estimated from the apical 4- and 2-chamber views using the area length method. Mitral inflow was assessed in the apical 4-chamber view with the pulsed wave Doppler sample volume placed at the tips of mitral leaflets during diastole. From the inflow, peak E wave velocity was measured. Mitral annular motion was assessed using pulsed wave tissue Doppler with the sample volume placed in the septal and lateral mitral annulus. The mean of the septal and lateral e' velocity was used for calculation of E/e'. Wall motion scores were assessed semiquantitatively using the standard 16 segmental model in accordance with current guidelines.<sup>16</sup> For Doppler recordings the average of 3 to 5 consecutive beats were measured using a horizontal sweep of 75 to 100 cm/s. The analyses were performed blinded to allocated treatment and to invasive measurements.



**Figure 1.** Consort diagram depicting the flow of participants through the Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction (SIDAMI) trial. LA indicates left atrial; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and IQR, interquartile range.

## Invasive Hemodynamic Measurements

Right heart catheterization was performed using a standard 7.5-F triple lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, CA). The catheter was introduced guided by ultrasound under local anesthesia using the Seldinger technique into the right internal jugular vein and advanced to the pulmonary artery. PCWP, right atrial pressure (RAP), systolic PAP, diastolic PAP, mean PAP, and cardiac output were measured at each level of exercise until exhaustion and after 5 minutes of rest. PCWP at rest and post exercise was measured at end-expiration. During exercise PCWP was averaged over 10 seconds. Cardiac output was measured using thermodilution as the average of 3 measurements with  $\leq 10\%$  variance. The pressure difference between LV diastolic pressure and pericardial pressure (transmural filling pressure) was estimated as the difference between PCWP and RAP.<sup>20–22</sup> Cardiac output and stroke volume (SV) were indexed to body surface area as CI and stroke volume index (SVI). Pulmonary vascular resistance index was calculated as follows:  $80 \times (\text{mean PAP} - \text{PCWP}) / \text{CI}$ . Systemic vascular resistance index was calculated as follows:  $80 \times (\text{mean arterial pressure} [\text{MAP}] - \text{RAP}) / \text{CI}$ . LV stroke Work Index was calculated as  $\text{SVI} \times (\text{MAP} - \text{PCWP}) \times 0.0136$ . At rest and at maximal exercise a central venous blood sample was drawn from the pulmonary artery and analyzed for lactate concentration, mixed venous oxygen saturation and pH. Arterial and venous oxygen content was calculated as follows:  $\text{Hemoglobin (g/dL)} \times 1.34 (\text{mLO}_2/\text{g hemoglobin}) \times \text{SatO}_2$ . Arterio-venous difference ( $a-v\text{O}_2$ ) was calculated as arterial oxygen content – venous oxygen content.

## Exercise Protocol

All patients performed a multistage symptom-limited supine cycle ergometer exercise test using an Echo Cardiac Stress Table (Lode B.V., The Netherlands). Workload started at 0 watt and increased by 25 watts every 2 minutes. Patients were encouraged to exercise until exhaustion (Borg $>18$ ).<sup>23</sup> Brachial blood pressure was measured by sphygmomanometry at baseline and at every 2 minutes until maximum workload was reached and repeated after 5 minutes of rest.

## End Points

The primary end points were resting and peak exercise PCWP after 9 weeks treatment. Secondary end points were resting and peak exercise CI and PAP after 9 weeks of treatment.

## Statistical Analysis

No reference data exist on pulmonary artery pressure or pulmonary capillary wedge pressure at exercise in a similar population. The sample size was therefore determined based on  $E/e'$ . With a standard deviation in  $E/e'$  of 5,<sup>24</sup>  $\alpha = 0.05$  and  $\beta = 0.80$ , a sample size of 60 patients allowed for the detection of a difference in  $E/e'$  of 3.6. After enrollment of 10 patients confirmatory sample-size estimation was performed based on PCWP. In this group peak-exercise PCWP was  $35 \pm 5$  mmHg. Based on these conservative cross sectional, 60 patients were needed to detect a true difference in PCWP of 4 mmHg with a power of 0.8, which was considered clinically relevant. To account for dropouts and noncompliance a sample size of 70 patients was enrolled.

Data are presented as mean $\pm$ SD or median (interquartile range) unless otherwise indicated. Normally distributed within-individual changes from baseline to follow-up were evaluated using the paired  $t$  test. Between-group differences from baseline to follow-up were evaluated using both a standard  $t$  test and a general linear model with treatment as fixed effect and baseline value as a covariate to adjust for small differences between groups at baseline due to small sample size. Estimated differences between groups are presented with 95% confidence limits (CL). For non-Gaussian distributed variables non-parametric rank sum test was used. Intention-to-treat analysis was performed for all variables. A probability value  $<0.05$  was considered

significant. Statistical analyses were performed using SAS version 9.2 (Cary, NC).

## Results

Seventy patients were randomized 32 (interquartile range, 23–43) days after admission for MI (Figure 1); 35 patients were randomized to receive sildenafil and 35 to receive placebo. Baseline characteristics for both groups are presented in Table 1. All subjects were on stable medications and free of angina, and were in New York Heart Association class I or II. At follow-up concomitant pharmacological treatment was unchanged in all but 4 patients in the placebo and 2 in the sildenafil group. In the sildenafil group 1 patient discontinued low-dose  $\beta$ -blocker treatment, and in both groups 1 patient discontinued ACE and calcium inhibitors due to presumed

**Table 1. Baseline Demographic and Clinical Characteristics and Cardiovascular Parameters in the Placebo and Sildenafil Groups**

	Placebo	Sildenafil
Age, y	62 $\pm$ 7	63 $\pm$ 8
Time from MI to randomization, d (IQR)	31 (22–42)	33 (23–43)
Male, n (%)	30 (86%)	31 (89%)
BMI, kg/m <sup>2</sup>	28 $\pm$ 5	27 $\pm$ 4
BSA, m <sup>2</sup>	2.1 $\pm$ 0.2	2.0 $\pm$ 0.2
Current smokers, n (%)	11 (31%)	7 (20%)
Hypertension, n (%)	15 (43%)	18 (51%)
Diabetes mellitus, n (%)	3 (9%)	3 (9%)
Drug therapy		
Diuretics, n (%)	2 (6%)	3 (9%)
$\beta$ -Blockers, n (%)	34 (97%)	27 (77%)
ACEI/ARB, n (%)	14 (40%)	9 (26%)
CA <sup>2+</sup> blockers, n (%)	5 (14%)	8 (23%)
Statins, n (%)	35 (100%)	35 (100%)
STEMI, n (%)	30 (86%)	30 (86%)
RCA culprit, n (%)	14 (40%)	20 (57%)
LCX culprit, n (%)	7 (20%)	5 (14%)
LAD culprit, n (%)	14 (40%)	10 (28%)
Multi vessel disease, (%)	3 (9%)	7 (20%)
Max TnT, $\mu\text{g/L}$ , median (IQR)	1280 (620–6000)	2680 (1250–5780)
FEV1 (l/min)	3.0 $\pm$ 0.7	3.0 $\pm$ 0.6
FEV1 (% of expected)	89 $\pm$ 14	96 $\pm$ 16
TAPSE, cm	2.6 $\pm$ 0.4	2.6 $\pm$ 0.4
E/A ratio	1.1 $\pm$ 0.4	1.1 $\pm$ 0.4
$E/e'$	10.8 $\pm$ 2.6	11.2 $\pm$ 2.7

Data are presented as mean $\pm$ SD, n (%) unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; BMI, body mass index; BSA, body surface area; E/A, ratio between early (E) and late (A) transmitral filling velocity;  $E/e'$ , ratio between early (E) transmitral filling velocity and early diastolic tissue Doppler velocity ( $e'$ ); FEV1, forced expiratory volume; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; TAPSE, tricuspid annular plane systolic excursion; and TnT, Troponin-T.

side effects. In the sildenafil group 1 patient initiated ACE inhibitor treatment, and in the placebo group 1 initiated diuretics and 1 patient initiated a calcium channel inhibitor.

**Resting Hemodynamic Variables**

**Primary End Point**

At baseline, resting central hemodynamic values were similar in the sildenafil and the placebo group (Table 2). After 9 weeks of treatment, there were no significant differences within or between group changes in resting unadjusted PCWP (-0.6±4.1 versus +0.6±3.6 mm Hg, P=0.25; Figure 2, placebo and sildenafil, respectively) or after adjustment of

prerandomization PCWP (-0.5 mm Hg; 95% CL, -2.2 to +1.2 mm Hg; P=0.56).

**Secondary End Points**

From baseline to follow-up there was a significant increase in CI in the sildenafil group compared with placebo (+0.2±0.4 versus -0.1±0.5 L/min/m<sup>2</sup>, P=0.02; Figure 3). CI remained higher in the sildenafil group after adjustment of prerandomization CI (+0.2 L/min/m<sup>2</sup>; 95% CL, +0.1 to +0.4 L/min/m<sup>2</sup>; P=0.006). There were no significant differences within or between groups in resting unadjusted or adjusted mean PAP or pulmonary vascular resistance index. Diastolic blood pressure (P=0.02), MAP (P=0.05), and systemic vascular resistance

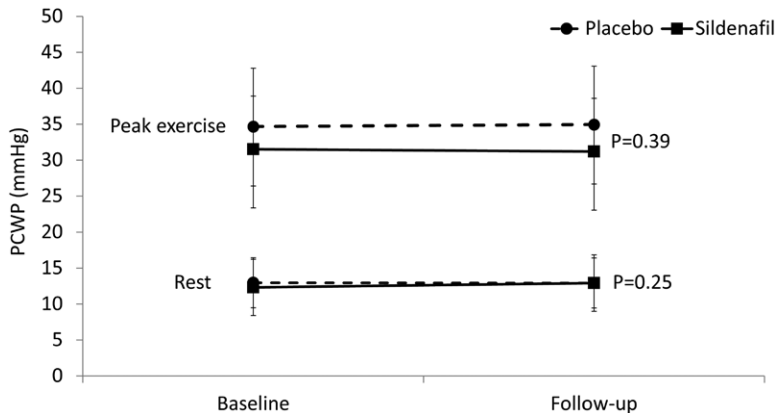
**Table 2. Exercise-Induced Changes in Invasive Hemodynamics and LV Volumes From Rest to Peak Exercise at Baseline**

	Placebo				Sildenafil			
	Baseline		Follow-Up		Baseline		Follow-Up	
	Rest	Peak Exercise	Rest	Peak Exercise	Rest	Peak Exercise	Rest	Peak Exercise
HR	62±11	124±16	59±9	119±18	61±10	124±17	59±9	123±17
Systolic BP, mm Hg	136±23	195±28	136±17	188±32	137±16	182±22	131±17	180±27
Diastolic BP, mm Hg	76±13	95±21	77±11	96±23	76±10	93±14	72±8*†	83±15*†
MAP, mm Hg	90±14	117±18	92±11	114±23	90±9	113±12	86±9*†	104±15†
CI, L/min/m <sup>2</sup>	2.7±0.7	7.5±1.5	2.6±0.4	7.0±1.3	2.6±0.6	7.5±1.5	2.8±0.5*†	7.8±1.4*
RAP, mm Hg	7±2	15±6	8±3	15±6	6±3	12±5	7±2	12±6
sPAP, mm Hg	27±6	62±12	28±6	63±13	26±5	57±13	26±6	58±13
dPAP, mm Hg	15±4	37±9	15±4	38±8	14±4	34±8	15±4	34±10
mPAP, mm Hg	20±5	49±10	21±4	50±8	19±5	44±9	20±4	44±10
PCWP, mm Hg	13±3	35±8	13±4	35±8	12±4	31±7	13±3	31±8
TMP, mm Hg	6±3	20±7	6±3	20±8	6±3	19±5	6±3	18±4
Watts		126±31		137±37		134±42		135±37
pH, mixed venous	7.40±0.02	7.23±0.07	7.40±0.02	7.23±0.06	7.41±0.02	7.25±0.06	7.41±0.02	7.24±0.06
SVO <sub>2</sub> , %	70±4	34±9	70±4	34±12	70±4†	38±14	71±5†	37±13
a-vO <sub>2</sub> difference, mL/dL	5.02±0.66	12.44±1.91	5.16±0.75	12.51±2.50	4.94±0.83	11.52±2.66	4.75±0.71*	11.86±2.60
Lactate, mmol/l	0.96±0.43	8.10±2.94	0.88±0.25	7.95±2.83	0.86±0.34	8.09±3.07	0.91±0.45	7.73±2.67
SVRI, dynes m <sup>2</sup> /sec cm <sup>-5</sup>	2633±801	1165±324	2660±587	1222±336	2646±552	1101±278	2269±467*†	993±181*
PVRI, dynes m <sup>2</sup> /sec cm <sup>-5</sup>	220±77	157±66	229±82	174±75	207±71	135±61	192±74	142±52
LVEDV Indexed, ml/m <sup>2</sup>	64±13	62±13	65±15	60±14	60±9	60±11	66±10†	59±11
LVESV Indexed, ml/m <sup>2</sup>	28±8	24±8	27±9	22.5±9.5	27±5	24±7	27±8	23±8
SV Indexed, ml/m <sup>2</sup>	36±7	38±8	38±9	37±10	33±7	36±6	39±8†	36±9
LVEF, %	56±7	61±7	59±8	63±10	55±6	59±7	60±9†	62±11
WMS	1.3±0.2	-	1.2±0.2	-	1.3±0.2	-	1.2±0.2	-
LA volume index, ml/m <sup>2</sup>	44±11	-	49±11	-	43±11	-	49±10†	-
LV mass index, g/m <sup>2</sup>	93±20	-	91±18	-	93±19	-	95±20	-
LVSWI, gm-m/beat	37.7±10.5	41.8±13.0	41.4±11.7	40.5±16.0	35.2±9.6	40.8±9.4	38.9±10.3	35.2±12.0
6 MWT, m	558±72	-	589±73†	-	568±77	-	589±83†	-
Nt-Pro-BNP, pg/L Median (IQR)	408 (236–846)	-	290 (140–363)†	-	576 (298–833)	-	293 (185–404)†	-
eGFR, ml/ m <sup>2</sup> /min	89±17	-	91±17	-	92±21	-	94±22	-

Data are presented as mean±SD. For between-group comparisons: \*P<0.05 sildenafil and placebo adjusted. For within group comparisons: †P<0.05; 6 MWT, 6-minute walk distance. BP indicates blood pressure; CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; IQR, interquartile range; LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVSWI, left ventricular stroke work index; MAP, mean artery pressure; mPAP, mean pulmonary arterial pressure; NT-ProBNP, N-terminal probrain natriuretic peptide; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SV, stroke volume derived from echocardiography; SVO<sub>2</sub>, mixed venous oxygen saturation; SVRI, systemic vascular resistance index; TMP, left ventricular transmural filling pressure; and WMS, wall motion score.

There were no differences between resting baseline values for placebo and sildenafil, all P>0.05.





**Figure 2.** Pulmonary capillary wedge pressure (PCWP) at rest and peak exercise from baseline to follow-up for placebo (dashed line and circle) and sildenafil (solid line and square). The error bars represent standard deviation. Statistical evaluations were performed using ANCOVA.

index ( $P=0.005$ ) were lower in the sildenafil group compared with placebo. This result did not change when adjusting for baseline values; the estimated mean difference was significantly lower for diastolic blood pressure ( $-6$  mmHg; 95% CL,  $-9$  to  $-2$  mmHg;  $P=0.005$ ), MAP ( $-5$  mmHg; 95% CL,  $-10$  to  $-1$  mmHg;  $P=0.01$ ), and systemic vascular resistance index ( $-390$  dynes. $\text{m}^2/\text{sec}.\text{cm}^{-5}$ ; 95% CL,  $-589$  to  $-192$  dynes. $\text{m}^2/\text{sec}.\text{cm}^{-5}$ ;  $P=0.0002$ ). Left ventricular end-diastolic volume index (LVEDVI) increased mean  $+6$  mL/ $\text{m}^2$  (95% CL,  $+3$  to  $+10$  mL/ $\text{m}^2$ ,  $P=0.001$ ) within the sildenafil group whereas LVEDVI did not change within the placebo group ( $+0$  mL/ $\text{m}^2$ ; 95% CL,  $-4$  to  $+4$  mL/ $\text{m}^2$ ,  $P=0.92$ , Figure 4). As a consequence of the different effect of sildenafil on LVEDVI there was a significant increase in SVI in the sildenafil group after 9 weeks of treatment when measured both by echocardiography ( $+6$  mL/ $\text{m}^2$ ; 95% CL,  $+3$  to  $+9$  mL/ $\text{m}^2$ ;  $P=0.0005$ ) and by thermodilution ( $+4$  mL/ $\text{m}^2$ ; 95% CL,  $+2$  to  $+7$  mL/ $\text{m}^2$ ;  $P=0.0006$ ). This enhancement in stroke volume and cardiac output with sildenafil coupled with a reduction in a- $\text{vO}_2$  difference compared with placebo between groups ( $4.75\pm 0.71$  versus  $5.16\pm 0.75$  mL/100mL,  $P=0.03$ ). There were no within- or between-group differences in RAP, N-terminal probrain natriuretic peptide or estimated glomerular filtration rate, right ventricular function (TAPSE),  $E/e'$ , LV mass, E-, A- velocities, or E deceleration time after 9 weeks of treatment (Table 2).

**Exercise Hemodynamic Variables**

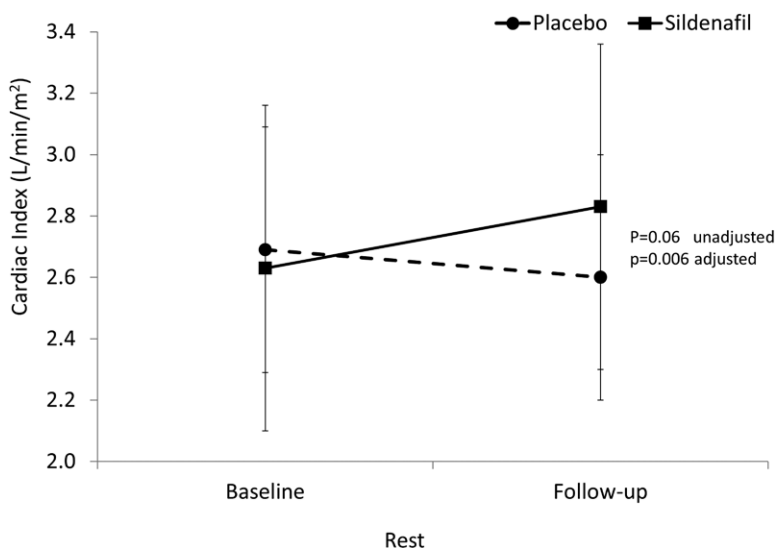
With exercise all subjects reached the anaerobic threshold as evidenced by significant increase in mixed venous blood lactate and significant drop in pH with no between-group differences (Table 2). There was no difference between groups in achieved watts during exercise at baseline ( $P=0.42$ ) or at follow-up ( $P=0.84$ ).

**Primary End Point**

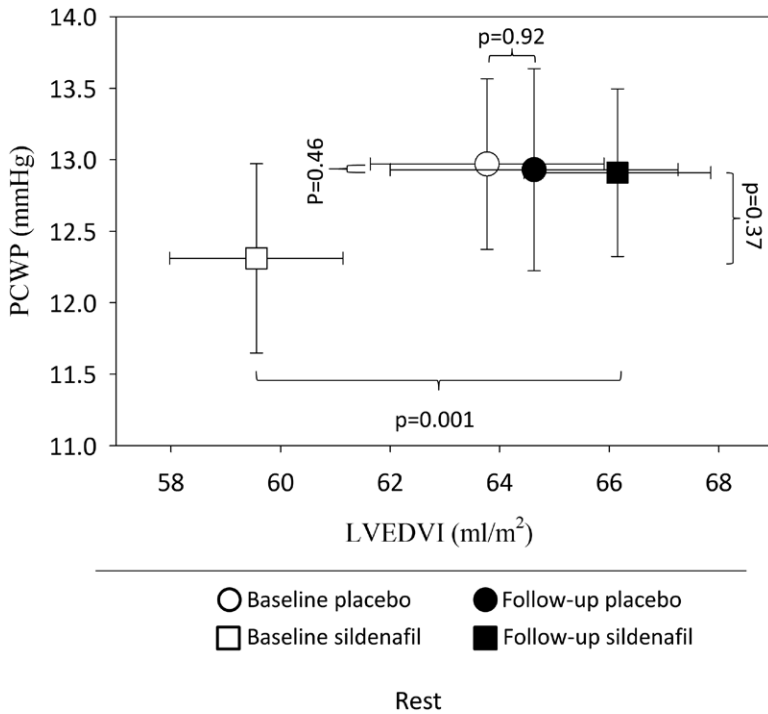
Both groups experienced a substantial and abnormal increase in PCWP and PAP with exercise (Table 2). After 9 weeks of treatment, there was a trend for higher peak PCWP in the placebo group compared with sildenafil ( $35\pm 8$  mmHg versus  $31\pm 7$  mmHg,  $P=0.07$ ). However, after adjusting for baseline values the estimated difference in PCWP between groups was only mean  $+1$  mmHg higher in the placebo group (95% CL,  $-2$  to  $+5$  mmHg;  $P=0.39$ ; Figure 2).

**Secondary End Points**

The change in peak exercise CI from baseline to 9 weeks was significantly higher in the sildenafil compared with placebo group ( $+0.2\pm 1.1$  versus  $-0.4\pm 1.3$  L/min/ $\text{m}^2$ ,  $P=0.05$ ) also when adjusting for baseline ( $+0.7$  L/min/ $\text{m}^2$ ; 95% CL,  $+0.1$  to  $+1.2$  L/min/ $\text{m}^2$ ;  $P=0.02$ ; Figure 5). There were no significant differences within or between-groups in heart rate ( $-3$  bpm; 95% CL,  $-9$  to  $+3$  bpm;  $P=0.28$ ), mean PAP ( $+0$  mmHg,



**Figure 3.** Cardiac index (CI) at rest from baseline to follow-up for placebo (dashed line and circle) and sildenafil (solid line and square). The error bars represent standard deviation. Statistical evaluations were performed using Student *t* test and ANCOVA.



**Figure 4.** Relationship between left ventricular end-diastolic volume index (LVEDVI; x axis) and pulmonary capillary wedge pressure (PCWP; y axis) in sildenafil (square) and placebo (circle) at baseline (empty legends) and at follow-up (solid legends). Error bars represent standard error of the mean. Statistical evaluations were performed using paired t test.

95% CL, -4 to +3;  $P=0.85$ ), or pulmonary vascular resistance index (+13 dynes.m<sup>2</sup>/sec.cm<sup>-5</sup>; 95% CL, -17 to +43 dynes.m<sup>2</sup>/sec.cm<sup>-5</sup>,  $P=0.38$ ) placebo and sildenafil, respectively.

Estimated difference in exercise diastolic blood pressure (-13 mmHg, 95% CL, -23 to -2 mmHg,  $P=0.02$ ), and estimated difference in systemic vascular resistance index (-205 dynes.m<sup>2</sup>/sec.cm<sup>-5</sup>, 95% CL, -349 to -60 dynes.m<sup>2</sup>/sec.cm<sup>-5</sup>,  $P=0.007$ ) were lower in the sildenafil group compared with the placebo group when adjusting for baseline values. At peak exercise there was no significant within- or between-group differences in LVEDVI (adjusted  $P=0.68$ , unadjusted  $P=0.93$ ).

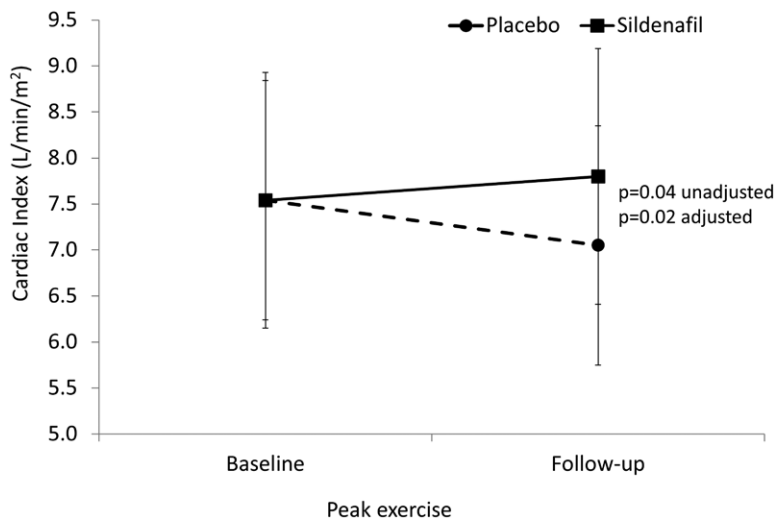
**Adverse Events and Compliance**

During treatment no serious adverse events or deaths occurred. Fourteen adverse events with possible relation to sildenafil

were reported during the study period (n=12 for the sildenafil group, and n=2 for the placebo group,  $P=0.006$ ; Table 3). Adverse events were generally mild and transient, and most resolved spontaneously. In 2 patients with dyspepsia a proton pump inhibitor was prescribed. One patient in the sildenafil group discontinued medication as a result of dyspnea, and 1 had the dose reduced to 20 mg thrice daily also as a result of dyspnea. In the placebo group 1 patient withdrew consent and another patient emigrated. Compliance by pill count was good; 58 (87%) of the 67 who completed the study were compliant.

**Discussion**

The Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction (SIDAMI) trial is to our knowledge the largest randomized, double-blind, placebo-controlled trial to invasively and echocardiographically investigate the



**Figure 5.** Cardiac index (CI) at peak exercise from baseline to follow-up for placebo (dashed line and circle) and sildenafil (solid line and square). The error bars represent standard deviation. Statistical evaluations were performed using Student t test and ANCOVA.

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**Table 3. Adverse Events**

Adverse Effects	Placebo	Sildenafil
Dyspepsia, n (%)	0 (0%)	6 (17%)
Headache and dyspepsia, n (%)	0 (0%)	2 (9%)
Headache alone, n (%)	1 (3%)	2 (6%)
Dyspnea, n (%)	0 (0%)	2 (6%)
Skin irritation, n (%)	1 (3%)	0 (0%)

Data are presented as number of patients (%).

hemodynamic response at rest and during exercise to PDE-5 inhibition, and the first study of PDE-5 inhibition in patients with preserved LVEF, diastolic dysfunction, and exercise-induced pulmonary venous hypertension post MI. Sildenafil did not lower LV filling pressure at rest or during exercise (primary end point). However, sildenafil treatment was associated with some beneficial hemodynamic effects, including increases in stroke volume, cardiac output, and reductions in LV afterload. These positive effects of PDE-5 inhibition observed in this trial must be interpreted as hypothesis-generating, but suggest that further studies evaluating the use of this class of medication in the post MI setting are warranted.

Despite the marked increase in LV filling pressure with exercise and contrary to our primary hypothesis, sildenafil did not lower LV filling pressure. The study was initially powered to detect a reduction of PCWP of  $\approx 4$  mmHg. With the characteristics of the final study population a difference in PCWP of 5 mmHg would be detectable with power of 80% and  $\alpha=0.05$ , corresponding to a  $\approx 15\%$  decrease of peak exercise PCWP. Thus the lack of effect on the primary end point is unlikely a result of inadequate power. The reason for the absence of effect on primary end point is unclear, but we speculate that this could be attributable to the relatively normal pulmonary vascular resistances noted in the current study. Despite severe elevations in pulmonary artery pressures with exercise, PVR was remarkably normal at rest and during exercise, in contrast with the reductions in systemic vascular resistance by sildenafil. Previous studies have demonstrated that PDE-5 is significantly more upregulated in the setting of heart failure with pulmonary vascular disease with high PVR as compared with normal pulmonary vasculature.<sup>25</sup> This could possibly also explain the apparently opposed results of the present study with a recent study by Guazzi et al.<sup>14</sup> In that study impressive improvements in pulmonary arterial pressure, RV function and dimension, LV size, and distensibility was observed after 12 months treatment with sildenafil in a group of patients with HFpEF. Opposed to the present study their patients were characterized by severe RV dysfunction and increased pulmonary vascular resistance. In addition to PDE-5 upregulation, an explanation may be that these patients with diastolic dysfunction are conditioned to tolerate a high LV filling pressure with exercise and thus will not stop exercising until this filling pressure is reached. This is supported by the low variability between baseline and follow-up in peak exercise PCWP observed in both groups. Finally, we cannot exclude the possibility that our sensitivity to detect PCWP effects of sildenafil might have been attenuated by performing exercise studies in the supine position, where venous return and preload is highest, although we have previously validated

the method in MI patients with and without diastolic dysfunction and healthy controls.<sup>4</sup>

In agreement with the observed changes in PCWP we did not detect any significant improvement in diastolic function as assessed by Doppler echocardiography. However, these negative results do not entirely preclude a subtle effect on diastolic function, as the sildenafil group was able to increase their peak cardiac output  $>1$  L/min compared with placebo without an increase in LV filling pressure. In addition, the observed increase in LVEDVI at an unchanged PCWP could suggest an increase in LV chamber compliance or capacitance (myocardial effect), as has recently been demonstrated in heart failure animal models with PDE-5 inhibition.<sup>26</sup>

Though filling pressure was unaffected we did observe an increase in cardiac output at rest and during exercise with sildenafil. This increase in CI was consistently observed using echocardiography, thermodilution, and indirectly by measuring a-v O<sub>2</sub> difference supporting a genuine effect of sildenafil. This increase in cardiac output could be attributable to a vascular effect of PDE-5 inhibition with vasodilation as a result of improved endothelial function.<sup>9,10,27,28</sup> The improvement in cardiac output is in agreement with previous smaller studies in patients with HFpEF,<sup>14</sup> HFrEF,<sup>13,29,30</sup> aortic stenosis,<sup>8</sup> and in animal models of severe pressure overload.<sup>10,12,31</sup> However, if the vascular effect were the only mechanism, a reduction in LVESVI would also have been anticipated. Therefore, the unexpected increase in LVEDVI with an unchanged LVESVI is unlikely alone a result of reduced afterload. Post-MI adverse remodeling with altered geometry and progressive LV dilatation is unequivocally a negative prognostic sign, where the increase in end-systolic and end-diastolic volumes occurs to maintain an adequate cardiac output to meet the metabolic demand and is closely associated with neurohormonal activation.<sup>6,32</sup> Usually adverse remodeling is seen in patients that have sustained large MI with marked depression of LVEF. This is a different population compared with the present study population, and we speculate that the slight increase in LVEDVI in the current study is not reflective of a negative effect on remodeling, but rather an enhancement in diastolic capacitance. A similar increase in end-diastolic volume has been demonstrated in HFpEF patients without MI<sup>14</sup> and in animal heart failure models with sildenafil.<sup>26</sup> Also, PDE-5 inhibition has been shown to be cardioprotective in ischemic models<sup>33</sup> and to attenuate maladaptive adrenergic stimulation,<sup>34</sup> processes which are thought to play key roles in the neurohormonal activation and eccentric remodeling after larger infarcts. Furthermore, we observed a significant decrease in N-terminal probrain natriuretic peptide in both groups after 9 weeks of treatment, all of which indicate that the observed increase in LVEDVI may not have been harmful. Larger studies of effects of PDE-5 inhibition in HFpEF ongoing where ventricular geometry and exercise capacity will be evaluated in detail (RELAX Clinicaltrials.gov:NCT00763867).<sup>35</sup>

### Limitations

Patients in the SIDAMI trial were required to undergo 2 cardiopulmonary exercise tests with simultaneous right heart catheterization and echocardiography, which may introduce selection bias for less symptomatic, more fit, and more

determined patients. Although the enrolled population did show extensive elevation in filling pressure with exercise, it is uncertain how the results might differ in more frail or more symptomatic patients. Subjects were studied during supine exercise, and results may differ with exercise performed in the upright position.

Although we found an acceptable compliance (>80% good compliance), an even better compliance could possibly have been achieved using a slow release tablet that could be administered once a day instead of 3 times a day. An improved compliance could possibly have augmented the results. The duration of the study was based on time to remodeling in previous MI studies,<sup>36</sup> and it is possible that longer treatment duration could have augmented the possible myocardial and vascular effects. The initiation of the study was delayed to at least 2 weeks post MI to minimize the risk of complications from femoral angiographic access site and to allow initiation and up-titration of concomitant medication. Exercise capacity was assessed using achieved watts and 6-minute walk test, which clearly is less optimal than measurement of peak oxygen consumption. However, adding expired gas analysis to the simultaneous right heart catheterization and echocardiography during maximum supine exercise was not considered feasible.

## Conclusion

Treatment with oral sildenafil is safe and well tolerated in patients with a recent MI and diastolic dysfunction. Despite marked increase filling pressure and pulmonary artery pressure with exercise in this population, this was not affected by sildenafil, thus the primary end point was not met. Sildenafil did however suggest increased cardiac output and reduced systemic resistance at a constant filling pressure. Although these results must be considered as hypothesis-generating only, the signal of possible enhancement in LV compliance with PDE-5 inhibition may merit further prospective studies in patients with diastolic dysfunction.

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## Disclosures

None.

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### CLINICAL PERSPECTIVE

Multiple observational studies suggest that patients with preserved systolic function and diastolic dysfunction post myocardial infarction have a worse prognosis than patients with infarcts of similar size but no diastolic dysfunction. In addition, the optimal management of these patients is unknown. This group of patients is characterized by an abnormal hemodynamic response to exercise with an abnormal increase in filling pressure and pulmonary artery pressure. The raised filling pressure during exercise could be a marker of increased risk of progression to overt heart failure, which possibly could be modulated by the selective phosphodiesterase-5 inhibitor sildenafil. Accordingly, we performed a double-blind, randomized, placebo-controlled trial in 70 patients with diastolic dysfunction and preserved systolic function after a myocardial infarction. All patients underwent supine exercise testing with simultaneous echocardiography and right heart catheterization to determine whether sildenafil 40 mg thrice daily over 9 weeks lowered pulmonary capillary wedge pressure (primary end point) or improved cardiac index and pulmonary arterial pressure (secondary end points) at rest and at peak exercise compared with matching placebo. After 9 weeks of treatment, sildenafil did not lower the primary end point (pulmonary capillary wedge pressure). Sildenafil did, however, increase cardiac output and reduce systemic resistance at a constant filling pressure. Although these results must be considered as hypothesis-generating only, the observed possible enhancement in LV compliance with PDE-5 inhibition merit further prospective studies in patients with diastolic dysfunction after myocardial infarction.

**Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction in Patients With Preserved Ejection Fraction: The Sildenafil and Diastolic Dysfunction After Acute Myocardial Infarction (SIDAMI) Trial**

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