

ORIGINAL ARTICLE

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension

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ABSTRACT

BACKGROUND

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Sildenafil inhibits phosphodiesterase type 5, an enzyme that metabolizes cyclic guanosine monophosphate, thereby enhancing the cyclic guanosine monophosphate-mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung.

METHODS

In this double-blind, placebo-controlled study, we randomly assigned 278 patients with symptomatic pulmonary arterial hypertension (either idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks. The primary end point was the change from baseline to week 12 in the distance walked in six minutes. The change in mean pulmonary-artery pressure and World Health Organization (WHO) functional class and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality. Patients completing the 12-week randomized study could enter a long-term extension study.

RESULTS

The distance walked in six minutes increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) for 20, 40, and 80 mg of sildenafil, respectively ($P < 0.001$ for all comparisons). All sildenafil doses reduced the mean pulmonary-artery pressure ($P = 0.04$, $P = 0.01$, and $P < 0.001$, respectively), improved the WHO functional class ($P = 0.003$, $P < 0.001$, and $P < 0.001$, respectively), and were associated with side effects such as flushing, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline at one year in the distance walked in six minutes was 51 m.

CONCLUSIONS

Sildenafil improves exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic pulmonary arterial hypertension.

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PULMONARY ARTERIAL HYPERTENSION is defined as a group of diseases characterized by a progressive increase in pulmonary vascular resistance, leading to right ventricular failure and premature death.^{1,2} Pathobiologic mechanisms of the disease include pulmonary endothelial dysfunction, which leads to impaired production of vasodilators, such as nitric oxide and prostacyclin, and overexpression of vasoconstrictors, such as endothelin-1.^{3,4} Treatment includes conventional agents (anticoagulants, diuretics, digoxin, and supplemental oxygen, as well as calcium-channel blockers in selected patients), vasodilators, and antiproliferative agents such as prostanoids and endothelin-receptor antagonists, which are targeted at abnormalities of endothelial function.^{5,6}

Four agents are currently approved for the treatment of pulmonary arterial hypertension in the United States and Europe⁵: intravenous epoprostenol, the inhaled prostacyclin analogue iloprost, the subcutaneously and intravenously administered prostacyclin analogue treprostinil, and the oral endothelin-receptor antagonist bosentan. Although these drugs are efficacious, adverse effects in terms of safety, tolerability, drug delivery, or all of these factors occur with all of these agents.^{5,6} In addition, some medical therapy may fail in some patients in which case they may be considered for lung transplantation.⁷

Changes in nitric oxide pathways have been detected in patients with pulmonary arterial hypertension,^{8,9} and although inhaled nitric oxide is used for testing acute vasoreactivity,^{5,6} the long-term administration of this agent is cumbersome and requires a complex delivery system.¹⁰ The pulmonary vasodilating effects of nitric oxide¹¹ are mediated through its second messenger, cyclic guanosine monophosphate (cGMP),¹² which is rapidly degraded by phosphodiesterases. Phosphodiesterase type 5 is the predominant phosphodiesterase isoform in the lung that metabolizes cGMP,¹³ and it has been shown to be up-regulated in conditions associated with pulmonary hypertension.^{14,15} By selectively inhibiting phosphodiesterase type 5, sildenafil citrate (Revatio, Pfizer) promotes the accumulation of intracellular cGMP¹⁶ and thereby enhances nitric oxide-mediated vasodilatation; it may also have antiproliferative effects on pulmonary vascular smooth-muscle cells.¹⁷ Initial studies involving animal models,^{14,18-22} data from open-label, uncontrolled trials involving patients with pulmonary arterial hypertension,²³⁻²⁸ and a small

randomized, controlled study involving patients with idiopathic pulmonary arterial hypertension²⁹ suggest that sildenafil is beneficial in the treatment of pulmonary arterial hypertension. The objectives of our double-blind, placebo-controlled clinical trial were to assess the efficacy and tolerability of three doses of sildenafil — 20, 40, and 80 mg given orally three times daily — in patients with pulmonary arterial hypertension.

METHODS

SELECTION OF PATIENTS

Patients were included if they had pulmonary arterial hypertension (idiopathic, associated with connective-tissue disease, or occurring after surgical repair of congenital systemic-to-pulmonary shunts that had been performed at least five years previously). Pulmonary arterial hypertension was defined as a mean pulmonary-artery pressure of 25 mm Hg or more and a pulmonary-capillary wedge pressure of 15 mm Hg or less at rest. Study medication was added to the patient's conventional therapy. Treatment with intravenous epoprostenol, oral bosentan, intravenous or inhaled iloprost, or subcutaneous treprostinil and supplementation with L-arginine were prohibited. Patients with a six-minute walking distance of less than 100 m or more than 450 m were excluded. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

STUDY DESIGN

The initial study was a 12-week, double-blind, placebo-controlled trial conducted in 53 centers in the United States, Mexico, South America, Europe, Asia, Australia, South Africa, and Israel between October 2002 and November 2003. A stratified central-randomization scheme was used to assign patients to four treatment groups — those receiving 20, 40, or 80 mg of sildenafil or placebo three times daily — in a 1:1:1:1 ratio. The randomization was stratified with respect to the baseline walking distance (<325 m or ≥325 m) and cause of pulmonary arterial hypertension. Patients randomly assigned to 80 mg of sildenafil three times daily received 40 mg of sildenafil three times daily for the first seven days before the dose was escalated to 80 mg; patients randomly assigned to the other three treatment groups underwent dummy dose escalation after seven days.

All patients who completed the 12-week, double-blind study were eligible to enter a long-term extension study. Patients originally assigned to the groups receiving placebo, 20 mg of sildenafil, and 40 mg of sildenafil received 40 mg of sildenafil for the first six weeks of the extension study, and the dose was then increased to 80 mg of sildenafil. Patients originally assigned to receive 80 mg of sildenafil continued to receive that dose in the extension study but underwent dummy dose escalation at week 6 to maintain the blinding.

OUTCOME MEASURES

The primary measure of efficacy was the change in exercise capacity, as measured by the total distance walked in six minutes, from baseline to week 12.³⁰ Other measures of efficacy were the changes in mean pulmonary-artery pressure, score on the Borg scale of dyspnea (with 0 representing no dyspnea and 10 maximal dyspnea), World Health Organization (WHO) functional classification of pulmonary arterial hypertension (an adaptation of the New York Heart Association classification),³¹ and time from randomization to clinical worsening (defined as death, transplantation, hospitalization for pulmonary arterial hypertension, or initiation of additional therapies for pulmonary arterial hypertension, such as intravenous epoprostenol or oral bosentan). Physical examinations and laboratory tests were performed, and investigators recorded adverse events throughout both studies.

STATISTICAL ANALYSIS

The database was retained by the sponsor, but the investigators had access to the complete database. The statistical analysis was performed by a statistician who is an employee of the sponsoring company; it was reviewed and approved by one of the academic authors, at the University of Washington, Seattle. The authors assume full responsibility for the completeness and accuracy of the content of the manuscript.

The primary end point was evaluated with the use of a sequential step-down, closed testing procedure,³²⁻³⁴ in which the mean response in each group receiving sildenafil was compared with that in the placebo group. The group receiving the highest dose of sildenafil (80 mg) was tested first, followed by the groups receiving 40 mg and 20 mg, provided that a significant benefit had been observed with the prior higher dose. If no significant benefit was observed in relation to a particular dose,

then no further comparisons among doses were made. All pairwise comparisons for the primary end point were carried out at the prespecified two-sided alpha level of 0.01 with the use of a two-sample t-test, stratified for baseline walking distance and for categories according to cause. Assuming that there was a treatment effect from sildenafil of 55 m, as compared with placebo, and a standard deviation of 75 m, a sample of 60 patients per treatment group would provide 90 percent power to detect this difference at the two-sided alpha level of 0.01. With the allowance of a withdrawal rate of 12.5 percent after randomization, 275 patients were required for randomization.

The same sequential step-down testing procedure was used for analysis of the secondary end points, with pairwise comparisons performed at the two-sided alpha level of 0.05. Mean pulmonary-artery pressure was analyzed with the use of a stratified t-test; the time to clinical worsening was analyzed with the use of a stratified log-rank test (data for patients with no documentation of clinical worsening were included in the analysis as censored observations); the score on the Borg scale of dyspnea was analyzed with the use of a stratified Wilcoxon's rank-sum test; and the change in the WHO functional class from baseline to week 12 was analyzed with the use of logistic regression.

Intention-to-treat analyses were performed for all variables. To be included in the intention-to-treat analysis for the primary end point, the Borg dyspnea score, and the mean pulmonary-artery pressure, a patient must have received the study drug and had both a baseline and at least one post-baseline measurement of the specific end point. To be included in the intention-to-treat analysis for time to clinical worsening, a patient must have received the study drug. Missing data for assessments at week 12 were imputed with the use of the last-observation-carried-forward method.

A sensitivity analysis was performed, which included patients who had not had a baseline walking test (the baseline walking distance was imputed with the use of results from the patients' screening walking test) and patients with no assessments of walking distance after baseline. In this analysis, for patients for whom no assessments had been performed after baseline, the six-minute walking distance at week 12 was set to the baseline result; for patients who had died, the distance at week 12 was set to 0; and for all other patients, either the distance at week 12 or the last assessment that had

been performed was carried forward. A per-protocol population analysis was also conducted.

RESULTS

A total of 278 patients were randomly assigned to receive placebo (70 patients) or sildenafil in doses of 20 mg (69 patients), 40 mg (68 patients), or 80 mg (71 patients) three times daily (Fig. 1); 277 of the randomized patients took at least one dose of the study medication.

BASELINE CHARACTERISTICS

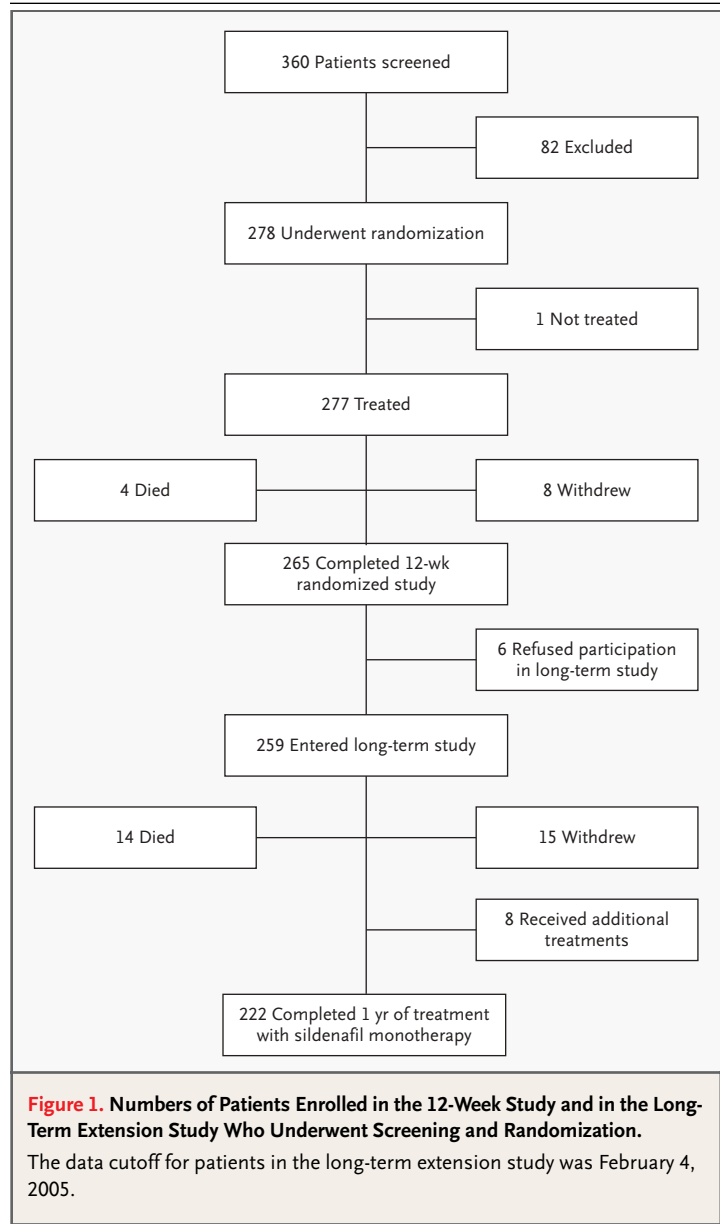
Baseline characteristics of the patients were similar among all four treatment groups (Table 1). Idiopathic pulmonary arterial hypertension was the most frequent diagnosis, and the predominant WHO functional classifications at baseline were class II (39 percent of patients) and class III (58 percent).

EXERCISE CAPACITY

An increase in the distance walked in six minutes was observed in all groups receiving sildenafil, as compared with placebo, at week 4, and this effect was maintained at weeks 8 and 12 (Fig. 2). The mean placebo-corrected treatment effects among 266 patients at week 12 were 45 m among those receiving 20 mg of sildenafil (99 percent confidence interval, 21 to 70; $P < 0.001$), 46 m for those receiving 40 mg (99 percent confidence interval, 20 to 72; $P < 0.001$), and 50 m for those receiving 80 mg (99 percent confidence interval, 23 to 77; $P < 0.001$). The sensitivity analysis that was performed with the use of alternative imputation methods for missing data corroborated the main analysis: the mean placebo-corrected treatment effects among 277 patients at week 12 were 38 m for those receiving 20 mg of sildenafil (99 percent confidence interval, 12 to 64; $P < 0.001$), 45 m for those receiving 40 mg (99 percent confidence interval, 21 to 70; $P < 0.001$), and 42 m for those receiving 80 mg (99 percent confidence interval, 9 to 75; $P < 0.001$). The results from the per-protocol population analysis also confirmed the main analysis ($P < 0.001$ for all three comparisons).

TREATMENT EFFECTS ACCORDING TO SUBGROUPS

The treatment effect on the primary end point in each group receiving sildenafil was descriptively assessed for subgroups of patients that were defined according to demographic features, disease characteristics, and baseline variables (Fig. 3). There was



placebo-corrected improvement in the mean six-minute walking distance in all subgroups receiving sildenafil.

BORG DYSPNEA SCORE

The change from baseline in scores on the Borg dyspnea scale among the patients treated with sildenafil did not differ significantly from the change in the placebo group. The median Borg dyspnea score decreased (reflecting improvement) by 1 point among patients receiving 20 mg of sildenafil (95 percent confidence interval, -1 to 0), by 0 for those receiv-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=70)	Sildenafil		
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)
Female sex — no. (%)	57 (81)	49 (71)	47 (70)	56 (79)
Age — yr	49±17	47±14	51±15	48±15
Race or ethnic background — no. (%)†				
White	61 (87)	59 (86)	58 (87)	58 (82)
Black	1 (1)	0	4 (6)	1 (1)
Asian	2 (3)	6 (9)	2 (3)	9 (13)
Other	6 (9)	4 (6)	3 (4)	3 (4)
Weight — kg	74±19	71±17	75±17	71±17
WHO functional class — no. (%)				
I	1 (1)	0	0	0
II	32 (46)	24 (35)	23 (34)	28 (39)
III	34 (49)	40 (58)	44 (66)	42 (59)
IV	3 (4)	5 (7)	0	1 (1)
Cause of pulmonary arterial hypertension — no. (%)				
Idiopathic	42 (60)	44 (64)	43 (64)	46 (65)
Connective-tissue disease				
Scleroderma	8 (11)	9 (13)	11 (16)	10 (14)
Systemic lupus erythematosus	4 (6)	6 (9)	3 (4)	6 (8)
Other	10 (14)	6 (9)	6 (9)	5 (7)
Repaired congenital S-P shunts	6 (9)	4 (6)	4 (6)	4 (6)
Walking distance at 6 min — m	344±79	347±90	345±77	339±79
Heart rate — beats/min	81±16	82±12	77±11	79±11
Pulmonary-artery pressure — mm Hg	56±16	54±13	49±13	52±16
Cardiac index — liters/min/m ²	2.2±0.6	2.4±0.7	2.3±0.7	2.5±0.8
Pulmonary vascular resistance — dyn·sec·cm ⁻⁵	1051±512	987±464	869±438	918±601
Right atrial pressure — mm Hg	9±4	8±5	9±6	9±5

* The groups shown represent all treated patients. Plus-minus values are means ±SD. WHO denotes World Health Organization, and S-P systemic-to-pulmonary.

† Race was self-reported.

ing 40 mg (95 percent confidence interval, -1 to 0), and by -1 for those receiving 80 mg (95 percent confidence interval, -1.5 to 0), as compared with placebo.

HEMODYNAMICS

The patients receiving sildenafil had decreases from the baseline value in mean pulmonary-artery pressure and in pulmonary vascular resistance, as well as an increase in the cardiac index. These changes differed significantly from those among the patients receiving placebo (Table 2).

CLINICAL WORSENING

No statistically significant decrease in the time to clinical worsening or in the incidence of clinical

worsening was observed with sildenafil as compared with placebo (Table 3). An exploratory analysis showed that the proportion of hospitalizations for worsening of pulmonary arterial hypertension was greater in the placebo group than in the combined sildenafil groups (P=0.02).

WHO FUNCTIONAL CLASS

Data on the WHO functional class were available for 273 patients. After 12 weeks of double-blind treatment, the proportions of patients with an improvement of at least one functional class were 7 percent for those receiving placebo, 28 percent for those receiving 20 mg of sildenafil (placebo-corrected difference, 21 percent; 95 percent confidence interval, 9 to 33 percent; P=0.003), 36 percent for those

receiving 40 mg (placebo-corrected difference, 29 percent; 95 percent confidence interval, 16 to 42 percent; $P < 0.001$), and 42 percent for those receiving 80 mg (placebo-corrected difference, 35 percent; 95 percent confidence interval, 22 to 48 percent; $P < 0.001$).

LONG-TERM TREATMENT

Of the 265 patients who completed the randomized 12-week study, 259 entered the long-term prospective extension study, and 6 declined enrollment (Fig. 1). Patients who had been assigned to receive placebo and were then titrated up to 80 mg of sildenafil during the first 12 weeks of the extension study (58 patients) had a mean increase from baseline in the six-minute walking distance of 42 m (95 percent confidence interval, 27 to 57 m) at week 12 of the extension.

Of the 259 patients enrolled in the extension study, 15 withdrew and 14 died before completing 12 months of treatment. As of February 4, 2005, 230 patients had been treated with sildenafil for at least 12 months (median, 589 days; range, 400 to 844). Eight of the 230 patients received additional treatment (with prostanoids or endothelin-receptor antagonists) for pulmonary arterial hypertension. An exploratory analysis was performed on the 222 patients receiving sildenafil monotherapy after 1 year; after 12 weeks of treatment, the mean change from baseline in the six-minute walking distance was 42 m (95 percent confidence interval, 40 to 55); after 12 months, the mean change was 51 m (95 percent confidence interval, 41 to 60).

SAFETY

Most adverse events were mild to moderate in intensity for all treatment groups (Table 3). No clinically significant changes were seen in any laboratory variables evaluated. Forty-two patients reported 68 serious adverse events. However, only two serious adverse events — left ventricular dysfunction in one patient receiving 20 mg of sildenafil and postural hypotension in another patient receiving an initial dose of 40 mg of sildenafil — were considered by the investigators to be related to the study medication. The distribution and incidence of adverse events were similar among patients with different types of pulmonary arterial hypertension, and the median times of first occurrence were clustered within the first four to five weeks of treatment.

One patient in the placebo group died from right heart failure, and one in the group receiving 20 mg

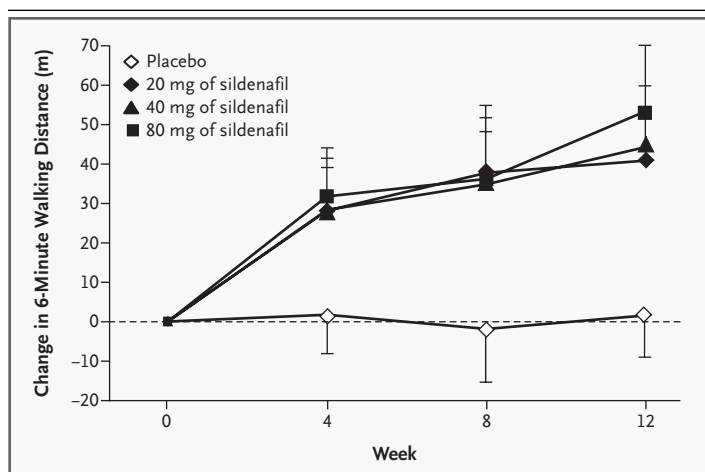


Figure 2. Mean Changes from Baseline, with 95 Percent Confidence Intervals, in the Six-Minute Walking Distance at Week 12 in the Placebo and Sildenafil Groups.

With the use of a two-sample t-test stratified according to baseline walking distance and cause of pulmonary arterial hypertension, $P < 0.001$ for the comparison of sildenafil in doses of 20, 40, and 80 mg with placebo. In this intention-to-treat analysis, 266 patients for whom outcome data were available were included. The dosing schedule for all study medication was three times daily.

of sildenafil died from acute pulmonary embolism and urosepsis. Two patients in the group receiving 80 mg of sildenafil died, one from acute myocardial infarction and one from pneumonia while receiving 40 mg three times daily during the first seven days of the titration period. No death was judged by the investigators to be causally related to the study treatment. Eight patients withdrew from the randomized 12-week study: two because of protocol violations, two because of withdrawal of consent, and four because of side effects (decreased renal function, lower-leg edema, cardiac arrhythmias, and headache).

DISCUSSION

In this multicenter, randomized, double-blind, placebo-controlled trial, sildenafil significantly improved exercise capacity, as assessed according to the six-minute walking test, in patients with pulmonary arterial hypertension, whether it was idiopathic or related to connective-tissue disease or surgical repair of congenital systemic-to-pulmonary shunts. Our findings show that there is a symptomatic benefit associated with the inhibition of phosphodiesterase type 5 in patients with pulmonary arterial hy-

pertension. All subgroups that were assessed had an improvement in exercise capacity with sildenafil treatment, regardless of demographic or disease characteristics or other baseline variables. The study was not designed to assess mortality.

The six-minute walking test is an independent predictor of death in patients with idiopathic pulmonary arterial hypertension³⁵ and has been used as the primary end point in most clinical trials involving patients with pulmonary arterial hypertension.⁵ The treatment-related increase in walking distance of 45 to 50 m observed in this study is similar to the increases observed with the use of intravenous epoprostenol (47 m),³⁶ inhaled iloprost (36 m),³⁷ and oral bosentan (44 m)³⁸ and is higher than the increase seen with the use of subcutaneous treprostinil (16 m).³⁹

It should be emphasized that most patients in the present study had pulmonary arterial hypertension of WHO class II or III, representing a less sick population than in the other studies. In those trials, the sickest patients (those with pulmonary arterial hypertension of WHO class III or IV) had the greatest improvement in the six-minute walking distance. The extension study suggests that the effect of sildenafil monotherapy on exercise capacity is maintained after one year of treatment. This open-label, prospective evaluation reinforces the clinical significance of the exercise improvements observed in the 12-week study.

Sildenafil also significantly improved cardiopulmonary hemodynamics at 12 weeks, as compared with changes at 12 weeks in the placebo group. The reductions in pulmonary-artery pressure and increases in cardiac index were similar to those observed with intravenous epoprostenol³⁶ and oral bosentan³⁸ in smaller studies. Hemodynamic variables are related to survival in patients with idiopathic pulmonary arterial hypertension,⁴⁰ and the results of this study confirm the clinical relevance of the effects of sildenafil. It is not clear what mechanisms are involved in the hemodynamic improvements seen in patients with pulmonary arterial hypertension who have predominantly fixed pulmonary vascular obstructive lesions.³ It has been suggested that there is possible reverse remodeling of pulmonary vascular changes with both prostanoids and endothelin-receptor antagonists, on the basis of their antiproliferative properties,⁶ and this may also explain the effects seen with sildenafil.¹⁷

The incidence of clinical worsening was not significantly different in the patients treated with

Figure 3 (facing page). Effect of Treatment on the Six-Minute Walking Distance from Baseline to Week 12 in Patient Subgroups.

The mean treatment effects, with 95 percent confidence intervals, are presented for each sildenafil dose. PAH denotes pulmonary arterial hypertension, CTD connective-tissue disease, S-P systemic-to-pulmonary, WHO World Health Organization, and PAP pulmonary-artery pressure. In this intention-to-treat analysis, 266 patients for whom outcome data were available were included. The dosing schedule for all study medication was three times daily.

sildenafil than in those treated with placebo. However, the overall incidence of clinical worsening in this study was low and may be related to the sizable cohort of patients with pulmonary arterial hypertension of WHO functional class II (39 percent) and to the short duration of the study (12 weeks). In fact, in our study, the overall incidence of clinical worsening in the placebo group was 10 percent (Table 3) and was lower than that in the placebo group of the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) study.³⁸ In addition, in the BREATHE-1 study, a statistically significant difference in the time to clinical worsening was observed after 16 weeks, not 12.³⁸

With all doses of sildenafil, most adverse events were of mild to moderate severity, and there were no clinically significant changes in laboratory variables. Complex delivery systems, significant side effects, or both, are associated with intravenous epoprostenol (e.g., catheter-related infections, sepsis, and pump malfunctions),³⁶ subcutaneous treprostinil (infusion-site pain),³⁹ inhaled iloprost (multiple daily inhalations),³⁷ and oral bosentan (abnormalities of hepatic function).³⁸

There was no evidence of a dose-response relationship associated with the primary end point (exercise capacity) or with tolerability in the 12-week study. The reason for this phenomenon is not clear but may be related to the complete inhibition of phosphodiesterase type 5 with the lowest dose.

Limitations of the study include the exclusion of certain patient populations with pulmonary arterial hypertension, such as patients in whom the pulmonary arterial hypertension is associated with the human immunodeficiency virus, patients with portal hypertension, and those with hypertension that is associated with uncorrected congenital systemic-to-pulmonary shunts. Additional studies involving these subgroups of patients are needed.

SILDENAFIL IN PULMONARY ARTERIAL HYPERTENSION

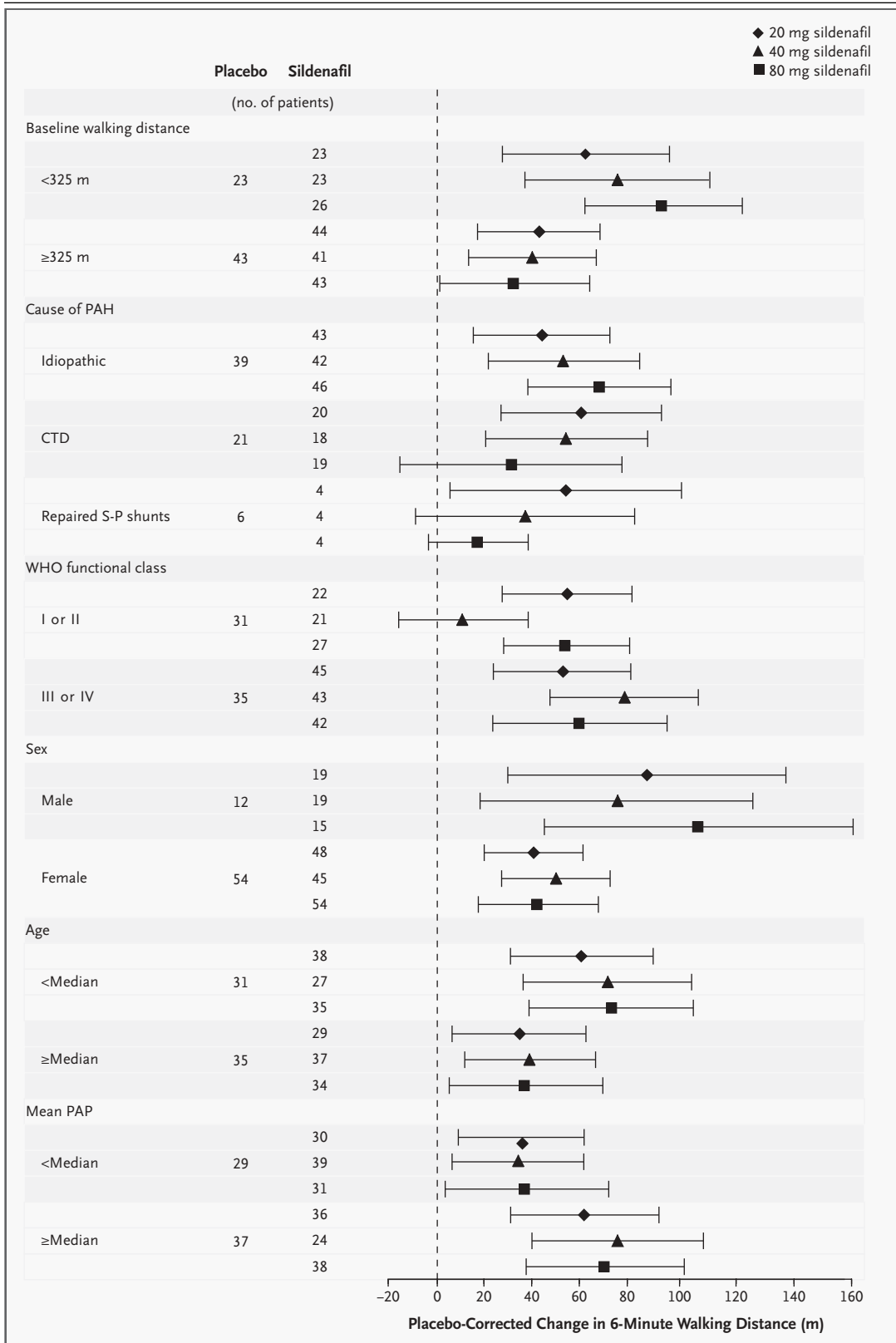


Table 2. Mean Change in Hemodynamic Variables from Baseline to Week 12.*

Variable	Placebo (N=65)			Sildenafil			
		20 mg (N=65)	P Value	40 mg (N=63)	P Value	80 mg (N=65)	P Value
Heart rate — beats/minute	-1.3 (-4.1 to 1.4)	-3.7 (-5.9 to -1.4)	0.18	-3.3 (-5.5 to -1.0)	0.27	-4.7 (-7.3 to -2.2)	0.05
Mean pulmonary artery pressure — mm Hg	0.6 (-0.8 to 2.0)	-2.1 (-4.3 to 0.0)	0.04	-2.6 (-4.4 to -0.9)	0.01	-4.7 (-6.7 to -2.8)	<0.001
Cardiac index — liters/min/m ²	-0.02 (-0.17 to 0.13)	0.21 (0.04 to 0.8)	0.06	0.24 (0.05 to 0.42)	0.03	0.37 (0.20 to 0.55)	0.001
Pulmonary vascular resistance — dyn·sec·cm ⁻⁵	49 (-54 to 153)	-122 (-217 to -27)	0.01	-143 (-218 to -69)	0.01	-261 (-365 to -157)	<0.001
Right atrial pressure — mm Hg	0.3 (-0.9 to 1.5)	-0.8 (-1.9 to 0.3)	0.19	-1.1 (-2.4 to 0.2)	0.10	-1.0 (-2.1 to 0.1)	0.11

* The values shown represent the mean change (with 95 percent confidence intervals). P values are for the comparison of each dose of sildenafil with placebo. With mean pulmonary-artery pressure included as a secondary end point, multiple testing was accounted for with the use of the closed testing procedure. None of the other P values were adjusted for multiple testing. The number of patients per treatment group varied slightly for each variable owing to missing data.

Table 3. Incidence of Clinical Worsening and of the Most Frequent Adverse Events in the Placebo and Sildenafil Groups.*

Event	Placebo (N=70)	Sildenafil		
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)
number (percent)				
Clinical worsening	7 (10)	3 (4)	2 (3)	5 (7)
Death	1 (1)	1 (1)	0	2 (3)
Hospitalization for pulmonary arterial hypertension	7 (10)	2 (3)	2 (3)	2 (3)
Initiation of prostacyclin	1 (1)	0	0	0
Initiation of bosentan	0	0	1 (1)	2 (3)
Adverse event†				
Headache	27 (39)	32 (46)	28 (42)	35 (49)
Flushing	3 (4)	7 (10)	6 (9)	11 (15)
Dyspepsia	5 (7)	9 (13)	6 (9)	9 (13)
Back pain	8 (11)	9 (13)	9 (13)	6 (8)
Diarrhea	4 (6)	6 (9)	8 (12)	7 (10)
Limb pain	4 (6)	5 (7)	10 (15)	6 (8)
Myalgia	3 (4)	5 (7)	4 (6)	10 (14)
Cough	4 (6)	5 (7)	3 (4)	6 (8)
Epistaxis	1 (1)	6 (9)	5 (7)	3 (4)
Pyrexia	2 (3)	4 (6)	2 (3)	7 (10)
Insomnia	1 (1)	5 (7)	4 (6)	3 (4)
Influenza	2 (3)	4 (6)	4 (6)	3 (4)
Visual disturbance	0	0	3 (4)	5 (7)
Gastritis	0	2 (3)	2 (3)	3 (4)

* The analysis included all patients who received study medication. Some patients had more than one event.

† Adverse events shown are those reported by 3 percent or more of patients and those reported more frequently with sildenafil than with placebo.

In conclusion, this study demonstrates the efficacy and safety of sildenafil in the treatment of patients with symptomatic pulmonary arterial hypertension. Our assessment of efficacy was limited to exercise capacity and hemodynamic measures, and the study was not designed to address the important end point of mortality.

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CORRECTION**Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension**

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension . The appendix listing principal investigators and locations of centers participating in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group was inadvertently omitted from the article. It appears below.

Appendix

The members of the SUPER study group were as follows (in order of the number of patients enrolled at each center): A. Manes, Bologna, Italy; W. Seeger, Giessen, Germany; A. Fijalkowska, Warsaw, Poland; M.R. Kramer, Petach Tikva, Israel; A.J. Peacock, Glasgow, United Kingdom; O. Sitbon, Clamart, France; H. Al-hiti, Prague, Czech Republic; T. Pulido, Mexico City; I. Ben-Dov, Tel-Hashomer, Israel; A.E. Frost, Houston; D.L. Zwicke, Milwaukee; S.M. Shapiro, Los Angeles; A. Keogh, Darlinghurst, Australia; C. Ickinger, Johannesburg; R.P. Frantz, Rochester, Minn.; N.S. Hill, Boston; R.J. Ouduz, Torrance, Calif.; K. Karlocai, Budapest, Hungary; C.M. Yu, Hong Kong; A. Boonstra, Amsterdam; M.A. Gomez-Sanchez, Madrid; Melvyn Rubenfire, Ann Arbor, Mich.; J.A. Barbera, Barcelona; R.N. Channick, San Diego, Calif.; R. Naeije, Brussels; C. Marini, Pisa, Italy; E. Berman-Rosenzweig, New York; I.M. Robbins, Nashville; R.E. Girgis, Baltimore; V.F. Tapson, Durham, N.C.; M. Delcroix, Leuven, Belgium; D.G. Kiely, Sheffield, United Kingdom; J. Wodniecki, Zabrze, Poland; J. Schauer, Leipzig, Germany; M. Hoeper, Hannover, Germany; S.T. Lim, Singapore; S.-J. Tack, Suwon, South Korea; H. Reuter, Parow, South Africa; J. Carlsen, Copenhagen; C.C. Lang, Kuala Lumpur, Malaysia; A. Roman, Barcelona; R.L. Benza, Birmingham, Ala.; T.J. Williams, Melbourne, Australia; P.A. Corris, Newcastle upon Tyne, United Kingdom; J. Pepke Zaba, Cambridge, United Kingdom; D. Apro, Zalaegerszeg, Hungary; J.K. Ghali, Shreveport, La.; D.B. Badesch, Denver; S. Rich, Chicago; D.J. Ross, Los Angeles; I. Schulze-Neick, Berlin; G. Martensson, Goteborg, Sweden; A.A. Lopes, Sao Paulo; and A.K. Andreassen, Oslo.