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A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

Abstract

BACKGROUND—Sildenafil, a phosphodiesterase-5 inhibitor, may preferentially improve blood flow to well-ventilated regions of the lung in patients with advanced idiopathic pulmonary fibrosis, which could result in improvements in gas exchange. We tested the hypothesis that treatment with sildenafil would improve walk distance, dyspnea, and quality of life in patients with advanced idiopathic pulmonary fibrosis, defined as a carbon monoxide diffusion capacity of less than 35% of the predicted value.

METHODS—We conducted a double-blind, randomized, placebo-controlled trial of sildenafil in two periods. The first period consisted of 12 weeks of a double-blind comparison between sildenafil and a placebo control. The primary outcome was the proportion of patients with an increase in the 6-minute walk distance of 20% or more. Key secondary outcomes included changes in oxygenation, degree of dyspnea, and quality of life. The second period was a 12-week open-label evaluation involving all patients receiving sildenafil.

RESULTS—A total of 180 patients were enrolled in the study. The difference in the primary outcome was not significant, with 9 of 89 patients (10%) in the sildenafil group and 6 of 91 (7%) in the placebo group having an improvement of 20% or more in the 6-minute walk distance (P = 0.39). There were small but significant differences in arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnea, and quality of life favoring the sildenafil group. Serious adverse events were similar in the two study groups.

CONCLUSIONS—This study did not show a benefit for sildenafil for the primary outcome. The presence of some positive secondary outcomes creates clinical equipoise for further research. (Funded by the National Heart, Lung, and Blood Institute and others; ClinicalTrials.gov number, NCT00517933.)

Idiopathic pulmonary fibrosis is a chronic, progressive lung disease of unknown cause that is characterized by the histopathologic pattern of usual interstitial pneumonia.[1] Progression to end-stage respiratory insufficiency and death within 5 years after the onset of symptoms is characteristic.[2,3] To date, no pharmacologic therapies have definitively been shown to improve survival or quality of life in patients with this disease.

Patients with severe idiopathic pulmonary fibrosis have abnormalities of the pulmonary vasculature leading to decreased levels of resting and exercise-induced production of nitric

*Members of the Idiopathic Pulmonary Fibrosis Clinical Research Network are listed in the Appendix.

The members of the writing committee — David A. Zisman, M.D., Sansum Clinic, Santa Barbara, CA; Marvin Schwarz, M.D., National Jewish Health and the University of Colorado, Denver; Kevin J. Anstrom, Ph.D., Duke Clinical Research Institute, Durham, NC; Harold R. Collard, M.D., University of California, San Francisco; Kevin R. Flaherty, M.D., University of Michigan, Ann Arbor; and Gary W. Hunninghake, M.D., University of Iowa, Iowa City — assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Zisman at the Sansum Clinic, 301 W. Pueblo St., Santa Barbara, CA 93105, or at dzisman@sansumclinic.org.

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oxide. Since nitric oxide is a potent pulmonary vasodilator, reduced levels are associated with pulmonary vasoconstriction and impaired gas exchange.[4]

Sildenafil (Revatio, Pfizer) is a phosphodiesterase-5 inhibitor that stabilizes the second messenger of nitric oxide, cyclic guanosine monophosphate, which leads to pulmonary vasodilatation. Sildenafil appears to preferentially induce vasodilatation in well-ventilated lung tissue. Such vasodilatation could improve ventilation–perfusion matching and thus gas exchange in patients with idiopathic pulmonary fibrosis.[5] Small case series of daily treatment with sildenafil in patients with this condition and known pulmonary vascular disease have suggested improved exercise tolerance, reduced degree of dyspnea, and improved quality of life.[6,7]

In this study, called the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF), we tested the hypothesis that treatment with sildenafil would improve walk distance, dyspnea, and quality of life in patients with advanced idiopathic pulmonary fibrosis. The trial was sponsored by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) of the National Heart, Lung, and Blood Institute.

METHODS

STUDY OVERSIGHT

The study was designed by the IPFnet steering committee and was carried out at 14 IPFnet centers. (For details about the study centers, see Section A in the Supplementary Appendix, available with the full text of this article at NEJM.org; the full trial protocol is available in Section H.) Pfizer donated sildenafil and identical tablets containing placebo but had no role in the study design, accrual or analyses of data, or preparation of the manuscript. The Duke Clinical Research Institute served as the data-coordinating center and oversaw all aspects of the study's conduct, data management, and statistical analysis. The independent IPFnet protocol review committee, the IPFnet data and safety monitoring board, and local institutional review boards approved the protocol. All patients provided written informed consent.

STUDY PATIENTS

Eligibility criteria included a diagnosis of idiopathic pulmonary fibrosis, as defined by consensus criteria (Section H in the Supplementary Appendix[1]), in an advanced stage, which was defined as a diffusing capacity for carbon monoxide of less than 35% of the predicted value. Key exclusion criteria were a 6-minute walk distance of less than 50 m (164 ft); a difference of more than 15% in the 6-minute walk distance between two prerandomization walks; an extent of emphysema greater than the extent of fibrotic change, as determined by high-resolution computed tomography (CT); treatment with medications containing nitrates (see Table 6 in Section C in the Supplementary Appendix); the presence of aortic stenosis or idiopathic hypertrophic subaortic stenosis; the initiation of pulmonary rehabilitation within 30 days after screening; the initiation or change in the dose of any investigational treatment for idiopathic pulmonary fibrosis within 30 days after screening; treatment for pulmonary hypertension with prostaglandins, endothelin-1 antagonists, or other phosphodiesterase inhibitors within 30 days after screening; a resting oxygen saturation of less than 92% while breathing 6 liters of supplemental oxygen; and being listed on an active waiting list for lung transplantation.

STUDY DESIGN AND RANDOMIZATION

STEP-IPF was a double-blind, randomized, placebo-controlled trial of oral sildenafil (20 mg three times daily). Patients meeting eligibility criteria were randomly assigned in a 1:1 ratio

to receive sildenafil or matched placebo with the use of a permuted-block design, with stratification according to clinical center. The trial was conducted in two periods: period 1 was a 12-week double-blind, placebo-controlled study of sildenafil; period 2 was a 12-week open-label extension with all patients receiving sildenafil (for details, see Section H in the Supplementary Appendix). The primary outcome was measured at the end of period 1 (12 weeks).

OUTCOME MEASURES

The primary outcome was the presence or absence of an improvement of at least 20% in the 6-minute walk distance at 12 weeks, as compared with baseline. Patients who withdrew from the study, died, or were unable to complete the walk test for any reason at 12 weeks were considered to have an improvement of less than 20%. Key secondary outcomes included changes in the 6-minute walk distance, degree of dyspnea, and quality of life.

Dyspnea levels were measured with the use of the University of California, San Diego, Shortness of Breath Questionnaire and the Borg Dyspnea Index. The Shortness of Breath Questionnaire asks patients to indicate the severity of dyspnea on a scale ranging from 0 to 5 on 21 activities of daily living, along with three ratings on limitations caused by dyspnea or fear of dyspnea, for a total score ranging from 0 to 120, with a higher score indicating more severe dyspnea. The minimally important difference (MID) for this instrument is reported to be 5 points.[8] The Borg Dyspnea Index measures perceived breathlessness on a scale of 0 (none) to 10 (maximum) and has a MID of 1 point.[9]

Quality of life was measured with the use of the St. George's Respiratory Questionnaire, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D). The St. George's Respiratory Questionnaire asks patients how breathing problems impair their life and is scored from 0 (no impairment) to 100 (maximum impairment.) The MID for this instrument in patients with idiopathic pulmonary fibrosis is 5 to 8 points.[10] The SF-36 measures functional health and well-being scores on eight scales that correlate with two aggregate scores. Each score ranges from 0 to 100, with a higher score indicating better function. For presentation, scores are normalized to a mean (±SD) of 50±10.[11] In patients with idiopathic pulmonary fibrosis, the MID for these scales is 2 to 4 points.[10] The EQ-5D measures general quality of life on a self-report questionnaire on a scale of −0.59 to 1.00 (with a higher score indicating a better quality of life and a negative value indicating a health state worse than death) and on a visual-analogue scale with a range of 0 to 100 (with a higher score indicating a better quality of life). The reported MID is approximately 0.08 for the self-report questionnaire and 7 points for the visual-analogue scale.[12]

Other secondary outcomes included a change in forced vital capacity, carbon monoxide diffusion capacity, arterial partial pressure of oxygen and arterial oxygen saturation, and the alveolar–arterial oxygen gradient while breathing ambient air. We recorded all adverse events, hospitalizations, and deaths. Each suspected acute exacerbation was adjudicated by a central committee in a blinded fashion.

STUDY VISITS

Screening procedures included the taking of a detailed history to rule out known causes of interstitial lung disease, a physical examination (including the measurement of oxygen saturation by pulse oximetry with patients breathing ambient air), spirometry, and measurements of lung volume on plethysmography, carbon monoxide diffusion capacity, and arterial blood gases. Echocardiography was performed to rule out aortic stenosis and idiopathic hypertrophic subaortic stenosis. High-resolution CT images were reviewed

locally and were provided for quality control to a central committee. Pathological specimens, if available, were reviewed centrally.

Eligible patients returned for an enrollment visit within 6 weeks after screening. During this visit, they received training in the proper administration and storage of the study drug and use of a diary. All patients received an initial dose of a study drug at this visit and were monitored for 60 minutes for adverse effects. Follow-up visits were scheduled at 1, 6, and 12 weeks. After completion of the 12-week visit, all patients were started on treatment with open-label sildenafil. Visits were scheduled at 13, 18, and 24 weeks; at 28 weeks, serious adverse events and vital status were documented.

Testing of the 6-minute walk distance was performed with the use of a standardized protocol at the time of screening and enrollment and at study visits at 6, 12, 18, and 24 weeks (Section G in the Supplementary Appendix). All 6-minute walk tests were conducted by study personnel who were not directly involved in study coordination. At screening, patients with a pulse oxygen saturation of 88% or more while at rest were tested breathing ambient air. All other patients received supplemental oxygen, titrated to a pulse oxygen saturation of at least 92% while at rest. Patients walked for 6 minutes or until their pulse oxygen saturation fell below 80% for 6 seconds; the distance walked at that point was recorded. Subsequent walk tests were performed with the use of the same amount of oxygen used at screening. Patients whose resting pulse oxygen saturation on follow-up testing did not reach 88% during administration of the baseline amount of oxygen were not retested and were recorded as having walked 0 m. At enrollment, patients were required to undergo two walk tests at least 1 hour apart. The distances that were recorded in the two tests could differ by no more than 15%; at follow-up visits, one test of the 6-minute walk distance was conducted.

STATISTICAL ANALYSIS

The study was powered to show an improvement of 20% or more on the 6-minute walk distance from enrollment to 12 weeks. According to available safety and efficacy data for sildenafil at the time that the protocol was designed, a response rate of 30% with sildenafil was expected.[6] On the basis of an assumed placebo response rate of 10%, with an overall type I error rate of 0.05 (allowing for one interim analysis and a 1:1 randomization ratio), 170 patients were needed to provide a power of 90%. These calculations were based on a chi-square test of equal proportions. The data and safety monitoring board reviewed data throughout the study, and one planned interim analysis for efficacy was conducted when 50% of the patients had completed the 12-week visit.

The primary test statistic was based on a chi-square test comparing the rates of improvement of 20% or more on testing of the 6-minute walk distance from baseline to 12 weeks in the two study groups. For the primary analysis, the baseline measurement of the 6-minute walk distance was calculated as the maximum of the prerandomization walks. In the intention-to-treat analysis, patients were deemed to have had no response if the rate of improvement was less than 20% at 12 weeks or if they died, withdrew from the study, or had missing data.

A post hoc sensitivity analysis of data from the 6-minute walk test was conducted to examine the effect of the prerandomization reference walk (maximum distance, mean distance, and the distances of the first and second walks at enrollment) and the definition of response (any improvement, 20% improvement, improvement of 30 m, and decline of 30 m) (Table 2 in Section C in the Supplementary Appendix). Several recent studies have suggested a minimally important difference of approximately 30 m on the 6-minute walk test for patients with idiopathic pulmonary fibrosis and other lung diseases.[13,14] Analysis of longitudinal continuous end points was conducted with the use of a linear mixed model with

slope measurements for fixed effects estimated from enrollment to 12 weeks and then from 12 weeks to 24 weeks to reflect the change to open-label administration of sildenafil. Adjustment variables in the linear mixed models included baseline measurements of age, sex, race, height, and carbon monoxide diffusion capacity. The treatment effect was summarized with a point estimate and 95% confidence intervals. Survival curves were constructed with the use of the Kaplan–Meier method with a statistical comparison that was based on the log-rank test statistic. A P value of less than 0.05 was considered to indicate statistical significance. For the primary analysis, a P value of 0.049 or less would have been required for statistical significance. All P values are two-sided, and no adjustment has been made for multiple comparisons.

RESULTS

BASELINE CHARACTERISTICS

From September 2007 through March 2009, we screened 303 patients with idiopathic pulmonary fibrosis for eligibility. Of these patients, 180 were enrolled: 89 in the sildenafil group and 91 in the placebo group (Fig. 1, and Section B in the Supplementary Appendix). The mean age of the patients was 69 years, 17% were women, and 91% were white (Table 1). The mean baseline 6-minute walk distance was 265 m, the mean percentage of the predicted forced vital capacity was 56.8%, and the mean percentage of the predicted carbon monoxide diffusion capacity was 26.3%.

PERIOD 1 (WEEKS 0 TO 12)

Improvement in the 6-minute walk distance of 20% or more over baseline occurred in 9 of 89 patients (10%) in the sildenafil group and 6 of 91 (7%) in the placebo group (P = 0.39). Of the 24 post hoc sensitivity analyses of walk-test data, none of the differences were significant (Table 2 in Section C in the Supplementary Appendix). On the basis of the linear mixed model that used a compound symmetry assumption, the average walk distance worsened in both groups (Table 3 in Section C in the Supplementary Appendix); the distance decreased by a mean of 28.5 m in the sildenafil group and 45.2 m in the placebo group at 12 weeks (P = 0.11).

When measured at rest, patients in the sildenafil group, as compared with the placebo group, had significant improvement in measurements of the percentage of predicted carbon monoxide diffusion capacity (difference, 1.55 percentage points; P = 0.04), the partial pressure of oxygen in arterial blood (difference, 3.02 mm Hg; P = 0.02), and arterial oxygen saturation (difference, 1.21 percentage points; P = 0.05) (Table 2). Scores remained stable in the sildenafil group but worsened in the placebo group on the Shortness of Breath Questionnaire (estimated difference, −6.58; P = 0.006) and the total score on the St. George's Respiratory Questionnaire (estimated difference, −4.08; P = 0.01). Similar findings were noted for symptom and activity subscores on the St. George's Respiratory Questionnaire. On the SF-36, there were no between-group differences in the aggregate physical or mental subscores; however, the general health subscore was better preserved in the sildenafil group than in the placebo group (absolute difference, 2.86; P = 0.008). No significant differences were observed in the Borg Dyspnea Index or the EQ-5D scores.

During period 1, 89.8% of patients in the sildenafil group and 85.7% of those in the placebo group reported that they missed no more than 1 day of medication per week.

PERIOD 2 (WEEKS 12 TO 24)

Among patients who were initially assigned to the placebo group but who received sildenafil during period 2, the 6-minute walk distance did not significantly change from week 12 to

week 24. There also was no significant change in measurements of the partial pressure of oxygen, arterial oxygen saturation, and the percentage of predicted carbon monoxide diffusion capacity or in the score on the Shortness of Breath Questionnaire, the activity score on the St. George's Respiratory Questionnaire, and the SF-36 general health and vitality scores (Table 3 in Section C in the Supplementary Appendix).

MORTALITY AND ACUTE EXACERBATIONS

At 12 weeks, there was no significant between-group difference in mortality, with two deaths in the sildenafil group and four in the placebo group (P = 0.43), or in the rate of acute exacerbations of idiopathic pulmonary fibrosis, with two exacerbations in the sildenafil group and four in the placebo group (P = 0.68) (Table 3).

ADVERSE EVENTS

During period 1, serious adverse events were reported in 15% of patients in the sildenafil group and in 16% of patients in the placebo group (P = 0.73) (Table 4). The most common serious adverse events were respiratory-related events, followed by infections and cardiac disorders. There were no significant between-group differences in the occurrence of specific serious adverse events. Orthostatic hypotension was not observed as a serious adverse event in the sildenafil group. Approximately 90% of patients in each group had at least one adverse event, with the most common being dyspnea, cough, and progression of idiopathic pulmonary fibrosis (Table 5 in Section C in the Supplementary Appendix).

DISCUSSION

The use of sildenafil did not cause a significant difference in the proportion of patients with an improvement of 20% or more in the 6-minute walk distance at 12 weeks (the primary outcome). There were small differences favoring sildenafil in some secondary outcomes, including the degree of dyspnea and quality of life. The magnitude of these differences has been shown to be clinically significant.

Sildenafil-treated patients had significant physiological stabilization, as documented by measurements of arterial blood gas and carbon monoxide diffusion capacity, as compared with placebo-treated patients. These findings are consistent with previously published data showing that sildenafil improved ventilation–perfusion matching in patients with pulmonary fibrosis.[5] There were few deaths during the study, and there were no significant treatment-related differences at 12 weeks.

We enrolled patients with advanced disease (as defined by severe physiological impairment), and such patients have been excluded from previous clinical trials since it was thought that they were less likely to have a response to disease-modifying therapies. In the absence of therapies that improve survival in patients with idiopathic pulmonary fibrosis, improvements in walk distance, degree of dyspnea, and quality of life are no doubt important to patients, especially those with disease as severe as the ones we enrolled. Although the between-group difference in the primary outcome, which was a physiological measure, was not significant, the patients receiving sildenafil during period 1 had symptomatic benefit of a magnitude that other observers have found to be clinically meaningful.

There were important limitations to this study. First, our findings are applicable only to patients with advanced idiopathic pulmonary fibrosis, as defined by a carbon monoxide diffusion capacity of less than 35%. Whether the same effects would be observed in patients with milder physiological impairment is unknown. Second, it is unknown whether the treatment effect was driven by a particular subgroup of patients (e.g., those with more severe

pulmonary vascular disease); data regarding right-heart catheterization, which could have suggested the presence of such subgroups, were not available. Third, the study was too short and enrolled too few patients to assess the duration of the effect of sildenafil or any potential effect of sildenafil on rates of acute respiratory worsening or death. Fourth, it is possible that the improvements in subjective outcomes, such as quality of life, were due to incomplete masking.

Although this study did not meet its pre-specified primary outcome and the therapeutic efficacy of sildenafil is far from established, our data provide the clinical equipoise needed to conduct further trials involving patients with advanced idiopathic pulmonary fibrosis. While such trials are being designed and implemented, our finding that sildenafil was associated with symptomatic improvement may be of value to patients with advanced idiopathic pulmonary fibrosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

The following IPFnet investigators participated in this study: **Protocol Committee** — University of Alabama, Birmingham: J. de Andrade; Duke Clinical Research Institute, Durham, NC: K.J. Anstrom; University of California, San Francisco: H.R. Collard; University of Michigan, Ann Arbor: K.R. Flaherty; National Jewish Medical and Research Center, Denver: S. Frankel; Weill Medical College of Cornell University, New York: R. Kaplan; Vanderbilt University, Nashville: L. Lancaster; University of Washington, Seattle: G. Raghu; National Jewish Health and the University of Colorado, Denver: M. Schwarz; Mayo Clinic, Rochester, MN: J.P. Utz; University of Chicago, Chicago: S.R. White; Sansum Clinic, Santa Barbara, CA: D.A. Zisman. **Steering Committee** — University of Iowa, Iowa City: G.W. Hunninghake (chair); Duke Clinical Research Institute, Durham, NC: K.J. Anstrom; National Jewish Health and the University of Colorado, Denver: K.K. Brown; University of Alabama, Birmingham: J. de Andrade; Weill Medical College of Cornell University, New York: R.J. Kaner; University of California at San Francisco, San Francisco: T.E. King, Jr.; Tulane University, New Orleans: J.A. Lasky; Vanderbilt University, Nashville: J.E. Loyd; University of Michigan, Ann Arbor: F.J. Martinez; University of Washington, Seattle: G. Raghu; Emory University, Atlanta: J. Roman; Mayo Clinic, Rochester, MN: J.H. Ryu; University of Chicago, Chicago: I. Noth; UCLA, Los Angeles: D.A. Zisman. **Clinical Centers** — Cleveland Clinic, Cleveland: J. Chapman, M. Olman, S.

Lubell; Duke University Medical Center, Durham, NC: L.D. Morrison, M.P. Steele, T. Haram; Emory University, Atlanta: J. Roman, R. Perez, T. Perez; Mayo Clinic, Rochester, MN: J.H. Ryu, J.P. Utz, A.H. Limper, C.E. Daniels, K. Meiras, S. Walsh; National Jewish Health and the University of Colorado, Denver: K.K. Brown, S. Frankel, M. Schwarz, D. Kervitsky; Tulane University, New Orleans: J.A. Lasky, S. Ditta; University of Alabama, Birmingham: J. de Andrade, V.J. Thannickal, M. Stewart; UCLA, Los Angeles: D.A. Zisman, J.P. Lynch III, E. Calahan, P. Lopez; University of California at San Francisco, San Francisco: T.E. King, Jr., H.R. Collard, J.A. Golden, P.J. Wolters, R. Jeffrey; University of Chicago, Chicago: I. Noth, D.K. Hogarth, N. Sandbo, M.E. Strek, S.R. White, C. Brown, I. Garic, S. Maleckar; University of Michigan, Ann Arbor: F.J. Martinez, K.R. Flaherty, M.L. Han, B. Moore, G.B. Toews, D. Dahlgren; University of Washington, Seattle: G. Raghu, J. Hayes, M. Snyder; Vanderbilt University, Nashville: J.E. Loyd, L. Lancaster, W. Lawson, R. Greer, W. Mason; Weill Medical College of Cornell University, New York: R.J. Kaner, V. Monroy, M. Wang. **Core Lab Chairs** — *Radiology*: National Jewish Health, Denver: D. Lynch; *Pathology*: Mayo Clinic, Scottsdale, AZ: T. Colby. **Data Coordinating Center** — *Duke Clinical Research Institute, Duke University Medical Center, Durham, NC*: K.J. Anstrom, R.C. Becker, E.L. Eisenstein, N.R. MacIntyre, L.D. Morrison, J. Rochon, M.P. Steele, J.S. Sundy, L. Davidson-Ray, P. Dignacco, R. Edwards, R. Anderson, R. Beci, S. Calvert, K. Cain, T. Gentry-Bumpass, D. Hill, M. Ingham, E. Kagan, J. Kaur, C. Matti, J. McClelland, A. Meredith, T. Nguyen, J. Pesarchick, R.S. Roberts, W. Tate, T. Thomas, J. Walker, D. Whelan, J. Winsor, Q. Yang, E. Yow. **NHLBI Representatives** — H.Y. Reynolds, X. Tian, J. Kiley.

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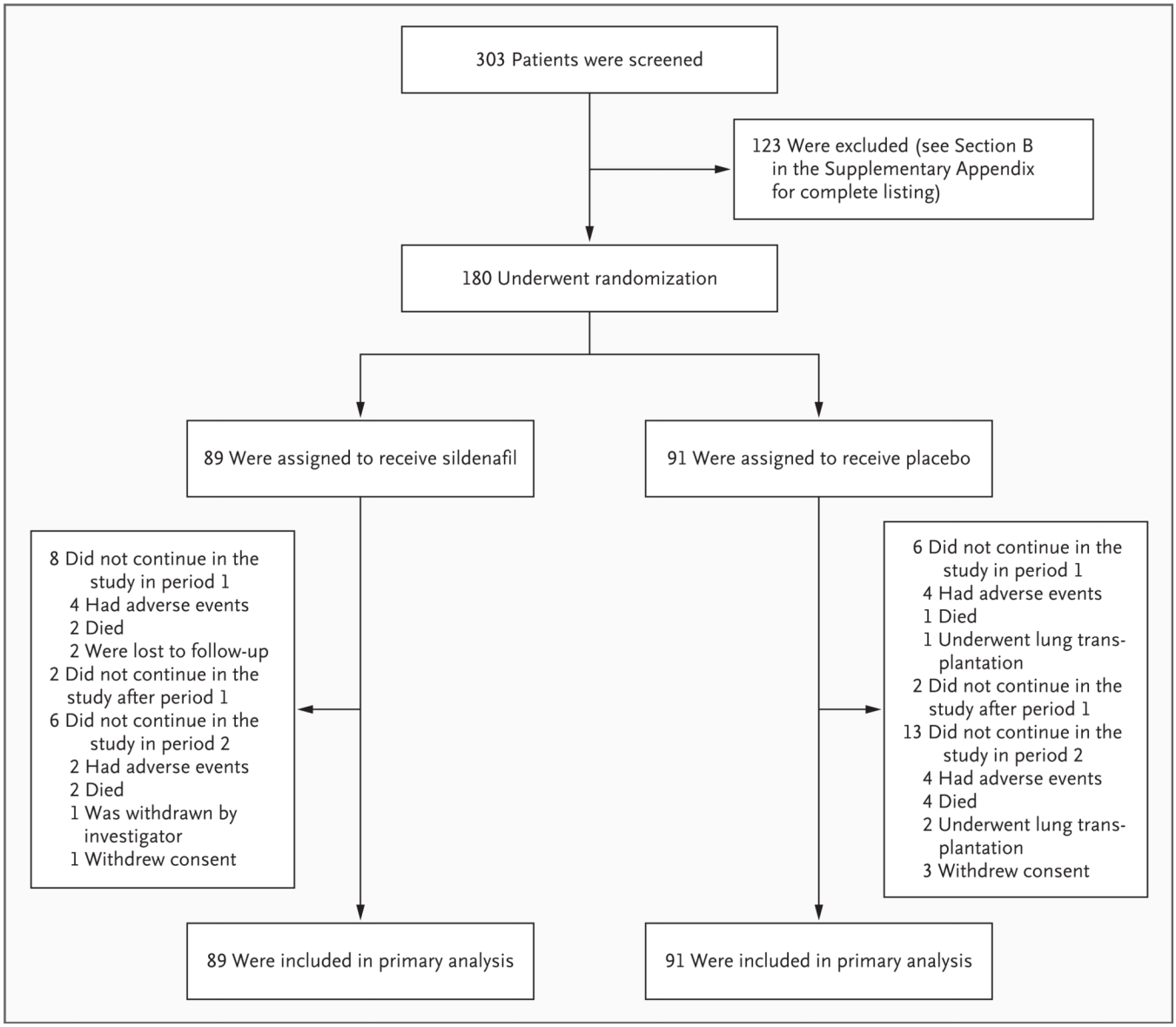

Figure 1.
Enrollment and Outcomes.

Table 1

Baseline Characteristics of the Patients.*

Characteristic	Sildenafil (N = 89)	Placebo (N = 91)
Age — yr	69.76±8.71	68.20±9.25
Female sex — no. (%)	14 (16)	16 (18)
Race — no. (%)†		
White	78 (88)	85 (93)
Black	5 (6)	1 (1)
Other	6 (7)	5 (5)
History of smoking — no. (%)	68 (76)	69 (76)
Time since diagnosis — yr	2.03±1.94	1.87±1.93
Supplemental use of oxygen during walk test — no. (%)	28 (31)	24 (26)
6-Minute walk distance — m		
First test	246.93±99.11	267.71±127.75
Second test	246.39±103.40	269.55±129.83
Score on Borg Dyspnea Index after walk test (range, 0–10)‡	3.82±1.95	3.33±1.73
Score on Shortness of Breath Questionnaire (range, 0–120)‡§	50.71±22.00	43.28±20.18
Total score on St. George's Respiratory Questionnaire (range, 0–100)‡	54.55±16.46	51.72±15.86
SF-36 (range for each subscale, 0–100)¶		
Aggregate physical score	33.17±9.19	34.84±8.69
Aggregate mental score	49.53±9.76	50.58±9.52
Score on EQ-5D¶		
Self-report questionnaire (range, −0.59 to 1.00)	0.71±0.24	0.74±0.19
Visual analogue scale (range, 0–100)	66.49±17.45	67.66±16.98
Forced vital capacity — % of predicted value	54.89±14.00	58.73±14.12
Carbon monoxide diffusion capacity — % of predicted value	25.81±6.03	26.73±6.16
Partial pressure of oxygen — mm Hg	66.22±12.22	69.88±12.85
Arterial oxygen saturation — %§	91.24±4.22	92.59±3.75

*Plus–minus values are means ±SD. EQ-5D denotes EuroQol Group 5-Dimension, and SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey. Percentages may not total 100 because of rounding.

†Race was self-reported.

‡A higher score indicates worse function.

§P<0.05.

¶A higher score indicates better function.

Table 2

Change in Prespecified Secondary Outcomes at 12 Weeks.*

Characteristic	Sildenafil (N = 89)	Placebo (N = 91)	Absolute Difference†	P Value
	mean change (95% confidence interval)			
Dyspnea				
Score on Borg Dyspnea Index after walk test‡	0.04 (−0.30 to 0.37)	0.37 (0.04 to 0.70)	−0.34 (−0.81 to 0.14)	0.16
Shortness of Breath Questionnaire‡	0.22 (−3.10 to 3.54)	6.81 (3.53 to 10.08)	−6.58 (−11.25 to −1.92)	0.006
Quality of life				
St. George's Respiratory Questionnaire‡				
Total score	−1.64 (−3.91 to 0.64)	2.45 (0.17 to 4.72)	−4.08 (−7.30 to −0.86)	0.01
Symptoms score	−3.58 (−7.02 to −0.13)	2.15 (−1.30 to 5.61)	−5.73 (−10.61 to −0.85)	0.02
Activity score	−1.15 (−3.68 to 1.38)	2.49 (0.00 to 4.99)	−3.64 (−7.20 to −0.09)	0.04
Impacts score (social function)	−0.88 (−3.78 to 2.02)	2.82 (−0.03 to 5.67)	−3.70 (−7.76 to 0.37)	0.07
SF-36§				
Aggregate physical score	−0.51 (−1.86 to 0.83)	−0.35 (−1.68 to 0.99)	−0.17 (−2.06 to 1.73)	0.86
Aggregate mental score	1.30 (−0.59 to 3.18)	3.02 (1.15 to 4.89)	−1.72 (−4.38 to 0.93)	0.20
Bodily pain score	−0.21 (−2.13 to 1.71)	1.97 (0.08 to 3.85)	−2.17 (−4.86 to 0.52)	0.11
General health score	−1.04 (−2.52 to 0.44)	−3.89 (−5.37 to −2.42)	2.86 (0.76 to 4.95)	0.008
Mental health score	−0.16 (−1.81 to 1.49)	−1.31 (−2.93 to 0.30)	1.15 (−1.15 to 3.46)	0.32
Physical functioning score	−0.93 (−2.24 to 0.38)	−1.46 (−2.76 to −0.17)	0.53 (−1.31 to 2.37)	0.57
Role–emotional score	−2.72 (−5.56 to 0.12)	−4.82 (−7.63 to −2.01)	2.10 (−1.90 to 6.10)	0.30
Role–physical score	−0.87 (−2.85 to 1.10)	−2.03 (−3.98 to −0.08)	1.16 (−1.62 to 3.93)	0.41
Social functioning score	−0.72 (−3.01 to 1.57)	−2.71 (−4.97 to −0.46)	1.99 (−1.22 to 5.21)	0.22
Vitality score	0.02 (−1.70 to 1.75)	−2.01 (−3.70 to −0.31)	2.03 (−0.39 to 4.44)	0.10
Score on EQ−5D§				
Self-report questionnaire	−0.01 (−0.06 to 0.03)	−0.03 (−0.08 to 0.01)	0.02 (−0.04 to 0.08)	0.54
Visual-analogue scale	0.48 (−3.10 to 4.06)	−1.81 (−5.34 to 1.73)	2.28 (−2.75 to 7.32)	0.37
Pulmonary function				
Forced vital capacity (% of predicted value)	−0.97 (−2.00 to 0.06)	−1.29 (−2.30 to −0.28)	0.32 (−1.12 to 1.76)	0.66
Carbon monoxide diffusion capacity (% of predicted value)	−0.33 (−1.36 to 0.71)	−1.87 (−2.91 to −0.83)	1.55 (0.08 to 3.01)	0.04
Partial pressure of oxygen (mm Hg)	−0.63 (−2.41 to 1.16)	−3.64 (−5.41 to −1.87)	3.02 (0.50 to 5.53)	0.02
Partial pressure of carbon dioxide (mm Hg)	−0.01 (−0.75 to 0.73)	−0.02 (−0.75 to 0.71)	0.01 (−1.03 to 1.05)	0.98
Alveolar–arterial gradient (mm Hg)	0.41 (−1.54 to 2.37)	2.95 (0.99 to 4.92)	−2.54 (−5.31 to 0.23)	0.07
Arterial oxygen saturation (%)	−0.17 (−1.02 to 0.69)	−1.38 (−2.23 to −0.52)	1.21 (0.00 to 2.42)	0.05

*Adjustment variables in the linear mixed models included baseline measurements of age, sex, race, height, and carbon monoxide diffusion capacity. The estimated change is for the 12-week period. EQ-5D denotes EuroQol Group 5-Dimension, and SF-36 Medical Outcomes Study 36-Item Short-Form Health Survey.

†This value is the absolute difference between the sildenafil group and the placebo group in the change from baseline.

[‡] A higher score indicates worse function.

[§] A higher score indicates better function.

Table 3

Death and Acute Exacerbation.

Variable	Sildenafil (N = 89)	Placebo (N = 91)	P Value
Death from any cause — no (%) *			
12 wk	2 (2)	4 (4)	0.43
24 wk	3 (3)	9 (10)	0.08
28 wk	4 (5)	11 (13)	0.07
Acute exacerbation — no./total no. (%)			
Period 1	2/89 (2)	4/91 (4)	0.68
Period 2	1/78 (1)	3/83 (4)	0.62
All patients	3/89 (3)	7/91 (8)	0.33

* Percentages of deaths are based on data from Kaplan–Meier analysis and were calculated as 1 minus the Kaplan–Meier survival rate. The numbers at risk in the sildenafil group were 84 at 12 weeks, 73 at 24 weeks, and 57 at 28 weeks; the numbers at risk in the placebo group were 85 at 12 weeks, 71 at 24 weeks, and 50 at 28 weeks.

Table 4

Serious Adverse Events at 12 Weeks.*

Event	Sildenafil (N = 89)	Placebo (N = 91)	P Value
	no. of patients (%)		
Any serious adverse event†	13 (15)	15 (16)	0.73
Respiratory, thoracic, or mediastinal disorder‡	7 (8)	9 (10)	0.63
Worsening of idiopathic pulmonary fibrosis	2 (2)	5 (5)	0.44
Worsening of dyspnea	2 (2)	1 (1)	0.62
Respiratory failure	1 (1)	2 (2)	0.99
Chronic obstructive pulmonary disease	0	1 (1)	0.99
Hypoxemia	1 (1)	0	0.49
Pleural effusion	0	1 (1)	0.99
Pneumothorax	0	1 (1)	0.99
Pulmonary embolism	1 (1)	0	0.49
Infection or infestation	3 (3)	2 (2)	0.68
Pneumonia	2 (2)	1 (1)	0.62
Bronchitis	0	1 (1)	0.99
Influenza	1 (1)	0	0.49
Viral infection	1 (1)	0	0.49
Cardiac disorder	1 (1)	3 (3)	0.62
Atrial fibrillation	0	2 (2)	0.50
Congestive heart failure	1 (1)	0	0.49
Coronary artery disease	0	1 (1)	0.99
Gastrointestinal disorder	2 (2)	1 (1)	0.62
Ischemic colitis	1 (1)	0	0.49
Intestinal obstruction	0	1 (1)	0.99
Peptic ulcer hemorrhage	1 (1)	0	0.49

*Listed are the numbers of patients who had at least one serious adverse event involving each organ system. All serious adverse events are listed in Table 4 in Section C in the Supplementary Appendix, available with the full text of this article at NEJM.org.

†Among all patients, 14 serious adverse events occurred in the sildenafil group and 23 in the placebo group.

‡Among patients in this category, 7 serious adverse events occurred in the sildenafil group and 11 in the placebo group.