

## ORIGINAL ARTICLE

# Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network\*

## ABSTRACT

**BACKGROUND**

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A combination of prednisone, azathioprine, and N-acetylcysteine (NAC) has been widely used as a treatment for idiopathic pulmonary fibrosis. The safety and efficacy of this three-drug regimen is unknown.

**METHODS**

In this randomized, double-blind, placebo-controlled trial, we assigned patients with idiopathic pulmonary fibrosis who had mild-to-moderate lung-function impairment to one of three groups — receiving a combination of prednisone, azathioprine, and NAC (combination therapy), NAC alone, or placebo — in a 1:1:1 ratio. The primary outcome was the change in longitudinal measurements of forced vital capacity during a 60-week treatment period.

**RESULTS**

When approximately 50% of data had been collected (with 77 patients in the combination-therapy group and 78 in the placebo group), a planned interim analysis revealed that patients in the combination-therapy group, as compared with the placebo group, had an increased rate of death (8 vs. 1,  $P=0.01$ ) and hospitalization (23 vs. 7,  $P<0.001$ ). These observations, coupled with no evidence of physiological or clinical benefit for combination therapy, prompted the independent data and safety monitoring board to recommend termination of the combination-therapy group at a mean follow-up of 32 weeks. Data from the ongoing comparison of the NAC-only group and the placebo group are not reported here.

**CONCLUSIONS**

Increased risks of death and hospitalization were observed in patients with idiopathic pulmonary fibrosis who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo. These findings provide evidence against the use of this combination in such patients. (Funded by the National Heart, Lung, and Blood Institute and the Cowlin Family Fund; ClinicalTrials.gov number, NCT00650091.)

\*Members of the Idiopathic Pulmonary Fibrosis Clinical Research Network are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**I**DIOPATHIC PULMONARY FIBROSIS IS A chronic, progressive lung disease of unknown cause characterized by the histopathological pattern of usual interstitial pneumonia.<sup>1</sup> The median survival of patients with idiopathic pulmonary fibrosis after diagnosis is 2 to 5 years.<sup>1</sup>

The use of glucocorticoids or immunosuppressive agents has been the conventional approach to the treatment of patients with this disease. A consensus-based guideline suggested that a two-drug regimen (a combination of prednisone and either azathioprine or cyclophosphamide) be used in a subgroup of patients with idiopathic pulmonary fibrosis.<sup>2</sup> A survey of pulmonologists showed that almost 50% used a regimen of either two drugs (azathioprine plus prednisone) or three drugs (azathioprine, prednisone, and *N*-acetylcysteine [NAC]) when therapy was offered to their patients with mild idiopathic pulmonary fibrosis.<sup>3</sup>

A trial of the three-drug regimen showed that this treatment preserved pulmonary function better than the two-drug regimen.<sup>4</sup> However, since no placebos for azathioprine and prednisone were included, the efficacy of this three-drug regimen has remained controversial.<sup>5</sup> Consequently, international guidelines have differed in giving this three-drug regimen a “weak no”<sup>1</sup> or “weak yes”<sup>6</sup> recommendation.

In this clinical trial, called Prednisone, Azathioprine, and *N*-Acetylcysteine: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis (PANTHER-IPF), we evaluated the three-drug regimen against NAC alone (plus matched identified placebos for prednisone and azathioprine), as compared with matched placebos for each of the active therapies, in patients with idiopathic pulmonary fibrosis who had mild-to-moderate impairment in pulmonary function. On the basis of a prespecified interim assessment by the data and safety monitoring board, the three-drug regimen was stopped on October 14, 2011; the NAC-only and placebo groups continue to recruit and be followed for the prespecified duration of 60 weeks. The prednisone and azathioprine placebos were discontinued in the remaining study groups. Here we report the results of the three-drug regimen as compared with the placebo group at the time of the interim assessment.

## METHODS

### STUDY OVERSIGHT

The study was designed and conducted by the Idiopathic Pulmonary Fibrosis Clinical Research

Network (IPFnet) steering committee and was carried out at 25 clinical centers. (A complete listing of IPFnet sites is included in the Supplementary Appendix, available with the full text of this article at NEJM.org.) An independent protocol review committee, appointed by the National Heart, Lung, and Blood Institute (NHLBI), reviewed and approved the protocol (available at NEJM.org) for scientific merit. An NHLBI-appointed data and safety monitoring board and all local institutional review boards approved the protocol and all amendments. All patients provided written informed consent.

The Duke Clinical Research Institute served as the data-coordinating center, and the IPFnet steering committee oversaw all aspects of the study's conduct. The scientific steering committee under the direction of the coprimary investigators developed the design and concept of the study, approved the statistical plan, had full access to all the data, and interpreted the data. The writing committee wrote the first draft of the manuscript. The steering committee made subsequent revisions, deemed the manuscript to be faithful to the protocol, and made the decision to submit it for publication. The PANTHER-IPF writing committee and the IPFnet steering committee approved the final manuscript. Prednisone and azathioprine were purchased, and matching placebos were produced during the overencapsulation process. NAC and matching placebo were donated by the manufacturer, Zambon. Zambon was apprised of the progress of the study and reviewed a draft of the manuscript before submission for publication. All authors assume responsibility for the overall content and integrity of the article.

### STUDY PATIENTS

Patients with idiopathic pulmonary fibrosis between the ages of 35 and 85 years who had mild-to-moderate lung-function impairment (defined as a forced vital capacity [FVC] of  $\geq 50\%$  and a carbon monoxide diffusing capacity of  $\geq 30\%$  of the predicted value) were potentially eligible. All patients met the modified criteria of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association for the diagnosis of idiopathic pulmonary fibrosis.<sup>1,7</sup> Patients had received the diagnosis of idiopathic pulmonary fibrosis on the basis of high-resolution computed tomography (CT) or biopsy 48 months or less before enrollment. Detailed exclusion criteria are listed in the study protocol.

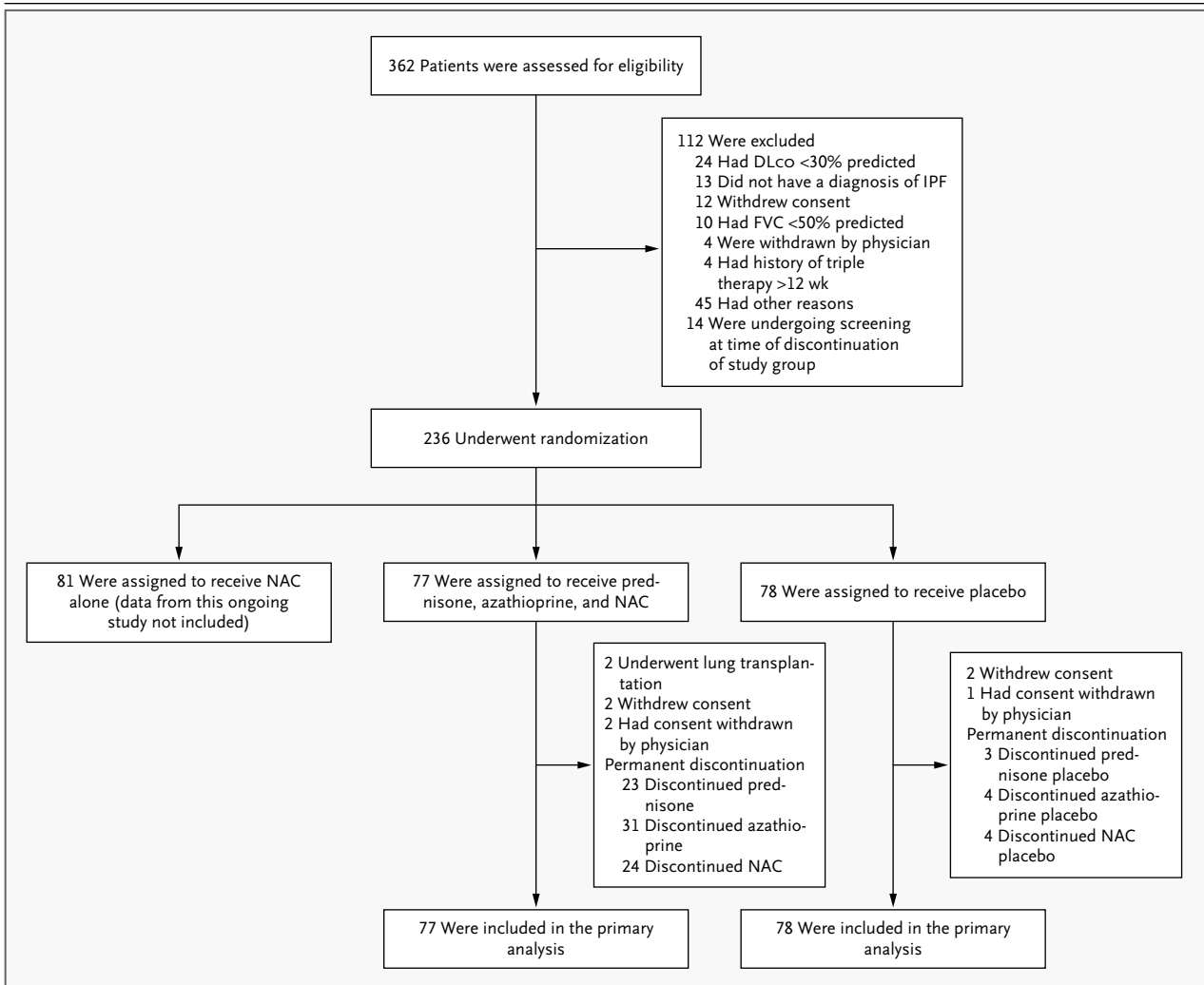
**STUDY DESIGN**

PANTHER-IPF was a randomized, double-blind, placebo-controlled trial of a combination of oral azathioprine, prednisone, and NAC (combination therapy) or NAC alone plus placebos for azathioprine and prednisone, as compared with matched placebos for each of the active therapies. The prednisone dose was started at 0.5 mg per kilogram of ideal body weight and was tapered to 0.15 mg per kilogram during a period of 25 weeks. The azathioprine dose (maximum, 150 mg per day) was based on the patient's ideal weight, concurrent use of allopurinol, and thiopurine methyltransferase (TPMT) activity. NAC was prescribed at 600 mg orally three times a day. Detailed algorithms were provided for dose adjustment in case

of potential adverse events. Patients were seen at the clinical centers for screening, at baseline, and at 4, 15, 30, 45, and 60 weeks. Patients with acute respiratory events were treated by their primary care physician if they were not seen at IPFnet sites. In the study protocol, specific guidelines were provided with respect to doses of glucocorticoids.

**RANDOMIZATION**

A permuted-block randomization plan was created with varying block sizes stratified according to clinical center. Once the screening process was completed, patients were randomly assigned to receive one of the three study regimens in a 1:1:1 ratio through telephone contact with a central interactive voice-response system.



**Figure 1. Enrollment and Outcomes.**

DLco denotes carbon monoxide diffusing capacity, FVC forced vital capacity, IPF idiopathic pulmonary fibrosis, and NAC N-acetylcysteine.

## OUTCOME MEASURES

The primary outcome was the change in FVC during the 60-week period, as derived from the serial measurements made at clinic visits. Secondary outcome measures included the rate of death, time until death, frequency of acute exacerbations, frequency of maintained FVC response, time to disease progression, and a broad panel of other clinical and physiological measures (Table S2 in the Supplementary Appendix). Predefined groups of interest included patients with a FVC value that was higher than the group median at enrollment, typical versus atypical results on the baseline high-resolution CT, the timing of the diagnosis of idiopathic pulmonary fibrosis (<1 year or  $\geq 1$  year before enrollment), a baseline composite physiological index<sup>8</sup> below the group median at enrollment, medical therapy for gastroesophageal reflux, ethnic background, sex, smoking history, and emphysema (>25% on high-resolution CT).

## ADJUDICATION

The IPFnet adjudication committee reviewed all deaths, hospitalizations, and suspected acute exacerbations for cause. The definition of an acute exacerbation was prespecified and was in accordance with criteria reported previously.<sup>9</sup>

## STATISTICAL ANALYSIS

On the basis of findings in previous clinical trials involving patients with idiopathic pulmonary fibrosis, we estimated that the decline in FVC would be approximately 0.20 liters during the 60-week study period in the placebo group. We determined that a difference of 0.15 liters from that in the placebo group (i.e., a decline in lung function of 0.05 liters from baseline) would be clinically meaningful. After accounting for potential dropout and imperfect compliance,<sup>10</sup> we determined that 130 patients per group would provide a power of 90% for the first step of the testing procedure under most scenarios.<sup>11</sup> The target sample size was expected to provide a power of approximately 93% to detect a significant difference at the two-sided 0.05 level for the hypothesized difference of 0.15 liters between study groups at 60 weeks.

All analyses are based on the intention-to-treat principle with data from all patients who underwent randomization. For continuous baseline factors, summary measures are presented using means ( $\pm$ SD) and medians and interquar-

tile ranges. For categorical variables, counts and percentages are presented.

The trial was designed with a two-step procedure to control the experiment-wise error rate at the 0.05 level. The first step was based on an overall test of 2 degrees of freedom. If any difference between study groups was statistically significant at the 0.05 level, then each of the three pairwise comparisons would be tested at the 0.05 level.

For the primary analysis, we used a mixed-model repeated-measures analysis to compare changes in FVC in the three study groups during the 60-week study period.<sup>12</sup> Variables in the regression model included study group, time, time according to treatment, age, sex, race, and height. Contrast estimates of differences in slopes of treatment according to time (along with confidence intervals) were used to estimate the treatment effect. For binary end points, statistical comparisons were based on two-sided Fisher's exact tests. For time-to-event outcomes, we used a Cox proportional-hazards regression model. Kaplan-Meier curves were used to display event rates. All test statistics were presented with two-sided P values.

The protocol specified that the data and safety monitoring board would meet multiple times approximately every 6 months to review data for safety and overall trial progress. During the one planned interim analysis for efficacy, a Bonferroni approximation was applied to protect against inflation of the type I error rate. For the interim analysis, the critical value for the test of 2 degrees of freedom in differences in FVC was set to have an alpha level of 0.0001 because of the importance of the secondary end points.

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## RESULTS

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### INTERIM ASSESSMENTS

After the planned midpoint interim analysis, the data and safety monitoring board recommended discontinuation of the three-drug regimen because of an excess in the number of deaths, hospitalizations, and serious adverse events among patients in the combination-therapy group, as compared with the placebo group. The NHLBI accepted this recommendation and on October 14, 2011, instructed the investigators to discontinue the three-drug regimen effective immediately. Data from the ongoing study of patients in

the NAC-only and placebo groups are not reported here.

#### BASELINE CHARACTERISTICS

From December 2009 through October 2011, a total of 77 patients were enrolled in the combination-therapy group and 78 in the placebo group

(Fig. 1). The mean age of the patients was 68 years; 25% were women, and 97% were white. The mean percent predicted FVC was 71%, and the mean percent predicted carbon monoxide diffusing capacity was 44%. The two groups were well matched with respect to demographic and clinical characteristics (Table 1). Findings on high-resolution CT

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	Combination Therapy (N=77)	Placebo (N=78)
Age — yr		
Mean	68.8±7.3	67.9±8.1
Median (IQR)	68.6 (63.9–74.3)	67.9 (62.4–74.0)
Female sex — no. (%)	18 (23)	21 (27)
Race or ethnic group — no. (%)†		
White	75 (97)	75 (96)
Black	1 (1)	0
Hispanic	1 (1)	5 (6)
History of smoking — no. (%)		
Current	3 (4)	4 (5)
Past	51 (66)	54 (69)
Never	23 (30)	20 (26)
Time since diagnosis — yr		
Mean	0.9±1.1	1.1±1.0
Median (IQR)	0.5 (0.2–1.1)	0.8 (0.2–1.6)
Coexisting illness — no. (%)		
Coronary artery disease	13 (17)	17 (22)
Diabetes	11 (14)	14 (18)
Gastroesophageal reflux disease	48 (62)	45 (58)
Lung function		
Forced vital capacity — %		
Mean	69.3±15.1	72.1±14.4
Median (IQR)	65.2 (56.6–80.3)	69.4 (63.2–80.5)
Carbon monoxide diffusion capacity corrected for hemoglobin — % of predicted value		
Mean	42.1±10.2	45.3±12.4
Median (IQR)	40.1 (34.5–47.6)	43.0 (37.4–50.1)
Partial pressure of oxygen in arterial blood while breathing ambient air — mm Hg		
Mean	79.6±9.7	78.8±12.6
Median (IQR)	80.0 (74.0–85.3)	81.0 (71.4–87.0)
Composite physiologic index‡		
Mean	53.7±11.7	49.8±13.5
Median (IQR)	56.8 (46.9–63.3)	51.9 (43.1–60.0)
6-Minute walk distance — m		
Mean	362.0±113.0	368.9±117.3
Median (IQR)	366.0 (300.0–439.0)	381.5 (320.0–447.0)

**Table 1. (Continued.)**

Characteristic	Combination Therapy (N=77)	Placebo (N=78)
Patient-reported outcome		
Score on Shortness of Breath Questionnaire <sup>§</sup>		
Mean	30.1±20.1	29.1±19.4
Median (IQR)	27.5 (14.0–39.0)	24.0 (16.0–40.0)
Total score on St. George's Respiratory Questionnaire <sup>¶</sup>		
Mean	38.7±17.4	39.4±17.4
Median (IQR)	38.0 (25.5–47.2)	37.3 (28.0–52.6)
SF-36 aggregate physical score <sup>  </sup>		
Mean	40.3±9.8	40.6±9.3
Median (IQR)	39.9 (33.4–46.5)	41.7 (35.0–47.7)
SF-36 aggregate mental score <sup>  </sup>		
Mean	53.9±9.6	55.7±7.4
Median (IQR)	55.7 (49.7–61.3)	56.5 (50.4–61.8)

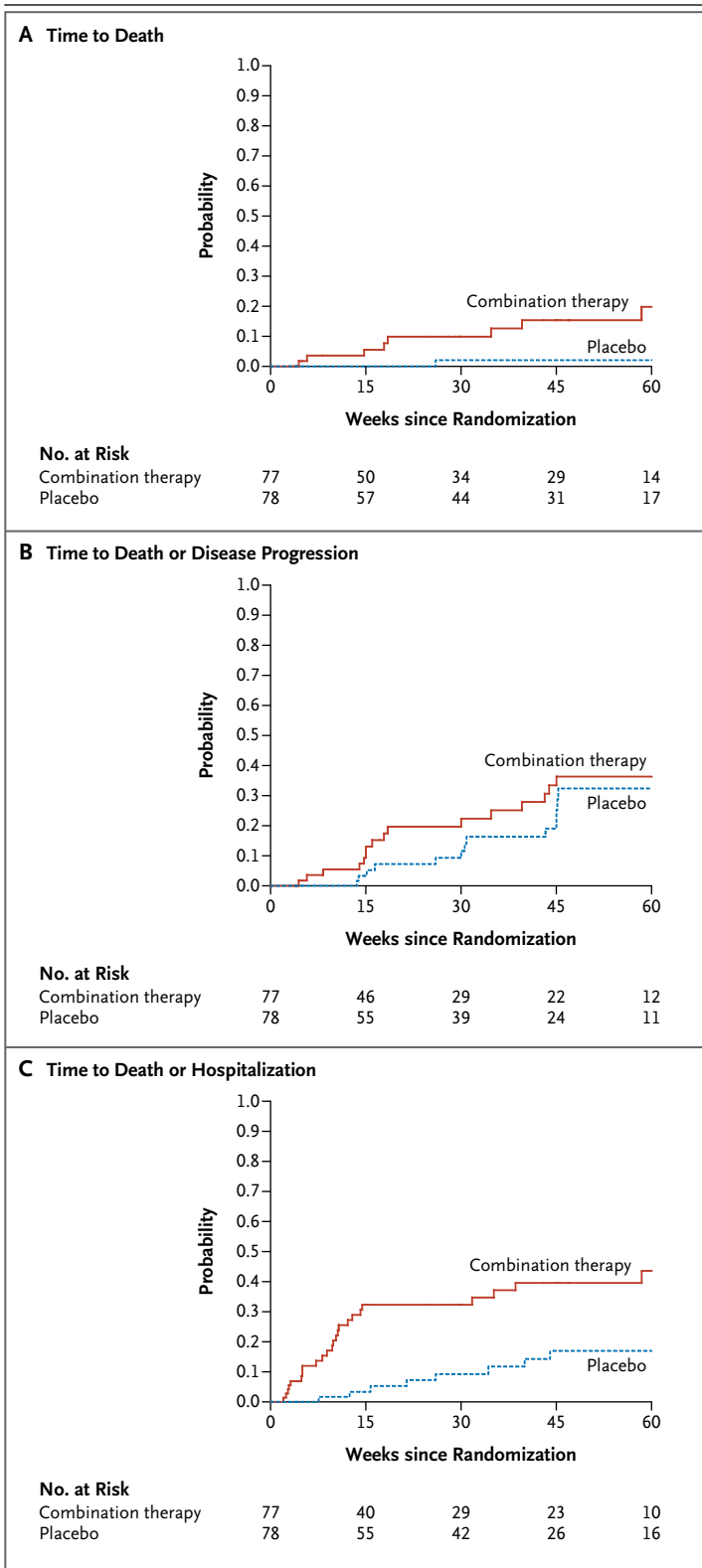
\* Plus–minus values are means ±SD. Combination therapy refers to a three-drug regimen consisting of prednisone, azathioprine, and N-acetylcysteine. There were no significant differences between groups. IQR denotes interquartile range.  
<sup>†</sup> Race or ethnic group was self-reported. Patients could select more than one category.  
<sup>‡</sup> There is no official upper or lower limit on the composite physiological index. Higher scores indicate more severe disease.  
<sup>§</sup> Scores on the Shortness of Breath Questionnaire range from 0 to 120, with higher scores indicating worse function.  
<sup>¶</sup> Scores on St. George's Respiratory Questionnaire range from 0 to 100, with higher scores indicating better function. The suggested minimal important difference for patients with idiopathic pulmonary fibrosis has been estimated at 5 to 8 points.<sup>13</sup>  
<sup>||</sup> Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better function. The suggested minimal important difference for patients with idiopathic pulmonary fibrosis has been estimated at 2 to 4 points.<sup>13</sup>

**Table 2. Safety End Points.\***

End Point	Combination Therapy (N=77)	Placebo (N=78)	Hazard Ratio	P Value
Death — no. (%)				
From any cause	8 (10)	1 (1)		0.01
From respiratory causes	7 (9)	1 (1)		0.02
Hospitalization for any cause — no. (%)	23 (30)	7 (9)		<0.001
Acute exacerbation — no. (%)	5 (6)	0		0.03
Serious adverse event — no. (%)	24 (31)	8 (10)		0.001
Based on Kaplan–Meier estimate at 60 wk — % (95% CI)				
Death from any cause	19.8 (9.9–37.2)	2.0 (0.3–13.6)	9.26 (1.16–74.1)	0.01
Death from any cause or hospitalization	43.6 (30.7–59.0)	16.9 (8.7–31.5)	3.74 (1.68–8.34)	<0.001
Death from any cause or ≥10% decline in FVC	36.3 (23.7–53.0)	32.4 (19.7–50.3)	1.46 (0.70–3.05)	0.30

\* FVC denotes forced vital capacity.





**Figure 2. Kaplan–Meier Curves for the Time until Death, Disease Progression, or Hospitalization.**

Shown are the time until death (Panel A), until a composite of death or disease progression (defined as a decrease in the forced vital capacity of  $\geq 10\%$ ) (Panel B), or until a composite of death or hospitalization (Panel C). Combination therapy refers to a three-drug regimen consisting of prednisone, azathioprine, and *N*-acetylcysteine.

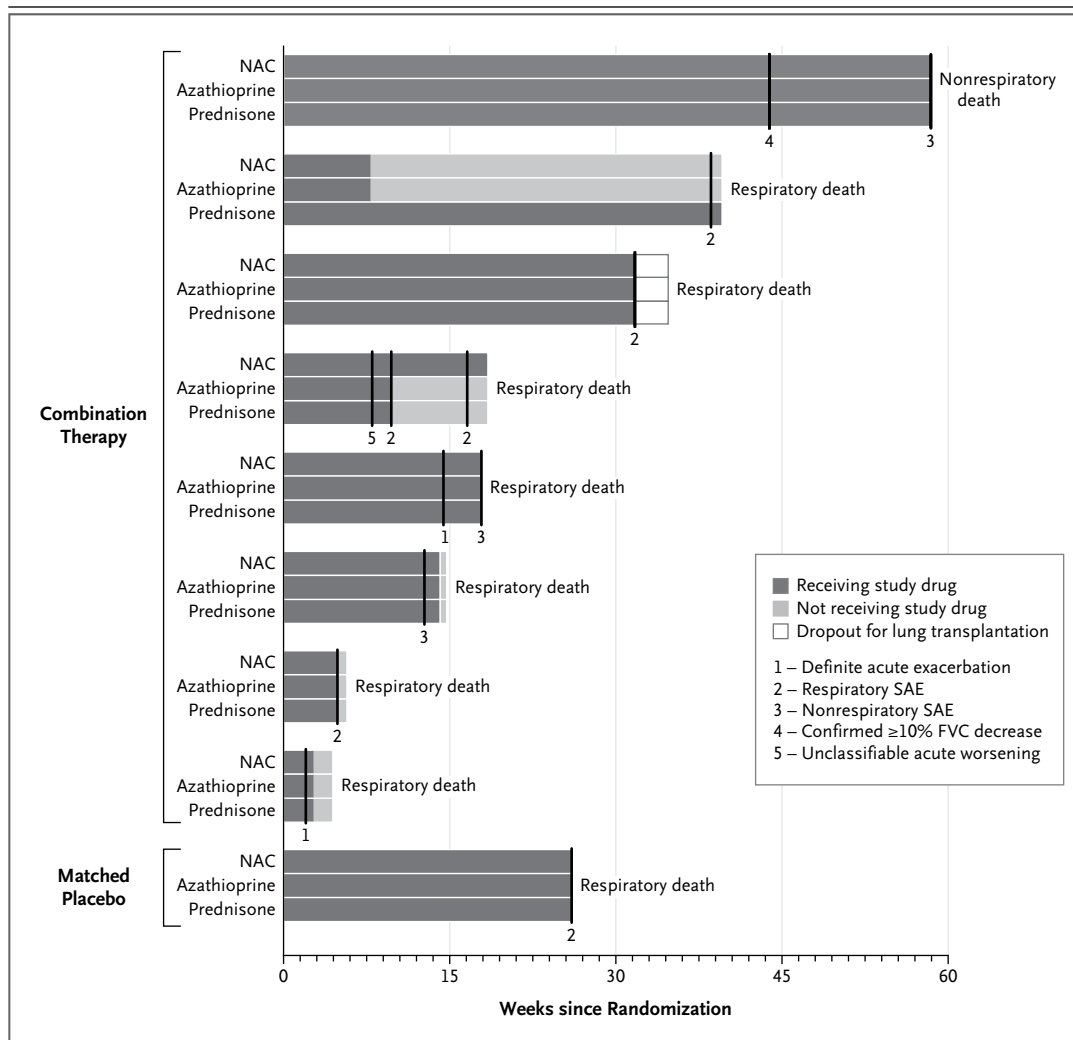
were sufficient to diagnose definite idiopathic pulmonary fibrosis in 66 patients (86%) in the combination-therapy group and 61 (78%) in the placebo group. The diagnosis of idiopathic pulmonary fibrosis was based on a surgical lung-biopsy sample in 38 patients (49%) in the combination-therapy group and 37 (47%) in the placebo group.

**STUDY-DRUG ADHERENCE**

A total of 20 of 77 patients in the combination-therapy group and 3 of 78 in the placebo group discontinued all three study medications. There were significant differences in the numbers of patients who discontinued prednisone (23 in the combination-therapy group and 3 in the placebo group), azathioprine (31 and 4, respectively), and NAC (24 and 4) ( $P < 0.001$  for all comparisons) (Table S1 in the Supplementary Appendix). Among patients who completed the 15-week visit, 38 of 52 (73%) in the combination-therapy group were taking all three study drugs, as compared with 56 of 57 (98%) in the placebo group ( $P < 0.001$ ). Similar results were observed at 30 weeks (64% vs. 98%,  $P < 0.001$ ), 45 weeks (66% vs. 97%,  $P = 0.003$ ), and 60 weeks (60% vs. 100%,  $P = 0.001$ ).

**PRIMARY OUTCOME**

Because the combination-therapy group was stopped early, it was not possible to assess the primary outcome at 60 weeks in all study patients. At the time of the interim analysis, there was no significant difference in the change in FVC between the combination-therapy group and the placebo group ( $-0.24$  liters vs.  $-0.23$  liters,  $P = 0.85$ ). There was no significant difference in the primary outcome in any of the predefined subgroups.



**Figure 3. Timeline until Death during the 60-Week Study Period, According to Study Group.** Shown are follow-up data for patients from randomization until death (from left to right). Each set of bars represents one patient who died, including eight patients receiving combination therapy and one patient receiving matched placebo. For each patient, three bars are plotted (for N-acetylcysteine [NAC], azathioprine, and prednisone), with darker shading indicating the interval in which the drug was administered and lighter shading indicating the interval in which the drug was not administered. The dark vertical lines with a corresponding number indicate the occurrence of a serious adverse event (SAE), as listed.

**SECONDARY OUTCOMES AND SAFETY**

The three-drug regimen provided little benefit with respect to the secondary outcomes (Table S2 in the Supplementary Appendix). There was an imbalance in all-cause mortality, with 8 deaths in the combination-therapy group and 1 in the placebo group (P=0.01) (Table 2 and Fig. 2A). The timeline for events preceding death is shown in Figure 3. An imbalance was noted in the combina-

tion-therapy group, as compared with the placebo group, for the number of all-cause hospitalizations (23 vs. 7, P<0.001). No significant difference was seen in the proportion of patients with disease progression (as defined by a composite outcome of death or a relative drop in FVC of >10%) (Fig. 2B). At 15 weeks, the composite outcome of all-cause mortality or hospitalization was higher in the combination-therapy group than in the pla-



## DISCUSSION

**Table 3. Adverse Events.**

Adverse Event	Combination Therapy (N=77) <i>no. of patients (%)</i>	Placebo (N=78) <i>no. of patients (%)</i>	P Value
<b>Serious adverse event</b>			
Any	24 (31)	8 (10)	0.001
Respiratory system	12 (16)	4 (5)	0.03
Infectious	5 (6)	1 (1)	0.12
Gastrointestinal system	1 (1)	3 (4)	0.62
Cardiac	3 (4)	0	0.12
General disorder*	3 (4)	0	0.12
Neoplasm	2 (3)	0	0.25
Metabolism	1 (1)	0	0.50
Musculoskeletal system	0	1 (1)	1.00
Nervous system	1 (1)	0	0.50
Reproductive system	1 (1)	0	0.50
<b>Adverse event†</b>			
Any	68 (88)	61 (78)	0.09
General disorder	34 (44)	21 (27)	0.03
Skin	13 (17)	4 (5)	0.02
Renal and urinary system	10 (13)	1 (1)	0.005

\* Included in this category were all serious adverse events that did not fall into another body-system category, including adverse drug reactions and drug fever.

† Listed are specific adverse events with a significant between-group difference. A complete list of adverse events is provided in Table S3 in the Supplementary Appendix.

cebo group, with estimated event rates of 32% versus 3% (hazard ratio, 12.11; 95% confidence interval [CI], 2.83 to 51.85;  $P < 0.001$ ) (Fig. 2C). Acute exacerbations occurred in 5 patients (6%) in the combination-therapy group and none in the placebo group. The adjudicated cause of death was related to respiratory events in 8 of the 9 patients.

Assessment of safety showed that treatment-related adverse events were common, with 129 patients (83%) reporting at least one adverse event (Table S3 in the Supplementary Appendix). Serious adverse events occurred more frequently in the combination-therapy group than in the placebo group (24 vs. 8,  $P = 0.001$ ) (Table 3). Patients receiving the three-drug regimen who had a serious adverse event were more likely to discontinue a study drug than were those receiving placebo.

Combined immunosuppression and NAC has been a widely used, conventional approach to the treatment of idiopathic pulmonary fibrosis,<sup>3</sup> despite conflicting recommendations by international guidelines.<sup>1,6</sup> In our study, we found that the combined three-drug regimen of prednisone, azathioprine, and NAC, compared with placebo, was associated with increased all-cause mortality, all-cause hospitalizations, and treatment-related severe adverse events. Deaths and hospitalizations happened early in the combination-therapy group. Although follow-up of the patients was limited, the three-drug regimen provided little or no benefit for primary and secondary outcomes.

In the Idiopathic Pulmonary Fibrosis International Group Exploring *N*-Acetylcysteine I Annual (IFIGENIA) study,<sup>4</sup> the only randomized clinical trial using the three-drug regimen, the patients had a physiological disease severity (mean FVC, 65.6% of the predicted value; mean carbon monoxide diffusing capacity, 43.9% of the predicted value) similar to that in the patients in our study. The rate of death in the combination-therapy group in the IFIGENIA study (9%) was similar to that in our study (10%). However, the Kaplan–Meier estimate of 60-week mortality in our combination-therapy group was higher (19.8%; 95% CI, 9.9 to 37.2). The rates of death among patients with idiopathic pulmonary fibrosis who were receiving placebo in several studies (3.6 to 9%)<sup>14–16</sup> are similar to that observed in our study (2.0%; 95% CI, 0.3 to 13.6). Given the differences in the study groups and the longer duration of the other clinical trials, comparison of mortality among these studies should be made with caution. Nonetheless, our findings show that the excess mortality was attributable to the three-drug therapy.

The merits of our study include a rigorous ascertainment of the diagnosis of idiopathic pulmonary fibrosis by multidisciplinary assessment. In addition, our algorithm-driven approach to dose selection, including measurement of TPMT levels, allowed consistency in the treatment protocol. Furthermore, the dose of azathioprine that was used in our trial was relatively lower than that used in previous clinical trials.

Our study has potential limitations. The early termination of the combination-therapy group limited our ability to address the effect on the primary outcome (FVC), on many of the secondary outcomes, and on various subgroups, as originally planned. Second, the precise reasons for the increased rates of death and hospitalization are unknown. And third, it is difficult to assess which components of the three-drug regimen may be responsible for the observed negative outcomes. The ongoing comparison of NAC alone and matching placebo will address the therapeutic role of NAC alone for patients with idiopathic pulmonary fibrosis. We anticipate screening of the last patient in the ongoing study groups by the second quarter of 2012.

It must be emphasized that our results are applicable only to patients with well-defined id-

idiopathic pulmonary fibrosis who meet the inclusion and exclusion criteria of this trial. Our data that show increased rates of death and hospitalization provide compelling evidence against the use of the combination of azathioprine, prednisone, and NAC for patients with idiopathic pulmonary fibrosis who have mild-to-moderate impairment in pulmonary function.

The views expressed are those of the authors and do not necessarily represent the official views of the NHLBI or the National Institutes of Health.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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