A Placebo-Controlled Randomized Trial of Warfarin in Idiopathic Pulmonary Fibrosis

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***Rationale*: Animal and human studies support the importance of the coagulation cascade in pulmonary fibrosis.**

***Objectives*: In a cohort of subjects with progressive idiopathic pulmonary fibrosis (IPF), we tested the hypothesis that treatment with warfarin at recognized therapeutic doses would reduce rates of mortality, hospitalization, and declines in FVC.**

***Methods*: This was a double-blind, randomized, placebo-controlled trial of warfarin targeting an international normalized ratio of 2.0 to 3.0 in patients with IPF. Subjects were randomized in a 1:1 ratio to warfarin or matching placebo for a planned treatment period of 48 weeks. International normalized ratios were monitored using encrypted home point-of-care devices that allowed blinding of study therapy.**

***Measurements and Main Results*: The primary outcome measure was the composite outcome of time to death, hospitalization (nonbleeding, nonelective), or a 10% or greater absolute decline in FVC. Due to a low probability of benefit and an increase in mortality observed in the subjects randomized to warfarin (14 warfarin versus 3 placebo deaths; $P = 0.005$) an independent Data and Safety Monitoring Board recommended stopping the study after 145 of the planned 256 subjects were enrolled (72 warfarin, 73 placebo). The mean follow-up was 28 weeks.**

***Conclusions*: This study did not show a benefit for warfarin in the treatment of patients with progressive IPF. Treatment with warfarin was associated with an increased risk of mortality in an IPF population who lacked other indications for anticoagulation.**

Clinical trial registered with www.clinicaltrials.gov (NCT00957242).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive interstitial lung disease with a median survival of 2 to 5 years from onset of symptoms. Despite multiple recent clinical trials, no definitive therapy is known to alter survival.

What This Study Adds to the Field

This study investigated the safety and efficacy of warfarin in IPF using a double-blind, placebo-controlled design. Treatment with warfarin was associated with no clinical benefit in patients with IPF.

Keywords: idiopathic pulmonary fibrosis; clinical trial; warfarin; anticoagulation

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease of unknown cause characterized by the histopathologic pattern of usual interstitial pneumonia (1, 2). The median survival of patients with IPF after the onset of symptoms is 2 to 5 years (3). To date, no pharmacologic therapies have definitively been shown to improve survival.

Prior animal and human studies in pulmonary fibrosis provide a compelling rationale to examine anticoagulation as a therapeutic approach in IPF (4, 5). Large epidemiologic studies link IPF with thrombosis-related clinical events, such as an increased risk of acute coronary syndrome and deep vein thrombosis (6–8). The suspected causal relationship may extend beyond simple coagulation cascade-induced thrombus formation, as procoagulant enzymes may directly stimulate fibrosis via cell surface receptor–mediated responses (9). A previous clinical trial provided direct evidence of the coagulation cascade in IPF. Furthermore, this unblinded, prospective clinical trial compared heparin, warfarin anticoagulation, and prednisolone with that of prednisolone alone, and demonstrated a 1-year survival benefit of anticoagulation (87 vs. 58%) in 56 patients with IPF who required hospitalization (10). As a result of this study, the most recent iteration of the joint American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines includes anticoagulation as a choice for a minority of patients, despite remaining uncertainty regarding its benefits and harms (1).

(*Received in original form February 22, 2012; accepted in final form April 23, 2012*)

*For a complete listing of IPFnet members, *see* Appendix EA in the online supplement.

AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) and the IPFnet were funded by the National Heart, Lung, and Blood Institute and The Chicago Community Trust; ClinicalTrials.gov Identifier: NCT00957242. Supported by grants (U10HL080413 [data coordinating center], U10HL080274, U10HL080370, U10HL080371, U10HL080383, U10HL080411, U10HL080509, U10HL080510, U10HL080513, U10HL080543, U10HL080571, U10HL080685 [clinical centers]) from the NHLBI. Additional funding was provided by the Cowlin Fund of the Chicago Community Trust. The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The writing committee and corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

Author Contributions: I.N. and M.A.O. were lead authors of the ACE-IPF protocol and cochairs of the protocol committee. K.J.A. was responsible for data management and statistical analyses. S.B.C. served as the anticoagulation monitor for the ACE-IPF trial. R.J.K. served as the chair of the IPFnet Adjudication Committee; J.A., K.R.F., C.G. and R.J.K. were responsible for implementation at the study sites and were the top enrollers of this study. All authors participated in the preparation, review, and critical revision of the manuscript and assume responsibility for its overall content and integrity.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 186, Iss. 1, pp 88–95, Jul 1, 2012

Originally Published in Press as DOI: 10.1164/rccm.201202-0314OC on May 3, 2012
Internet address: www.atsjournals.org

The Anticoagulant Effectiveness in Idiopathic Pulmonary Fibrosis (ACE-IPF) trial was designed to test the hypothesis that treatment with warfarin at recognized therapeutic doses would reduce the frequency of the composite endpoint of mortality, hospitalization, and 10% or greater absolute decline in FVC in subjects with progressive IPF.

METHODS

Study Oversight

The study was designed and conducted by the IPFnet Steering Committee, and was performed at 22 U.S. clinical centers (*see* Appendix EA in the online supplement for a complete listing of IPFnet sites and Appendix EB for the ACE-IPF protocol). An independent protocol review committee, appointed by the National Heart, Lung, and Blood Institute (NHLBI), reviewed and approved the protocol for scientific merit. An NHLBI-appointed data and safety monitoring board (DSMB), an NHLBI-appointed Protocol Review Committee, and local institutional review boards approved the protocol. All patients provided written informed consent. The DSMB approved all protocol amendments and oversaw conduct of the trial.

Study Patients

Patients aged 35 to 80 years with progressive IPF were potentially eligible. All participants met modified American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association criteria for the diagnosis of IPF (bronchoscopies were not required) (1, 11). Progressive IPF was defined as a history of (*1*) worsening of dyspnea, or (*2*) physiologic deterioration defined as an absolute decline of either FVC greater than or equal to 10% or $D_{L_{CO}}$ greater than or equal to 15%, a reduction in arterial oxygen saturation of greater than or equal to 5%, or progression of radiographic findings. Participants needed to be willing and able to perform home International Normalized Ratio (INR) testing.

Participants were excluded if they met any of the following criteria: current indication for, or treatment with, warfarin, prasugrel, or clopidogrel combined with aspirin; the presence of an increased risk of bleeding; a recent cerebral vascular accident or gastrointestinal bleeding; any current signs or symptoms of severe, progressive, or uncontrolled comorbid illness; and their presence on the active list for lung transplantation. For a complete list of exclusions, see the ACE-IPF protocol (Appendix EB).

Study Design

ACE-IPF was a double-blind, randomized, placebo-controlled trial of an oral warfarin dose adjusted to an INR response of 2.0 to 3.0, compared with a sham dose-adjusted placebo. The trial was originally designed as an event-driven study with a treatment period of up to 144 weeks. Given the slow rate of recruitment and higher than anticipated event rates seen in another IPFnet trial, the protocol was modified to have a maximum treatment period of 48 weeks after 11 patients were enrolled in the study. Participants were to be seen at screening, baseline, and at 16, 32, and 48 weeks after enrollment (*see* Appendix EB).

Outcome Measures

The primary outcome was a composite endpoint based on the time to all-cause mortality; nonelective, nonbleeding hospitalization; or a decrease in the absolute FVC greater than or equal to 10% from baseline value. Secondary outcome measures included rates of mortality, hospitalization, respiratory-related hospitalization, acute exacerbation, bleeding, cardiovascular events, and changes over time in FVC, 6-minute walk test distance, $D_{L_{CO}}$, plasma fibrin D-dimer levels, and quality of life (QOL) assessments.

Data Analysis

Continuous variables at baseline were expressed as means (SDs) and medians (25th and 75th percentiles). Categorical variables at baseline were expressed as counts and percentages. Unadjusted estimates of

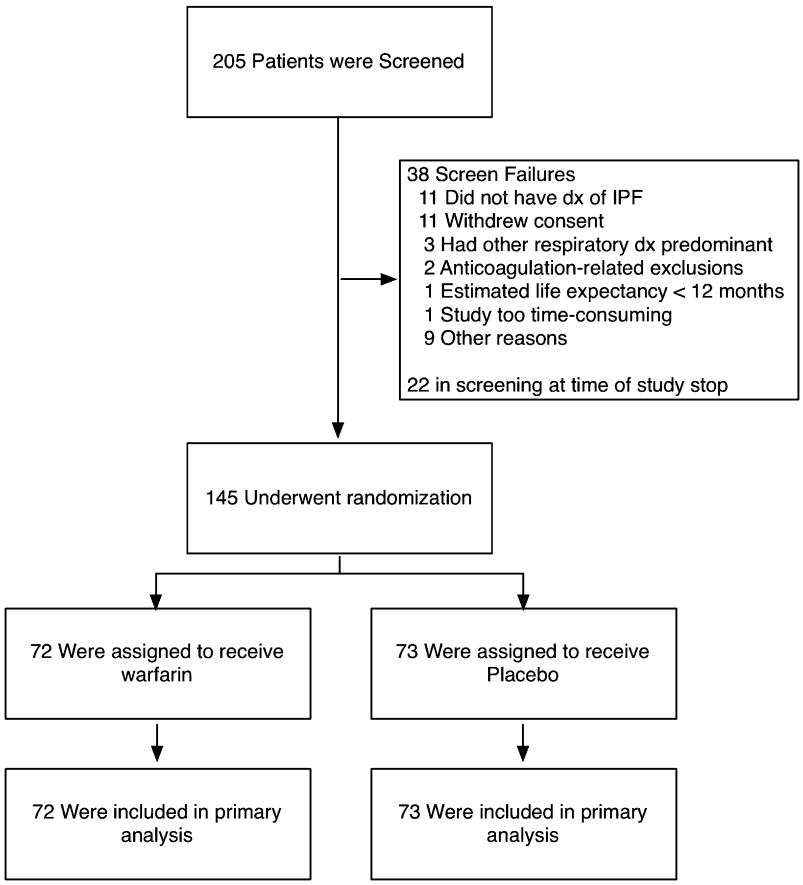


Figure 1. Enrollment and outcomes. IPF = idiopathic pulmonary fibrosis.

event rates for time-to-event variables were computed using the Kaplan-Meier estimator with comparisons based on the log-rank test statistic. The primary hypothesis was tested using a Cox proportional hazards regression model, comparing the treatment effect on the primary composite endpoint. Prespecified covariates in this model included an indicator variable for the treatment group and the D_{LCO} measurement from the baseline assessment.

Randomization and Masking

Subjects were randomly assigned to study arms in a 1:1 ratio, using a permuted-block design with varying block sizes, to receive either warfarin or matched placebo. Subjects were stratified by clinical center and a D_{LCO} threshold of 35% of predicted. Randomization lists were generated by the study data coordinating center and provided to a phone- and web-enabled registration system (Almac Clinical Services, Inc.) that allowed sites to enroll subjects and receive study kits while keeping the study team and subjects blinded to treatment assignment.

INR Testing and Monitoring

Study subjects were provided two strengths of warfarin tablets (1 mg and 2.5 mg) or matching placebos. Subjects measured their INR with encrypted meters (INRatio; Alere, San Diego, CA) at least weekly. Home monitoring was validated by plasma INR measurement at the week 1 and 16 visits. Individual INR meters and test strips were replaced and subjects were reinstructed if meter INR readings varied by more than 30% from the laboratory INR. Efficacy of home INR measures was determined by time-in-target INR range of all patients, calculated on the basis of linear interpolation (12), after excluding readings taken at baseline, during initial warfarin titration (until INR $\geqslant$ 2.0), study drug interruption, or after the discontinuation of study drug.

Statistical Design and Analysis

Sample size justification. The study was designed to have 90% power to detect a difference in 48-week event-free rates of 70% for the warfarin group versus 50% for the placebo group. A total of at least 95 adjudicated primary endpoints were required to achieve 90% power with a two-sided, type I error rate of 0.05 and a 1:1 randomization ratio (13). These calculations yielded a requisite total sample size of 256 subjects.

Interim Assessments

At the outset of the study, the investigators provided the DSMB with stopping guidelines for safety concerns or a large efficacy benefit. The Haybittle-Peto boundary was applied, with a boundary requiring P less than 0.001 for benefit or harm for the endpoint of all-cause mortality; the O'Brien-Fleming spending function for group sequential

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	Warfarin ($n = 72$)	Placebo ($n = 73$)
Age, yr	67.3 ± 7.1	66.7 ± 7.4
	67.8 (63.9, 72.3)	66.1 (60.5, 72.8)
Female sex	24 (33)	15 (21)
White	65 (90)	68 (93)
Black	3 (4)	3 (4)
History of smoking	49 (68)	58 (79)
Time since diagnosis, yr	1.8 ± 1.9	2.1 ± 2.4
	1.0 (0.4,3.0)	1.1 (0.4, 3.0)
Taking prednisone at baseline	18 (25)	23 (32)
History of thrombosis*	17 (24)	15 (21)
FVC % predicted	58.9 ± 16.2	58.7 ± 16.1
	54.6 (47.9, 66.6)	57.8 (46.5, 72.6)
D_{LCO} % predicted	33.8 ± 12.4	34.6 ± 13.4
	33.6 (25.8, 40.8)	33.8 (23.8, 45.0)
D_{LCO} % predicted < 35%	40 (56)	36 (49)
Pa_{O2}, mm Hg	71.3 ± 13.9	72.7 ± 15·5
	74.1 (60.1, 80.5)	72.1 (62.0, 81.0)
Sa_{O2}, %	93.2 ± 4.2	92.4 ± 5.9
	94.5 (92.0, 96.0)	93.9 (91.0, 96.0)
D-dimer	0.9 (1.69)	0.5 (0.3)
	0.5 (0.3, 0.7)	0.4 (0.3, 0.7)
6-min walk distance, m	289.2 ± 146.3	280.2 ± 136.2
	305.0 (178.4, 375.0)	300.0 (180.0, 387.0)
Score on Borg Dyspnea Index after walk test (range, 0†–10)	2.7 ± 1.7	3.0 ± 1.8
	3.0 (1.0, 4.0)	3.0 (2.0, 4.0)
Score on Shortness of Breath Questionnaire (range 0†–120)	33.9 ± 20.7	42.0 ± 23.5
	30.5 (18.0, 43.0)	40.0 (25.0, 61.0)
Total score on St. George's Respiratory Questionnaire (range, 0–100†)	46.2 ± 18.0	50.1 ± 17.2
	43.8 (35.5, 55.8)	50.1 (39.4, 62.9)
SF-36 (range for each subscale, 0-100†)		
Aggregate physical score	38.4 ± 9.5	34.8 ± 9.1
	40.2 (32.4, 44.7)	33.5 (28.8, 40.4)
Aggregate mental score	48.2 ± 8.6	48.4 ± 9.6
	46.2 (42.2, 52.0)	44.4 (41.3, 57.2)
Score on EQ-5D		
Self-report questionnaire (range, −0.59 to 1.00†)	0.8 ± 0.2	0.7 ± 0.2
	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)
Visual analog scale (range, 0–100†)	73.3 ± 15.6	71.0 ± 17.1
	76.0 (60.0, 85.0)	75.0 (60.0, 84.0)

Definition of abbreviation: D_{LCO} = carbon monoxide diffusion capacity; EQ-5D = European Quality of Life—5 Dimensions.
Data are presented as mean ± standard deviation, median (25th, 75th percentile), or n (%).
*History of thrombosis includes baseline history of coronary artery disease, pulmonary embolism, deep venous thrombosis, claudication, cerebrovascular accident, myocardial infarction, or stroke.
† Indicates better score.

TABLE 2. TIME TO EVENT RESULTS

	Warfarin ($N = 72$)*	Placebo ($N = 73$)*	Log-Rank *P* Value	Adjusted Hazard Ratio†
Primary endpoint	23/72 42.1% (29.6%, 57.3%)	17/73 39.0% (25.8%, 55.9%)	0.271	1.32 (0.70, 2.47)
All-cause mortality	14/72 28.1% (16.8%, 44.8%)	3/73 6.2% (2.0%, 18.1%)	0.005	4.85 (1.38, 16.99)
Combined all-cause mortality or nonelective, nonbleeding hospitalizations	21/72 38.4% (26.4%, 53.6%)	10/73 23.7% (13.4%, 40.1%)	0.020	2.12 (1.00, 4.52)
Combined all-cause mortality or ⩾10% FVC drop	18/72 37.0% (24.0%, 54.2%)	12/73 25.1% (14.9%, 40.2%)	0.280	1.44 (0.69, 2.99)

Definition of abbreviations: CI = confidence interval; D_{LCO} = carbon monoxide diffusion capacity.

* Data are presented as number of events/number of subjects (top rows) and 48-week Kaplan-Meier event rate estimate (95% CI) (bottom rows).

† Hazard ratio (warfarin vs. placebo) with a 95% CI adjusting for baseline D_{LCO}.

monitoring was planned to assess the primary endpoint approximately once per year. After a trend in mortality was detected, a general-purpose futility assessment was conducted to calculate the likelihood that warfarin therapy would be beneficial in this patient population (14).

RESULTS

Interim Assessments

On April 5, 2011, an unscheduled interim analysis, as requested by the DSMB, was conducted due to excess mortality in the warfarin cohort. The DSMB recommended terminating the study for futility; the excess of mortality in the warfarin treatment group made any benefit of warfarin highly unlikely and created important safety concerns. The NHLBI accepted the recommendation of the DSMB.

Baseline Characteristics

Between December 14, 2009 and April 1, 2011, 145 subjects were enrolled: 72 in the warfarin group and 73 in the placebo group (Figure 1 and Table 1). The mean age for the population was 67 years. Twenty-seven percent of the subjects were women and 92% were white. The mean percent predicted FVC was 59%, and the mean percent predicted D_{LCO} was 34%. The warfarin and placebo groups demonstrated no statistically significant differences (all *P* values > 0.05) with respect to demographics and baseline physiologic parameters. All patients were dosed as if they were warfarin naive. Forty-one (28%) participants were on prednisone at study entry. A complete listing of concomitant medications is provided in Appendix EC.

Primary Endpoint, All-Cause Mortality, and All-Cause Hospitalizations

A total of 23 primary endpoint events were observed in the warfarin-treatment group compared with 17 for the placebo-treatment group ($P = 0.27$) (Figure 2A and Table 2). The warfarin group was associated with greater all-cause mortality compared with the placebo group (14 vs. 3; $P = 0.005$) (Figure 2B). Reported causes of death indicated 11 of the 14 were respiratory-related in the warfarin group versus three of the three in the placebo group (Figure 3 and Table 3). There were also three cardiovascular deaths in the warfarin group versus none in the placebo group. No deaths were attributed to bleeding. The warfarin group also demonstrated an increased rate of combined all-cause hospitalization and all-cause mortality ($P = 0.034$) (Figure 2C).

Safety and Secondary Endpoints

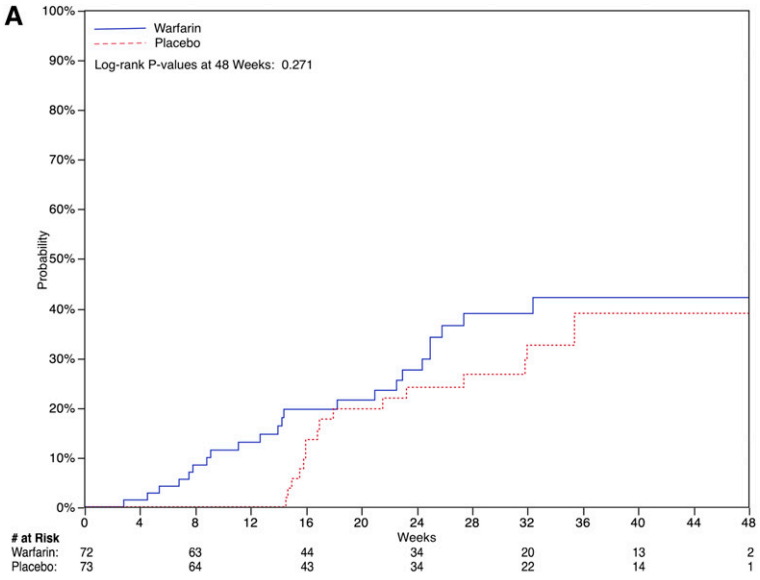
There were no significant treatment effects observed in the physiologic secondary endpoints (FVC, 6-minute walk distance, D_{LCO}), or in the QOL indicators from baseline to 48 weeks (for complete listing of results, *see* Appendix EC). Additionally, warfarin did not benefit any of the predefined patient subgroups (Figure 4). Central adjudication confirmed the occurrence of acute exacerbations of IPF in six participants in the warfarin group compared with two participants in the placebo group ($P = 0.17$). During the course of the trial, five of the eight participants with confirmed acute exacerbations died. Adjudication further confirmed two participants with major bleeding events in the warfarin group compared with one participant with a major bleeding event in the placebo group ($P = 0.62$) and six participants with minor bleeding events in warfarin group compared with two participants with minor bleeding events in the placebo group ($P = 0.17$). INR monitoring demonstrated values less than 1.5 or greater than 3.0 only 6.8% and 9.3% of the time, respectively, with a median time in target range (2.0–3.0) of 59%. The median time to reach an INR greater than or equal to 2.0 was 10 days (25th and 75th percentiles of 7 and 18 d). Additionally, compared with the placebo group, the D-dimer levels were significantly suppressed in the warfarin-treatment group at the 16-week measure relative to baseline.

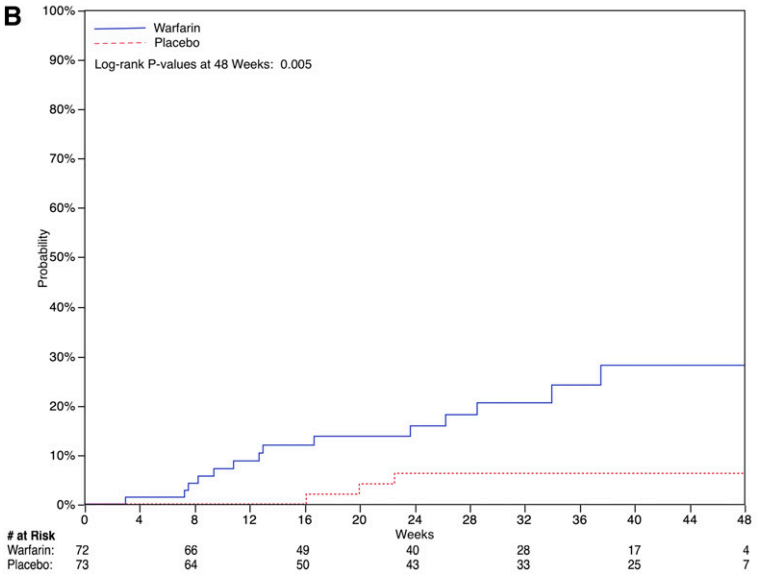
DISCUSSION

The ACE-IPF trial is the first placebo-controlled, double-blind study with an intent-to-treat evaluation of anticoagulation therapy in IPF. In this study, the use of warfarin in patients with progressive IPF was associated with increased mortality when compared with placebo (adjusted hazard ratio, 4.85; 95% confidence interval, 1.38–16.99). Warfarin did not impact QOL measures or secondary endpoints. The DSMB recommended discontinuation of the study based on the low probability of demonstrating study drug efficacy and an excess of mortality in the warfarin treatment arm. The cause of the excess mortality events remains unknown, but the events do not appear to be related to the known safety profile of warfarin.

The ACE-IPF study was stopped before reaching the prespecified interim analysis boundaries for the composite primary endpoint or all-cause mortality. However, a trend of higher mortality in the warfarin group was observed along with similar trends in all-cause hospitalization, respiratory-related hospitalization, and acute exacerbation of IPF. Together, these trends pointed to the possibility that warfarin treatment contributed to a worsening of the underlying respiratory status in these patients. This effect did not appear to be explained by baseline imbalances or influenced by individual centers, and, if proven true, worsening of respiratory status by warfarin is an entirely novel consequence of this therapy.

Point-of-care INR monitoring has been used in prior trials. To our knowledge, this is the first clinical trial to double-blind





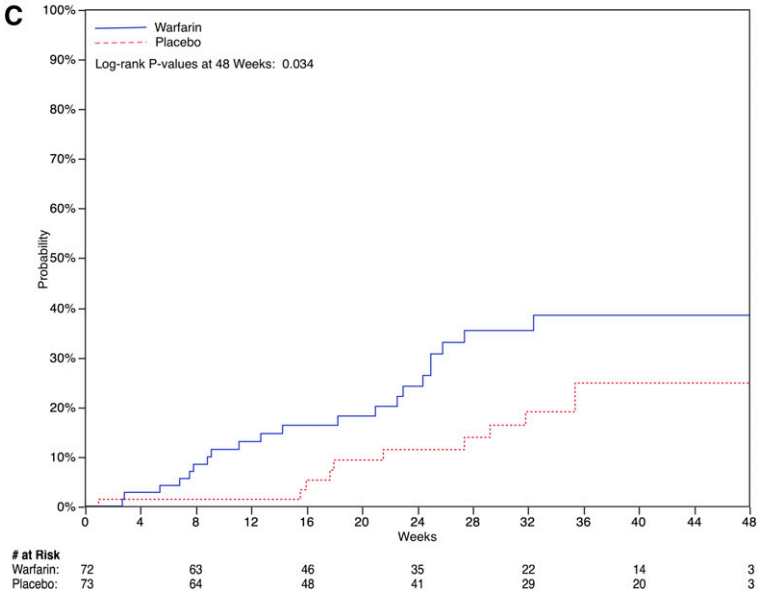


Figure 2. (*A*) Comparison of warfarin with placebo for the primary endpoint. (*B*) Comparison of warfarin versus placebo for time to all-cause mortality. (*C*) Comparison of warfarin versus placebo for time to all-cause mortality or all-cause hospitalization.

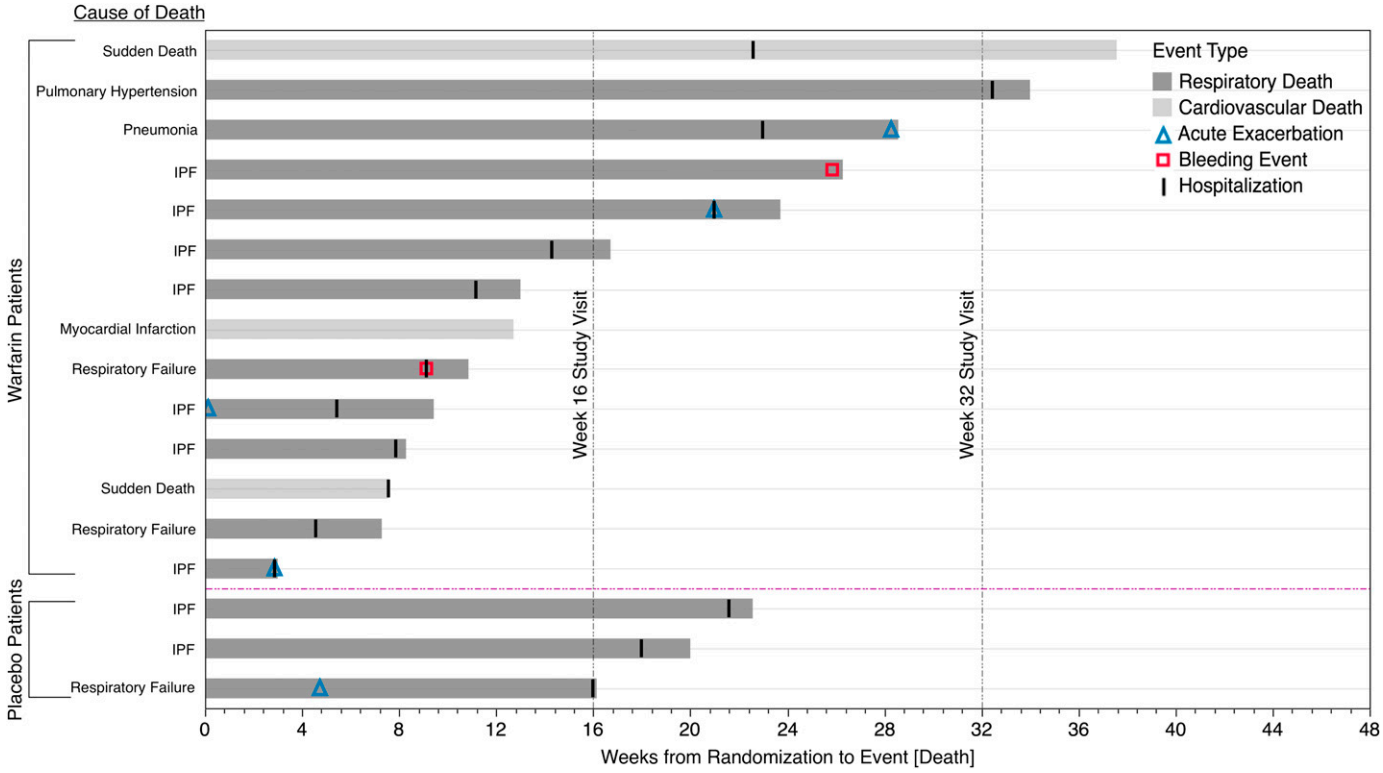


Figure 3. Mortality listing with clinical events. IPF = idiopathic pulmonary fibrosis.

warfarin therapy based on internet-directed, encrypted INR monitoring at the subject's home. No patients in our trial were on warfarin at the time of randomization. The time in target range of the INR by this home point-of-care methodology was similar to that achieved in the warfarin-naive cohort of a recent clinical trial over a similar treatment period (15).

In contrast to our findings, a prior smaller study demonstrated a significant survival benefit for anticoagulation with prednisolone compared with prednisolone alone in patients with IPF (10). Our overall trial design included a matched, placebo control group, double blinding, and an intention-to-treat data analysis. Additionally, our treatment protocol did not include low molecular weight heparin or mandated prednisolone in all subjects. It is unknown if the potential effects of corticosteroids or short-term heparin administration may have contributed to the beneficial outcome (16). Additionally, our trial enrolled patients with a significantly lower D_{LCO} (mean, 34% vs. 62% predicted), with all deaths in both treatment arms occurring among subjects with enrollment D_{LCO} less than 45%.

TABLE 3. CHARACTERISTICS OF PARTICIPANTS WHO DIED

Cause of Death	Acute Exacerbation Occurred	D_{LCO} % Predicted	FVC % Predicted	Age (*yr*)
Warfarin				
Respiratory: pulmonary hypertension	No	28	75	72
Respiratory: IPF	No	14	37	78
Respiratory: IPF	No	18	33	72
Cardiovascular: myocardial infarction	No	43	61	67
Cardiovascular: sudden cardiovascular death	No	36	53	68
Respiratory: IPF	No	27	43	68
Respiratory: IPF	No	18	37	63
Respiratory: respiratory failure	No	44	86	71
Cardiovascular: sudden cardiovascular death	No	25	48	76
Respiratory: respiratory failure	No	8	39	77
Respiratory: IPF	Yes	17	44	65
Respiratory: IPF	Yes	21	58	81
Respiratory: IPF	Yes	17	37	66
Respiratory: pneumonia	Yes	36	53	69
Summary	4	25.1 ± 11.06	50.3 ± 15.51	70.9 ± 5.37
Placebo				
Respiratory: IPF	No	18	53	73
Respiratory: IPF	No	12	39	72
Respiratory: respiratory failure	Yes	16	34	69
Summary	1	15.3 ± 3.06	42.0 ± 9.85	71.3 ± 2.08

Definition of abbreviations: D_{LCO} = carbon monoxide diffusion capacity; IPF = idiopathic pulmonary fibrosis.

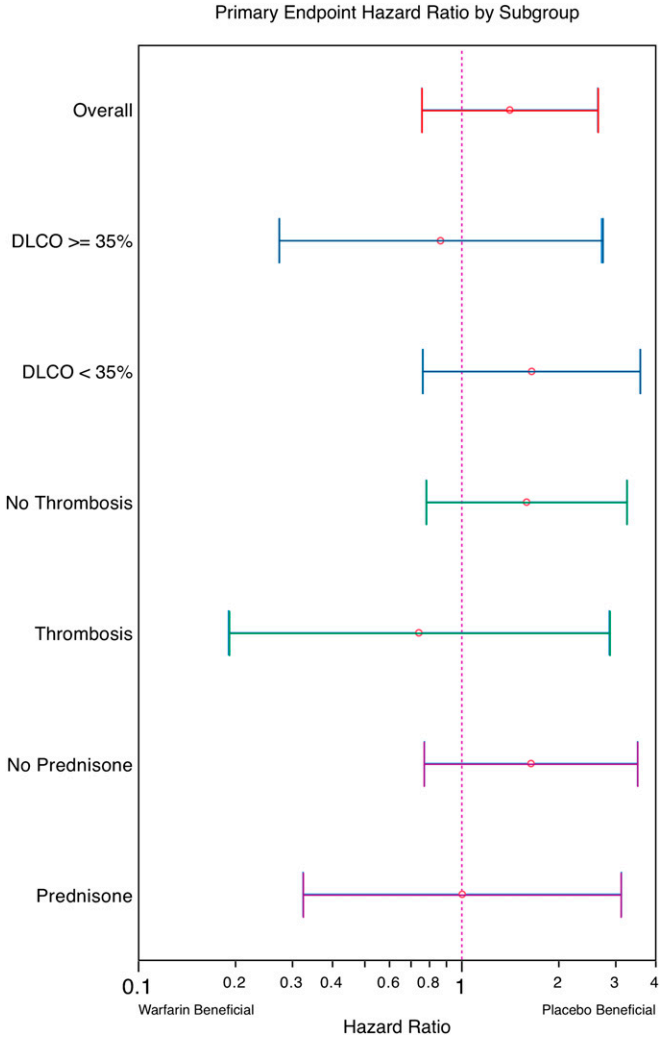


Figure 4. Subgroup analysis of the key clinical subgroups. D_{LCO} = diffusing capacity of carbon monoxide.

The reduction in D-dimer levels in the warfarin group at 16 weeks is evidence for suppression of thrombosis and fibrinolysis in our IPF population (*see* Appendix EC). Despite this biologic effect, the excess mortality and hospitalizations noted in the warfarin-treated group were not a consequence of major and minor bleeding, as assessed by blinded adjudication. Furthermore, INR safety data showed no indication that the deaths were associated with INR values outside the target range (2.0 – 3.0). Thus, we are left with the unexplained clinical observation that respiratory worsening, the common mode of disease progression in patients with IPF, was the most common feature contributing to the excess mortality in the warfarin group. Biologically plausible explanations for our observations include, but are not limited to, worsening of respiratory disease due to alveolar hemorrhage; unexpected detrimental effects of inhibiting the activity of factor II, VII, IX, and X simultaneously or on noncoagulant, vitamin K–dependent proteins; or loss of the beneficial effects of protein C on inflammation and remodeling (4, 9, 17).

There were several strengths related to study design and execution. We successfully randomized and blinded the study using an encrypted home INR monitoring system. Also, the observed rates of mortality in both groups had 95% confidence intervals that were comparable to patients with IPF with similar disease severity, supporting the general applicability of our findings to patients with IPF with similar physiologic impairment (18–20). Additionally, a central adjudication committee evaluated the key components of the composite endpoint while being blinded to treatment arm.

The study was not designed to address the molecular mechanisms involved in the treatment effect or to address the potential benefits of alternative forms of anticoagulation, such as heparin, or direct inhibitors of either factor Xa or thrombin. Therefore, we are unable to offer evidence of a mechanism for the outcome in this trial or comment on the usefulness of alternative anticoagulants. Last, early discontinuation of the study limited the available information for secondary endpoints.

The excess mortality in the warfarin arm appeared to be due to respiratory worsening (exacerbation or progression), which accounted for greater than two-thirds of the observed deaths. We must emphasize that patients who required anticoagulation for non–IPF-related reasons were excluded from this study. Therefore, our findings do not address the use of warfarin in patients with IPF who have acknowledged indications for anticoagulation. This trial demonstrated the success of the encrypted INR home monitoring system and consequent low frequency of major bleeding events. This study has significantly altered the balance of evidence related to the use of warfarin in patients with IPF. Based on our results, warfarin, as studied in this trial, should not be used for the treatment of progressive IPF.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the faculty, staff, and patients at all participating IPFnet medical centers. They also thank the IPFnet data and safety monitoring board (Gerald S. Davis, M.D., chair; Robert Levine, M.D., Steven D. Nathan, M.D., Sharon Rounds, M.D., B. Taylor Thompson, M.D., Bruce Thompson, Ph.D., and Gilbert C. White II, M.D.), its NHLBI representatives (Hannah Peavy, M.D., and Barry Schmetter, B.S.), and the IPFnet protocol review committee (Peter B. Bitterman, M.D., chair; Teri J. Franks, M.D., Steven Idell, M.D., Steven Piantadosi, M.D., Ph.D., William N. Rom, M.D., M.P.H., Moises Selman, M.D., and David S. Wilkes, M.D.) for their dedication and oversight.

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