

## INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

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### ABSTRACT

**Background** Uncontrolled studies suggested that aerosolized iloprost, a stable analogue of prostacyclin, causes selective pulmonary vasodilatation and improves hemodynamics and exercise capacity in patients with pulmonary hypertension.

**Methods** We compared repeated daily inhalations of 2.5 or 5.0  $\mu\text{g}$  of iloprost (six or nine times per day; median inhaled dose, 30  $\mu\text{g}$  per day) with inhalation of placebo. A total of 203 patients with selected forms of severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (New York Heart Association [NYHA] functional class III or IV) were included. The primary end point was met if, after week 12, the NYHA class and distance walked in six minutes were improved by at least one class and at least 10 percent, respectively, in the absence of clinical deterioration according to predefined criteria and death.

**Results** The combined clinical end point was met by 16.8 percent of the patients receiving iloprost, as compared with 4.9 percent of the patients receiving placebo ( $P=0.007$ ). There were increases in the distance walked in six minutes of 36.4 m in the iloprost group as a whole ( $P=0.004$ ) and of 58.8 m in the subgroup of patients with primary pulmonary hypertension. Overall, 4.0 percent of patients in the iloprost group (including one who died) and 13.7 percent of those in the placebo group (including four who died) did not complete the study ( $P=0.024$ ); the most common reason for withdrawal was clinical deterioration. As compared with base-line values, hemodynamic values were significantly improved at 12 weeks when measured after iloprost inhalation ( $P<0.001$ ), were largely unchanged when measured before iloprost inhalation, and were significantly worse in the placebo group. Further significant beneficial effects of iloprost treatment included an improvement in the NYHA class ( $P=0.03$ ), dyspnea ( $P=0.015$ ), and quality of life ( $P=0.026$ ). Syncope occurred with similar frequency in the two groups but was more frequently rated as serious in the iloprost group, although this adverse effect was not associated with clinical deterioration.

**Conclusions** Inhaled iloprost is an effective therapy for patients with severe pulmonary hypertension. (N Engl J Med 2002;347:322-9.)

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A CONTINUOUS infusion of prostacyclin was the first therapy shown to reduce mortality in a controlled study of patients with severe pulmonary hypertension.<sup>1</sup> However, its use is associated with a number of serious drawbacks. The lack of pulmonary selectivity results in systemic side effects, tolerance leads to progressive increases in the dose, and there may be recurrent infections of the intravenous catheter.<sup>2</sup> As an alternative, inhaled nitric oxide possesses pulmonary selectivity, but it is less potent than prostacyclin in the pulmonary vasculature.<sup>3,4</sup> Moreover, an interruption in the inhalation of continuous nitric oxide may cause rebound pulmonary hypertension.<sup>5,6</sup> Designed to combine the beneficial effects of prostacyclin with those of an inhalational application, aerosolized prostacyclin was found to be a potent pulmonary vasodilator in patients with acute respiratory failure, exerting preferential vasodilatation in well-ventilated lung regions.<sup>7-10</sup> Similar results were obtained in spontaneously breathing patients who had lung fibrosis and severe pulmonary hypertension.<sup>11</sup>

Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilatation.<sup>12</sup> When administered during a short aerosolization ma-

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neuver to patients with pulmonary hypertension, its pulmonary vasodilative potency was similar to that of prostacyclin, but its effects lasted for 30 to 90 minutes, as compared with 15 minutes.<sup>4,11,13-15</sup> Several open-label, uncontrolled studies of patients with severe pulmonary hypertension suggested that long-term use of aerosolized iloprost results in substantial clinical improvement.<sup>11,13,16-20</sup> Our objective in this trial was to evaluate the effects of inhaled iloprost using a rigorous end point of clinical efficacy.

**METHODS**

**Selection of Patients**

Patients with primary pulmonary hypertension and selected forms of nonprimary pulmonary hypertension were candidates for the study. The forms of nonprimary pulmonary hypertension included appetite-suppressant-associated and scleroderma-associated pulmonary hypertension as well as inoperable chronic thromboembolic pulmonary hypertension. The inclusion criteria were a mean pulmonary-artery pressure greater than 30 mm Hg, the ability to cover between 50 and 500 m without encouragement on a six-minute walk test,<sup>21</sup> and a New York Heart Association (NYHA) functional class of III or IV<sup>22</sup> despite the use of standard conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers, and supplemental oxygen). Patients who were taking investigational drugs, prostanoids, or beta-blockers were excluded. The doses of calcium-channel blockers had to be constant for more than six weeks before study entry. Exclusion criteria were a pulmonary-artery wedge pressure at rest of more than 15 mm Hg, a cardiac index at rest of less than 1.5 or more than 4 liters per minute per square meter of body-surface area, bleeding disorders, a bilirubin level of more than 3 mg per deciliter (51 μmol per liter), creatinine clearance below 30 ml per minute, a forced vital capacity below 50 percent, a forced expiratory volume in one second that was less than the mean normal value minus twice the standard deviation, and clinical instability.

**Study Design**

A total of 203 patients participated after giving written informed consent and after the study had been approved by the local ethics committees at 37 European specialist centers. Patients were randomly assigned to receive iloprost (Ilomedin, Schering) or placebo after stratification according to NYHA functional class (III or IV) and type of pulmonary hypertension (primary or nonprimary) by an independent committee whose members were unaware of patients' identities. A total of 101 patients were randomly assigned to the iloprost group, and 102 were assigned to the placebo group.

For inhalation, iloprost or placebo was diluted with saline to a concentration of 10 μg per milliliter, and 2 ml was added to a nebulizer (HaloLite, MedicAid). This device delivered short pulses of aerosolized particles (geometric median [±SD] aerodynamic diameter of particles, 4.3±0.05 μm)<sup>23</sup> during the first part of each inspiration until a predefined total inhaled dose of 2.5 μg had been dispensed. The inhalation was then stopped or repeated once, to achieve a total dose of 5.0 μg, depending on how well the patient tolerated the treatment. After each inhalation, the residual volume in the nebulizer was discarded. This maneuver was repeated six or nine times daily, with an overnight break. The frequency of inhalation and the dose were individually determined within the first eight days of therapy according to a predefined dosing algorithm.

Right-heart catheterization was performed in all patients at base line and after 12 weeks. The acute effects of inhaled iloprost were evaluated after 12 weeks in all patients, but not at base line, to avert unblinding. At base line and after 4, 8, and 12 weeks, patients completed a six-minute walk test, the Mahler Dyspnea Index ques-

tionnaire,<sup>24</sup> the EuroQol questionnaire,<sup>25</sup> and the 12-item Medical Outcomes Study Short-Form General Health Survey.<sup>26</sup>

Patients were removed from the study if they met two or more of the following predefined criteria for a deterioration in their condition: refractory systolic arterial hypotension (blood pressure, less than 85 mm Hg); worsening right ventricular failure (e.g., as indicated by the development of refractory edema or ascites); rapidly progressing cardiogenic, hepatic, or renal failure; a decrease of at least 30 percent in the distance walked in six minutes; and a decline in measures of hemodynamic function, such as central venous pressure and mixed venous oxygen saturation.

**Outcome Measures**

The primary end point of the study consisted of an increase of at least 10 percent in the distance walked in six minutes and an

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)
Age — yr	51.2±13.2	52.8±12.0
Weight — kg	71.3±14.6	72.6±13.9
Sex — %		
Male	31.7	33.3
Female	68.3	66.7
Underlying disease — no. (%)		
Primary pulmonary hypertension	51 (50.5)	51 (50.0)
Nonprimary pulmonary hypertension	50 (49.5)	51 (50.0)
Appetite suppressants	4 (4.0)	5 (4.9)
Collagen vascular disease	13 (12.9)	22 (21.6)
Chronic thromboembolic pulmonary hypertension	33 (32.7)	24 (23.5)
Oral vasodilator therapy — no. (%)	52 (51.5)	58 (56.9)
NYHA functional class — no. (%)		
III	60 (59.4)	59 (57.8)
IV	41 (40.6)	43 (42.2)
Mahler Dyspnea Index†	4.14±1.8	4.27±1.8
6-Minute walk distance — m	332±93	315±96
Hemodynamic variables‡		
Pulmonary-artery pressure — mm Hg	52.8±11.5	53.8±14.1
Cardiac output — liters/min	3.8±1.1	3.8±0.9
Pulmonary vascular resistance — dyn·sec·cm <sup>-5</sup>	1029±390	1041±493
Systemic vascular resistance — dyn·sec·cm <sup>-5</sup>	1872±673	1827±503
Central venous pressure — mm Hg	9.2±5.3	8.2±5.0
Pulmonary-artery wedge pressure — mm Hg	7.5±3.3	7.6±3.9
Arterial oxygen saturation — %	92.6±4.4	92.2±5.0
Mixed venous oxygen saturation — %	60.4±7.5	60.5±8.2
Heart rate — beats/min	83.9±12.2	81.8±15.4

\*Plus-minus values are means ±SD. NYHA denotes New York Heart Association. There were no significant differences between the iloprost and the placebo groups. Data on all variables were available for all patients except in the following categories: pulmonary-artery pressure, 1 patient in each group; cardiac output, 1 patient in the iloprost group and 6 in the placebo group; pulmonary vascular resistance, 10 and 6, respectively; systemic vascular resistance, 11 and 14; central venous pressure, 5 and 7; pulmonary-artery wedge pressure, 8 and 3; arterial oxygen saturation, 35 and 31; mixed venous oxygen saturation, 16 and 18; and heart rate, 2 and 3.

†On this 12-point scale, higher scores indicate less dyspnea.

‡Patients who were receiving long-term oxygen therapy received nasal oxygen during the measurement of base-line hemodynamic variables.

improvement in the NYHA functional class in the absence of a deterioration in the clinical condition or death during the 12 weeks of the study. Secondary efficacy variables were changes in the values for the six-minute walk test, the NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, and the quality of life; clinical deterioration; death; and the need for transplantation.

### Statistical Analysis

The primary evaluation of efficacy included all randomized patients. Data are presented as means  $\pm$ SD, unless otherwise stated. We included data on patients who prematurely discontinued the study using a last-observation-carried-forward analysis for the six-minute walk test. Patients who died were assigned a value of 0 m. All statistical tests for efficacy variables were two-tailed, with an alpha level of 0.05.

To analyze the primary efficacy end point and the improvement criteria, we used the Mantel–Haenszel test,<sup>27</sup> stratified according to the type of pulmonary hypertension (primary or nonprimary) and NYHA class (III or IV). Patients with missing data on the primary end point at week 12 were considered not to have had a response.

Changes in the results of the six-minute walk were evaluated with use of nonparametric analysis of covariance stratified according to the type of pulmonary hypertension (primary or nonprimary) and the NYHA class (III or IV), with use of the base-line value as the covariate (analysis of covariance), and the Wilcoxon signed-rank test.

Changes from base line in hemodynamic values were analyzed with t-statistics. The investigators had full access to the data and performed the analyses independently of the sponsor.

## RESULTS

Base-line demographic and hemodynamic data are given in Table 1. The mean frequency of inhalation was 7.5 times per day. Ninety-one percent of patients received 5.0  $\mu$ g per inhalation, and 9 percent received 2.5  $\mu$ g, corresponding to a median inhaled dose of 30  $\mu$ g per day.

### Primary Efficacy End Point

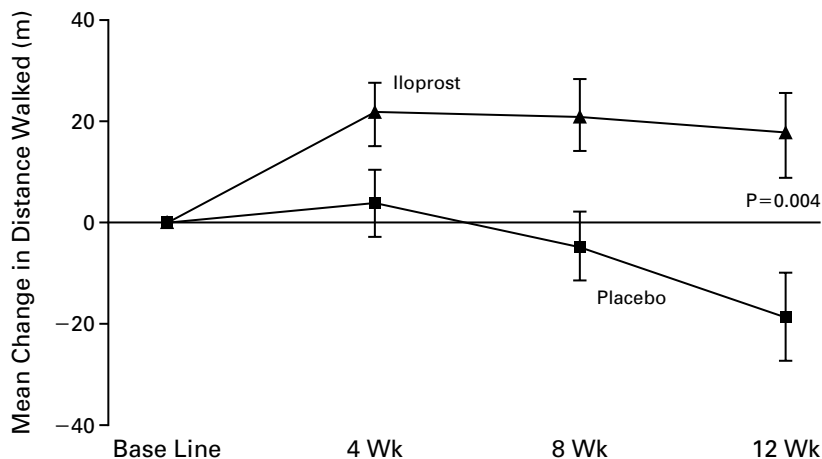
For the primary end point, we found a significant effect of treatment in favor of iloprost ( $P=0.007$ ) (Fig. 1). The estimated odds of an effect in the iloprost group, as compared with the placebo group, were 3.97 (95 percent confidence interval, 1.47 to 10.75, by the Mantel–Haenszel test), with no significant heterogeneity among the four subgroups categorized according to type of pulmonary hypertension and NYHA class at base line ( $P=0.79$  by the Breslow–Day test). The secondary analysis of the primary end point was a logistic-regression model that included treatment assignment, demographic data, and base-line characteristics. Only treatment assignment ( $P=0.01$ ) contributed significantly to the probability of a response.

### Secondary End Points

#### Six-Minute Walk Test

The percentage of patients who had an increase of at least 10 percent in the distance walked in six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group ( $P=0.06$ ) (Table 2). The type of pulmonary hypertension had no significant effect on the outcome in either group ( $P=0.90$ ). A higher percentage of patients in the placebo group than in the iloprost group had a decrease in the distance walked of at least 10 percent or did not complete the study (Table 2).

The absolute change in the distance walked in six minutes was significantly larger (by 36.4 m) in the



**Figure 1.** Effect of Inhaled Iloprost and Placebo on the Mean ( $\pm$ SE) Change from Base Line in the Distance Walked in Six Minutes, According to an Intention-to-Treat Analysis.

The P value was obtained with Wilcoxon's test for two independent samples.

iloprost group than in the placebo group ( $P=0.004$ ) (Fig. 1): 58.8 m among those with primary pulmonary hypertension and 12 m among those with non-primary pulmonary hypertension. A parametric analysis of covariance, which included the absolute value on the six-minute walk test at week 12 as a dependent variable and the treatment assignment ( $P=0.02$ ), type of pulmonary hypertension ( $P=0.06$ ), and distance walked at base line ( $P<0.001$ ) did not show a statistically significant interaction between treatment and type of pulmonary hypertension ( $P=0.09$ ).

#### NYHA Class

More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the NYHA class ( $P=0.03$ ) (Table 2). The type of pulmonary hypertension had no effect on the outcome in either group ( $P=0.39$ ). The percentage of patients with a deterioration in NYHA class did not differ significantly between the groups, but the analysis did not include patients who left the study early owing to death or other reasons. A larger proportion of patients in the placebo group than in the iloprost group did not complete the study (Table 2 and Fig. 2). Reasons included death, discontinuation of study medication, and withdrawal of con-

sent, mostly owing to clinical deterioration, insufficient clinical benefit, or both.

#### Hemodynamics and Gas Exchange

In the placebo group, cardiac output, systemic arterial oxygen saturation, and mixed venous oxygen saturation decreased significantly after 12 weeks and pulmonary vascular resistance and right atrial pressure increased significantly (Table 3). In the iloprost group, values assessed at 12 weeks, before the first morning dose of inhaled iloprost, were largely unchanged from base line, whereas values assessed after inhalation were significantly decreased (in the case of pulmonary-artery pressure, pulmonary vascular resistance, systemic arterial pressure, and systemic arterial oxygen saturation) or increased (in the case of carbon monoxide and pulmonary-artery wedge pressure). At the completion of the 12-week study, acute hemodynamic responsiveness to inhaled iloprost was equivalent in the placebo group and the iloprost group, though the latter group had been exposed to daily iloprost inhalation for three months (data not shown).

#### Mahler Dyspnea Index

The mean Mahler Dyspnea Index transition score was significantly better at week 12 in the iloprost

**TABLE 2.** EFFECTS OF 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO ON THE NEW YORK HEART ASSOCIATION (NYHA) CLASS AND THE SIX-MINUTE WALK TEST.

VARIABLE	ILOPROST GROUP			PLACEBO GROUP		
	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION
	percentage of patients					
Change in NYHA class						
Improved by 2 classes	1.0*	1.9	0.0	0.0	0.0	0.0
Improved by 1 class	23.8*	22.6	25.0	12.7	7.3	19.1
Unchanged	64.4	66.0	62.5	65.7	69.1	61.7
Worsened	5.9	3.8	8.3	7.8	10.9	4.3
Data missing	1.0	1.9	0.0	0.0	0.0	0.0
Noncompletion of study	4.0	3.8	4.2	13.7	12.7	14.9
Death	1.0	1.9	0.0	3.9	3.6	4.3
Other	3.0†	1.9	4.2	9.8‡	9.1	10.6
Change in 6-minute walk distance						
≥10% increase	37.6§	49.1	25.0	25.5	30.9	19.1
<10% increase to <10% decrease	42.6	37.7	47.9	32.4	20.0	46.8
≥10% decrease	13.9	5.7	22.9	25.5	32.7	17.0
Data missing	5.9	7.5	4.2	16.7	16.4	17.0
Combined end point	16.8¶	20.8	12.5	4.9	5.5	4.3

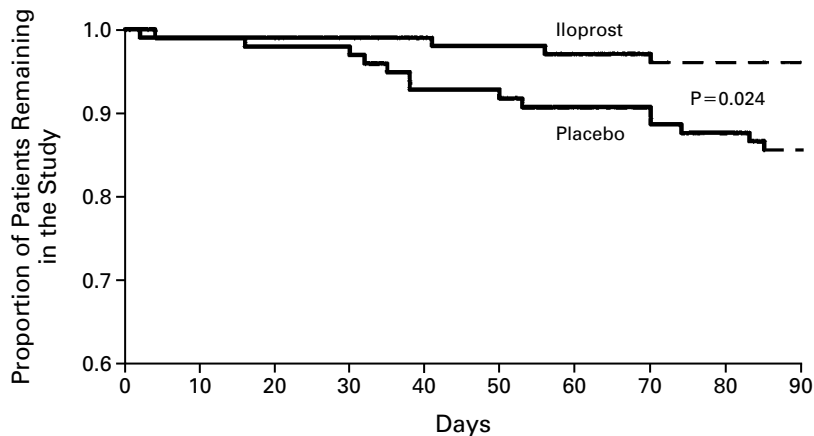
\* $P=0.03$  for the comparison of rates of improvement (by one or two classes) with the placebo group.

†Treatment was discontinued in all three patients.

‡Treatment was discontinued in seven patients, and three patients withdrew their consent.

§ $P=0.06$  for the comparison with the placebo group.

¶ $P=0.007$  for the comparison with the placebo group.



**Figure 2.** Kaplan–Meier Estimates of the Likelihood of Completing the 12-Week Study. Reasons for not completing the study included death, discontinuation of study medication, and withdrawal of consent (see Table 2).

**TABLE 3.** MEAN ( $\pm$ SD) CHANGE FROM BASE LINE IN HEMODYNAMIC VALUES DURING 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO.\*

VARIABLE	PLACEBO GROUP	ILOPROST GROUP	
		BEFORE INHALATION	AFTER INHALATION
		mean $\pm$ SD	
Pulmonary-artery pressure (mm Hg)	$-0.2 \pm 6.9$	$-0.1 \pm 7.3$	$-4.6 \pm 9.3$ †
Cardiac output (liters/min)	$-0.19 \pm 0.81$ ‡	$+0.05 \pm 0.86$	$+0.55 \pm 1.1$ †
Pulmonary vascular resistance ( $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$ )	$+96 \pm 322$ ‡	$-9 \pm 275$ §	$-239 \pm 279$ †
Systemic arterial pressure (mm Hg)	$-0.2 \pm 12.4$	$-1.7 \pm 12.8$	$-4.3 \pm 13.6$ ¶
Right arterial pressure (mm Hg)	$+1.4 \pm 4.8$ ‡	$+0.5 \pm 4.6$	$-0.8 \pm 4.6$
Pulmonary-artery wedge pressure (mm Hg)	$+0.7 \pm 3.6$	$+1.1 \pm 4.7$ ‡	$+1.8 \pm 5.3$ ¶
Arterial oxygen saturation (%)	$-1.6 \pm 4.4$ ‡	$-0.4 \pm 3.7$	$-1.4 \pm 3.7$ ‡
Mixed venous oxygen saturation (%)	$-3.2 \pm 6.7$ †	$-1.1 \pm 7.6$	$+1.8 \pm 8.3$
Heart rate (beats/min)	$-1.2 \pm 9.5$	$-1.8 \pm 12.4$	$-2.25 \pm 12.6$

\*For the iloprost group, both preinhalation and postinhalation values after 12 weeks are compared with the base-line values at study entry.

† $P < 0.001$  for the difference from base-line values.

‡ $P < 0.05$  for the difference from base-line values.

§ $P < 0.01$  for the comparison with the placebo group.

¶ $P < 0.01$  for the difference from base-line values.

group than in the placebo group (change,  $+1.42 \pm 2.59$  vs.  $+0.30 \pm 2.45$ ;  $P = 0.015$ ). The type of pulmonary hypertension had no effect on this outcome.

#### Quality of Life

Mean scores on the EuroQol visual-analogue scale improved significantly (from  $46.9 \pm 15.9$  to  $52.8 \pm 19.1$ ) in the iloprost group but were virtually unchanged

in the placebo group (dropping from  $48.6 \pm 16.9$  to  $47.4 \pm 21.1$ ,  $P = 0.026$  by analysis of covariance). The EuroQol health-state score improved from  $0.49 \pm 0.28$  to  $0.58 \pm 0.27$  in the iloprost group and was unchanged in the placebo group ( $0.56 \pm 0.29$  to  $0.56 \pm 0.31$ ,  $P = 0.11$  by analysis of covariance). None of the other measures of the quality of life were significantly different between the groups.

**Clinical Deterioration and Death**

One patient died in the iloprost group during the 12-week study, as compared with four patients in the placebo group (P=0.37) (Table 2). Criteria for clinical deterioration were met in 4.9 percent of patients in the iloprost group and 8.8 percent of those in the placebo group (P=0.41). This indicated that fewer patients either died or deteriorated in the iloprost group than in the placebo group (4.9 percent vs. 11.8 percent, P=0.09). The type of pulmonary hypertension had no effect on the outcome. During the study period, none of the patients received a lung transplant.

**Safety**

The total number of patients who had serious adverse events did not differ significantly between the groups (Table 4). Right ventricular failure and edema were more than twice as frequent in the placebo group as in the iloprost group. The total number of syncopal events in each of the two groups was similar (eight in the iloprost group and five in the placebo group), but these events were more often considered serious in the iloprost group. Syncope was not associated with clinical deterioration or premature withdrawal from the study. Syncopal events occurred more than two hours after the last inhalation (often after an overnight break), were exercise-induced in two patients, were induced by bradycardia in two patients (associated with gastroenteritis in one patient and with verapamil therapy in the other), and resulted in head trauma in one patient. Flushing and jaw pain were more common in the iloprost group, but these adverse effects were mostly transient and mild and were not considered to be serious in any patient.

**DISCUSSION**

The results of this clinical trial demonstrate that long-term inhaled administration of aerosolized iloprost, a stable analogue of prostacyclin, improves a clinically important combined end point consisting of exercise capacity, NYHA class, and clinical deterioration in patients with selected forms of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Moreover, iloprost improved several secondary end points.

Since intravenous epoprostenol was shown to improve survival among the most severely ill patients with primary pulmonary hypertension, it has been unethical to perform randomized clinical trials among patients with pulmonary hypertension in which survival is used as an end point. We chose a combined rather than a single end point (e.g., the distance walked in six minutes) in order to make a more rigorous determination of whether inhaled iloprost was efficacious. Nearly 40 percent of all patients who were treated with iloprost increased their six-minute walk-

ing distance by at least 10 percent. However, only half as many patients also had improvement in the NYHA class; conversely, not all patients with an improvement in NYHA class had an increase of at least 10 percent in the distance walked in six minutes. Thus, although only 17 percent of patients in the iloprost group reached the combined end point, a substantial number of the remaining patients met less strict criteria for clinical improvement that would warrant continued therapy. Furthermore, significantly fewer patients in the iloprost group than in the placebo group prematurely discontinued the study as a result of lack of efficacy or other reasons, suggesting that even when iloprost therapy does not produce substantial improvement, it may stabilize the clinical condition.

The mean inhaled dose of iloprost corresponded to 0.37 ng per kilogram of body weight per minute, which is considerably lower than an effective intravenous or subcutaneous dose.<sup>2,28</sup> Thus, targeted delivery of prostanoids to the pulmonary vasculature by means of inhalation may substantially reduce the drug requirements.

**TABLE 4.** INCIDENCE OF SERIOUS AND OTHER ADVERSE EVENTS.\*

VARIABLE	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)	P VALUE
	no. of patients (%)		
Serious adverse event			
Any event	28 (27.7)	25 (24.5)	0.63
Right ventricular failure and edema	4 (4.0)	10 (9.8)	0.16
Syncope	5 (5.0)	0	0.03
Other†	33 (32.7)	35 (34.3)	0.88
Adverse event‡			
Any event	91 (90.1)	90 (89.2)	0.82
Increased cough	39 (38.6)	26 (25.5)	0.05
Headache	30 (29.7)	20 (19.6)	0.11
Flushing	27 (26.7)	9 (8.8)	0.001
Influenza-like syndrome	14 (13.9)	10 (9.8)	0.39
Peripheral edema	13 (12.9)	16 (15.7)	0.69
Nausea	13 (12.9)	8 (7.8)	0.26
Jaw pain	12 (11.9)	3 (2.9)	0.02
Hypotension	11 (10.9)	6 (5.9)	0.22
Diarrhea	9 (8.9)	11 (10.8)	0.81
Vertigo	7 (6.9)	11 (10.8)	0.46
Syncope	8 (7.9)	5 (4.9)	0.41
Other adverse events§	296	277	

\*The most common adverse events are listed.

†These events included an aggravation reaction (an event causing concern about possible deterioration) in four patients in the iloprost group and five patients in the placebo group, hypoxemia in two patients in the placebo group, pneumonia in two patients in the iloprost group, tachycardia in two patients in the iloprost group and one in the placebo group, laboratory-test abnormalities in two patients in the iloprost group, chest pain in two patients in each group, and dyspnea in two patients in each group.

‡Data were available for 101 patients in the placebo group.

§The number is the total number of other adverse events.

Like other investigators, we found that the benefit was greatest among patients with primary pulmonary hypertension and was similar to that of epoprostenol<sup>1</sup> and bosentan.<sup>29</sup> Although patients with nonprimary pulmonary hypertension had improvement in the scores for the Mahler Dyspnea Index and quality-of-life measures that were similar to those achieved in patients with primary pulmonary hypertension, fewer such patients reached the combined end point, and they also had a smaller absolute change in the distance walked in six minutes. Similar results have been obtained with the use of other drugs for pulmonary hypertension, including epoprostenol,<sup>30</sup> beraprost,<sup>31</sup> and treprostinil.<sup>28</sup>

Hemodynamic assessments of preinhalation values showed that values stabilized in the iloprost group, whereas they deteriorated in the placebo group. The degree of deterioration may be underestimated, since patients who discontinued treatment prematurely did not undergo follow-up hemodynamic examination. Postinhalation assessments of hemodynamic variables demonstrated a significant improvement in the iloprost group, as was anticipated on the basis of previous reports.<sup>4,11,13,16</sup> Since the acute hemodynamic response did not differ between the groups, it appears unlikely that tolerance developed over the 12-week course of iloprost treatment. During long-term treatment, the patients' hemodynamic status is somewhere between preinhalation and postinhalation values. In comparison, continuous intravenous therapy may result in a more sustained hemodynamic improvement<sup>32</sup>; however, continuous intravenous therapy also poses considerable risks, including relapse after the interruption of therapy and complications, and is difficult to administer.

With respect to adverse events, flushing was more common in the iloprost group, but the frequency of most of the other inhalation-associated side effects was similar. There were more syncopal episodes in the iloprost group than in the placebo group (eight vs. five), and these episodes were more frequently defined as serious adverse events, but they were not associated with clinical deterioration. Since syncope occurred a relatively long time (two to nine hours) after the last inhalation, the loss of an effect of iloprost may have caused these events. However, the same side effect was observed with bosentan therapy, suggesting that these drugs may have a more pronounced effect on blood pressure during exercise. Alternatively, patients who had clinical improvement with therapy may have become more physically active, challenging the limits of their cardiac reserve. We would advise patients to increase their physical activity gradually after the initiation of therapy for pulmonary hypertension.

The inhalation device that we used provided accurate doses of iloprost. However, it is not battery-driven,

and inhalation commonly required 10 minutes. Different techniques of administering aerosolized iloprost result in similar acute hemodynamic effects as long as identical doses are delivered to the respiratory tract in a particle size suitable for alveolar deposition.<sup>14,33</sup> With other techniques, the duration of inhalation may be shortened considerably.<sup>14</sup>

In conclusion, this large, placebo-controlled trial demonstrates the efficacy and safety of inhaled iloprost for the treatment of severe primary pulmonary hypertension and selected forms of pulmonary arterial and chronic thromboembolic pulmonary hypertension. The advantages of intermittent inhaled therapy over intravenous therapy, coupled with the improvement in a number of clinically meaningful variables, suggest that inhaled iloprost therapy is effective. It may be a suitable alternative to continuous intravenous prostacyclin, especially in patients who do not derive a clear survival benefit with intravenous therapy.

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## APPENDIX

The members of the AIR study group were as follows: *Steering Committee* — W. Seeger (chair), N. Galiè, T. Higenbottam, S. Nikkho, R. Naeije, H. Olschewski, L.J. Rubin, G. Simonneau; *Other Investigators* — H. Fabel and E. Spiekertötter (Medizinische Hochschule, Hannover, Germany); E. Grimminger and R. Wiedemann (University Clinic, Giessen, Germany); H. Leuchte (University Clinic Großhadern, Munich, Germany); M. Aquilina (Università di Bologna, Bologna, Italy); K. Amsha and R. Lawson (Royal Hallamshire Hospital, Sheffield, United Kingdom); R. Alcock (Freeman Hospital, Newcastle-upon-Tyne, United Kingdom); A. Pforte (Universitätsklinik Eppendorf, Hamburg, Germany); J. Schauer (Medizinische Klinik und Poliklinik Universitätsklinik, Leipzig, Germany); W. Budts (Gasthuisberg University Clinic, Leuven, Belgium); P. Escríbano and M. Lázaro (Hospital 12 de Octubre, Madrid); E. Huchalla (Hôpital Claude-Huriez, Lille, France); M. Borst (Ludolf-Krehl-Klinik, Heidelberg, Germany); C.M. Black (Royal Free Hospital, London); C. Bravo, A. Román, and V. Monforte (Centro Sanitario, Vall d'Hebron, Barcelona, Spain); A. Peacock (West Infirmary, Glasgow, United Kingdom); A. Boonstra (Academic Hospital, Free University, Amsterdam); C. Fracchia (Fondazione Salvatore Maugeri, Montescano, Italy); C. Marini (Istituto di Fisiologia Clinica Consiglio Nazionale della Ricerche, Pisa, Italy); L. Nicod (Hôpital Cantonal Universitaire, Geneva); J. Pepke-Zaba (Papworth Hospital, Cambridge University, Cambridge, United Kingdom); G. Sybrecht and H. Wilkens (Pneumologie Uniklinik, Homburg, Germany); A. Torbicki (National Institute of Tuberculosis and Lung Disease, Warsaw, Poland); P. Diot (Hôpital Bretonneau, Tours, France); T. Mota (Hospital de Pulido Valente, Lisbon, Portugal); J.L. Pennaforte (Centre Hospitalier Universitaire [CHU] Reims, Reims, France); T. Perez and E. Radenne (CHU Lille, Lille, France); C. Pison (CHU Hôpital Nord, Grenoble, France); J.L. Vachiery (Hôpital Erasme, Brussels, Belgium); P. Hallgren (Kardiologkliniken, Goteborg, Sweden); E.-X. Kleber (Unfallkrankenhaus, Berlin, Germany); L. Providencia (Hospitais de Universidade de Coimbra, Coimbra, Portugal); V.R.G. Ribeiro (Vila Nova de Gaia, Portugal); M. Soler (Kantonsspital, Basel, Switzerland); and H. Stricker (Ospedale Regionale di Locarno La Carità, Locarno, Switzerland).

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