Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension

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Aims To describe the long-term clinical efficacy of inhaled iloprost as first-line vasodilator mono-therapy in patients with idiopathic pulmonary arterial hypertension (IPAH).

Methods and results Seventy-six IPAH patients were prospectively identified and treated with inhaled iloprost. Clinical, haemodynamic, and exercise parameters were obtained at baseline, after 3 and 12 months of therapy and yearly thereafter. Four endpoints were prospectively defined as follows: (i) death, (ii) transplantation, (iii) switch to intravenous (i.v.) therapy, or (iv) addition of or switch to other active oral therapy. During follow-up (535±61 days), 11 patients died, six were transplanted, 25 were switched to i.v. prostanoids, 16 received additional or other oral therapy, and 12 patients discontinued iloprost inhalation for other reasons. Event-free survival at 3, 12, 24, 36, 48, and 60 months was 81, 53, 29, 20, 17 and 13%, respectively. Among haemodynamic and exercise parameters, mixed venous oxygen saturation (P<0.001), right atrial pressure (P=0.001), and peak oxygen uptake (P=0.002) were associated with event-free survival.

Conclusion In this study, only a minority of patients could be stabilized with inhaled iloprost mono-therapy during a follow-up period of up to 5 years. In the presence of multiple treatment options, chronic iloprost inhalation as mono-therapy appears to have a limited role.

KEYWORDS Pulmonary arterial hypertension; Inhaled iloprost; Chronic therapy

Introduction Idiopathic pulmonary arterial hypertension (IPAH) is a rapidly progressing disease with a devastating prognosis. Even with the most effective treatment strategies, only 50–60% of patients survive >5 years.1–3 Since the reports describing beneficial effects of continuous intravenous (i.v.) epoprostenol on symptomatology and prognosis in patients with IPAH,4 several new treatment strategies based on different agents and distinct forms of administration have been developed.5–8 Among these new treatment options, inhaled iloprost has been shown to have favourable effects on pulmonary haemodynamics, symptomatology, and exercise capacity and is therefore a suggested treatment option in IPAH.7–11 However, data on the effects of long-term therapy with inhaled iloprost are lacking and considerable disease progression in patients receiving this treatment has been reported.

Therefore, it was the aim of this study to assess the long-term clinical efficacy of a treatment strategy using inhaled iloprost as first-line vasodilator mono-therapy in patients with symptomatic IPAH.

Methods Patients

Between October 1996 and October 2002, we consecutively enrolled 76 IPAH patients at four participating study centres according to the following inclusion criteria:

- diagnosis of IPAH as established by a mean pulmonary artery pressure (PAP) >30 mmHg and by exclusion of secondary causes
of pulmonary hypertension according to the diagnostic criteria reported by Rich et al.,12 modified according to the WHO proposal;13

- symptomatic disease, despite optimized conventional treatment corresponding to New York Heart Association (NYHA) Class II or III;
- patients referred initially with NYHA IV symptoms, who could be stabilized to NYHA Class III on intensified conventional treatment at our institutions;
- documented tolerability of inhaled iloprost during acute testing; and
- written informed consent.

In order to exclude other forms of pulmonary hypertension, patients underwent scintigraphy and/or spiral computed tomography (chronic thromboembolic pulmonary hypertension), high resolution computed tomography (lung disease), serologic testing (HIV-infection, connective tissue disease), and comprehensive pulmonary and liver function studies (lung or liver disease).13

Chronic treatment with inhaled iloprost was administered in a constant dose of 100 μg nebulized iloprost per day, divided into six single inhalations, as previously described.14 In contrast to other studies, no dose escalation was performed. There have been no controlled studies defining the role of dose escalation with iloprost inhalation. All patients used the identical nebulizer throughout the entire study period (Ilo-Neb, NebuTech, Elsenfeld, Germany). This device delivers an inhaled dose of ~24 μg iloprost when a total dose of 100 μg iloprost is nebulized.15

At the time of study initiation, no drugs were available in Germany specifically approved for the treatment of patients with IPAH. Therefore, only the compassionate use of iloprost inhalation was possible. The study was approved by the Institutional Ethics Board of each participating centre.

Haemodynamic measurements

To characterize the baseline haemodynamic profile and haemodynamic response to inhaled iloprost, all patients underwent right heart catheterization. This was performed via the right internal jugular or the right subclavian veins and an 8F Swan-Ganz catheter (Swan Ganz InteliCath, Baxter, USA) was used. Monitoring of arterial blood pressure (AP) and arterial blood gases was undertaken by an arterial line inserted into the radial artery. Cardiac output (CO, Fick method), cardiac index (CI), AP, PAP, right atrial pressure (RAP), and pulmonary capillary wedge pressure were measured at baseline and at the end of iloprost inhalation. Iloprost was administered by a jet nebulizer at a concentration of 10 μg/mL. According to an average nebulization rate of 1.7 mL/min, after 10 min a cumulative dose of 17 μg iloprost is nebulized (corresponding to an inhaled dose of 4.3 μg).15 Irrespective of their vasodilator response, patients were treated with inhaled iloprost as first-line therapy. A cumulative nebulized dose of 17 μg was chosen because this had been reported as safe and effective for the long-term treatment of pulmonary hypertension, when used as a single inhalation dose as part of a daily therapy regimen consisting of six inhalations.7

Cardiopulmonary exercise test

A symptom-limited exercise test was performed in a subgroup of 51 (67%) patients. Exercise testing was performed on a treadmill in 34 patients or on a cycle ergometer in 17 patients, according to the equipment of the including centre. Two of the participating centres (recruiting 21 patients) were not equipped for gas exchange measurements. Four patients were not able to perform an incremental exercise test at the time of inclusion into the study.

The modified Naughton protocol for treadmill exercise testing was used.11 Exercise testing with the use of a cycle ergometer (ER900; Jaeger, Würzburg, Germany) was started at 20 W with a stepwise increment of 16 W/min.11 Oxygen uptake (VO2), carbon dioxide output (VCO2), instantaneous expiratory gas concentrations throughout the respiratory cycle, and minute ventilation (VE) were measured continuously on a breath-by-breath basis (CPX/D, MedGraphics, St Paul, MN, USA or Jaeger Oxycon, Würzburg, Germany).

Peak VO2 was defined as the highest 30 s average of VO2 in the last minute of exercise. Pulmonary gas exchange was assessed with the VE/VCO2 ratio and end-tidal partial pressure of carbon dioxide (PTECO2) at rest, the VE/VCO2-slope16 during exercise, and percutaneous oxygen saturation (SaO2). Heart rate and blood pressure (by sphygmomanometer) were measured at rest, during each stage of exercise, and at peak exercise.

Follow-up

Patients were recruited from October 1996 to October 2002 and follow-up data until October 2003 were analysed for this report. During the first year, clinical and functional status were re-evaluated every 12 weeks, thereafter patients were seen at 6 months intervals. Repeated right heart catheterizations were planned at 3 and 12 months and, with stable clinical conditions, yearly thereafter. Although recommended, the individual decision to perform these renewed invasive studies in stable patients was left to the treating physician at each centre. In the absence of clinical deterioration, the results of these haemodynamic studies did not affect the treatment strategy. In case of clinical deterioration, defined as a persistent (>10 days) decline by at least one NYHA class, renewed right heart catheterization was recommended. If this revealed a decrease in mixed venous oxygen saturation (SvO2) <60% or a decrease in CI <2.0 L/min/m2, we suggested a switch to i.v. iloprost therapy.17–19 In patients with clinical deterioration who did not fulfil these haemodynamic switch criteria, additional or alternative oral therapy (beraprost or bosentan) was prescribed. In most of these patients, bosentan was added with continued iloprost inhalation. In case of further clinical deterioration, patients were listed for lung or heart-lung transplantation according to international guidelines.20

Applying this treatment strategy, patients were followed with the intention to use inhaled iloprost as single active therapy until one of the following four endpoints occurred: (i) death, (ii) transplantation, (iii) switch to i.v. therapy, or (iv) addition of other active oral therapy (beraprost, bosentan). Patients who did not reach any of these endpoints but discontinued iloprost treatment for various reasons (patient request, discontinuation of reimbursement, etc.) are reported as ‘others’. These patients, however, were included in the intention to treat analysis evaluating the clinical efficacy of inhaled iloprost.

Statistical analysis

All data are expressed as mean ± standard error of the mean values. Comparisons between haemodynamic parameters at baseline and 12 weeks were performed by using a paired t-test or Wilcoxon signed rank sum test, as appropriate. To compare responders and non-responders as well as patients in different NYHA classes, a two-sided t-test or a Mann–Whitney U test (for not normally distributed data) was used. In all instances, two-sided tests were done. No adjustments for the inflation of the Type I error were made due to the exploratory nature of the study. Kaplan–Meier survival curves were constructed to assess overall survival and event-free survival (defined as the non-occurrence of death, transplantation, switch to i.v. therapy, or addition of oral therapy). The log-rank test was performed to compare the event-free survival with the survival as estimated from the NIH registry. Univariate Cox proportional-hazards analysis was performed to assess the association between haemodynamic variables at baseline and at 3 months of chronic iloprost treatment and event-free survival. In addition, the association between haemodynamic variables at base line and at 3 months and the risk of death or transplantation (survival defined as the non-occurrence of death and transplantation) was evaluated. Similarly, the association between baseline
spiroergometric data and event-free survival was assessed. Subsequently, forward stepwise multivariable analyses were performed for the parameters that were predictive on univariate testing. This is in line with our exploratory approach. Once the significant predictors are identified, then we assessed the impact of all the other predictors by including them into the model sequentially. Change in estimated relative hazard of variables of interest and precision were used as criteria. This modelling approach was employed to identify the most parsimonious model. In all the models, the assumption of proportionality was assessed by plotting the time-varying component of each regression coefficient in the model against time. There was not any marked deviation from the assumption of proportional hazards for any of the covariates considered in the model as these plots were virtually flat. Furthermore, we carried out the test for proportional hazards for each covariate (scatter plots described earlier) and all the tests turned out to be non-significant. In the case of continuous covariates, the assumption of linearity was assessed graphically by plotting Martingale residuals against continuous covariates of interest. There was not any indication of violation of the assumptions of proportionality and linearity. Follow-up was discontinued on 1, October, 2003. Hazard ratio (HR) and 95% CI for risk factors as well as levels for risk factors as well as levels for the overall model (i.e. test for significant slope in the scatter plots described earlier) and all the tests turned out to be non-significant. In the case of continuous covariates, the assumption of linearity was assessed graphically by plotting Martingale residuals against continuous covariates of interest. There was not any indication of violation of the assumptions of proportionality and linearity. Follow-up was discontinued on 1, October, 2003. Hazard ratio (HR) and 95% CI for risk factors as well as levels for χ²-test (likelihood ratio test) are given (StatView 5, Abacus Concepts, Berkeley, CA, USA). For all statistical analyses, a P-value of < 0.05 was considered significant.

Results

Patients

According to the inclusion criteria, 76 patients with IPAH were enrolled (Table 1). The diagnostic work-up included contrast enhanced transesophageal echocardiography revealing a patent foramen ovale in 24 (32%) patients. At initial presentation, chronic medication included low-dose calcium channel blockers (n = 19), oral anticoagulation (n = 36), nasal oxygen therapy (n = 9), and diuretics in all patients. Throughout the study, low-dose calcium channel blocker therapy was kept constant. Oral anticoagulation was started prior to the study, when appropriate, and diuretics were adjusted according to the fluid status.

Cardiopulmonary exercise test

No adverse events occurred in relation to the exercise tests. The performance-limiting symptom was intolerable shortness of breath in all patients. There was a marked reduction in peak VO₂ and a pronounced increase in resting VE/VCO₂ ratio and VE/VCO₂ slope with exercise (Table 2). This reduction in peak VO₂ reflected functional capacity assessed by NYHA class. Patients in NYHA Class II and III showed a peak VO₂ of 13.8 ± 1.3 and 10.2 ± 0.5 mL/kg/min (P < 0.05) and an exercise time of 453 ± 61 and 297 ± 30 s (P < 0.05), respectively.

Haemodynamic data: baseline

Baseline haemodynamic data (n = 76) and the acute haemodynamic response to the inhalation of iloprost (n = 72) are given in Table 3.

Table 1 Clinical characteristics of 76 patients with IPAH at initial presentation

<table>
<thead>
<tr>
<th></th>
<th>(n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 ± 0.1</td>
</tr>
<tr>
<td>Gender, male n(%)</td>
<td>22(29)</td>
</tr>
<tr>
<td>NYHA Class, n(%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>18(24)</td>
</tr>
<tr>
<td>III</td>
<td>51(67)</td>
</tr>
<tr>
<td>IV</td>
<td>7(9)</td>
</tr>
<tr>
<td>Time from development of dyspnoea (days)</td>
<td>1152 ± 133</td>
</tr>
<tr>
<td>Time from diagnosis of IPAH to start of iloprost (days)</td>
<td>560 ± 110</td>
</tr>
<tr>
<td>Patent foramen ovale, n(%)</td>
<td>24(32)</td>
</tr>
</tbody>
</table>

Table 2 Baseline cardiopulmonary exercise test parameters (n = 51)

|                                | (
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Test duration (sec)</td>
<td>339 ± 27</td>
</tr>
<tr>
<td>HR rest (beats/min)</td>
<td>94 ± 3</td>
</tr>
<tr>
<td>HR peak exercise (beats/min)</td>
<td>129 ± 3</td>
</tr>
<tr>
<td>SBP rest (mmHg)</td>
<td>114 ± 3</td>
</tr>
<tr>
<td>SBP peak exercise (mmHg)</td>
<td>128 ± 3</td>
</tr>
<tr>
<td>DBP rest (mmHg)</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>DBP peak exercise (mmHg)</td>
<td>84 ± 2</td>
</tr>
<tr>
<td>P₄̄CO₂ rest (mmHg)</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>VE/VCO₂ slope (36/51)</td>
<td>58 ± 3</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>11.2 ± 0.5</td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Haemodynamic parameters at baseline and following acute vasodilator challenge with inhaled iloprost in 76 IPAH patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 76)</th>
<th>Inhaled iloprost (n = 72)</th>
<th>Relative change (%)</th>
<th>P-value (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>86 ± 2</td>
<td>83 ± 2</td>
<td>-4.0 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APmean (mmHg)</td>
<td>88 ± 1</td>
<td>85 ± 1</td>
<td>-2.5 ± 1.1</td>
<td>0.006</td>
</tr>
<tr>
<td>PAPmean (mmHg)</td>
<td>61 ± 2</td>
<td>53 ± 2</td>
<td>-13.5 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.9 ± 0.5</td>
<td>6.3 ± 0.5</td>
<td>-25.6 ± 4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>92 ± 1</td>
<td>95 ± 1</td>
<td>3.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>58 ± 1</td>
<td>63 ± 1</td>
<td>12.4 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>1.8 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>12.5 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR (dyne s cm⁻⁵)</td>
<td>2202 ± 96</td>
<td>1992 ± 93</td>
<td>-8.2 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (dyne s cm⁻⁵)</td>
<td>1639 ± 88</td>
<td>1261 ± 87</td>
<td>-24.0 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR, heart rate; SVR, systemic vascular resistance.
Haemodynamic parameters at baseline and after 3 months of inhaled iloprost therapy in 48 IPAH patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 48)</th>
<th>After 12 weeks of inhaled iloprost (n = 48)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>86 ± 2</td>
<td>85 ± 2</td>
<td>0.18</td>
</tr>
<tr>
<td>AP (mmHg)</td>
<td>88 ± 2</td>
<td>87 ± 2</td>
<td>0.77</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>7.0 ± 0.4</td>
<td>7.0 ± 0.4</td>
<td>0.73</td>
</tr>
<tr>
<td>PAPmean (mmHg)</td>
<td>59 ± 2</td>
<td>60 ± 2</td>
<td>0.41</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.0 ± 0.6</td>
<td>8.0 ± 0.7</td>
<td>0.17</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>92 ± 1</td>
<td>92 ± 1</td>
<td>0.26</td>
</tr>
<tr>
<td>SVo2 (%)</td>
<td>57 ± 1</td>
<td>54 ± 1</td>
<td>0.010</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>3.1 ± 0.1</td>
<td>2.9 ± 0.1</td>
<td>0.007</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>1.7 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>0.011</td>
</tr>
<tr>
<td>SVR (dyne s cm⁻²)</td>
<td>2259 ± 116</td>
<td>2341 ± 100</td>
<td>0.34</td>
</tr>
<tr>
<td>PVR (dyne s cm⁻²)</td>
<td>1671 ± 115</td>
<td>1801 ± 111</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Haemodynamic data: 12 weeks

Haemodynamic 3-months follow-up data for 48 patients with paired invasive studies are described in Table 4. All 48 patients had been clinically stable at the time of the measurements and, therefore, the results of these haemodynamic studies did not influence the decision for a switch to i.v. iloprost therapy. All measurements were performed at least 4 h following the last iloprost inhalation. Despite the 12 weeks of active vasodilator treatment with inhaled iloprost, a minor (although significant) deterioration with respect to CO-related parameters was observed.

Follow-up

The group of 76 patients initially treated with inhaled iloprost, as first-line mono-therapy, was followed for a median period of 383 days (interquartile range 133–733 days). Overall, chronic iloprost inhalation was well tolerated during long-term treatment. With repeated inhalations for up to 5 years, no serious side effects causing drug withdrawal were observed. Only two patients stopped therapy after a few days due to non-specific airway irritation. Furthermore, there were only rare instances of device failure or difficulties with the dilution of the drug by the patients prior to inhalation.

First 3 months

Of the initial 76 patients, 54 were on inhaled iloprost as mono-therapy at 3 months. Up to this point, five patients died due to right heart failure, five were switched to i.v. therapy, in four patients beraprost was added, and eight patients discontinued iloprost inhalation for other reasons. These eight patients requested discontinuation of iloprost inhalation because of missing subjective improvement. Serious side effects related to iloprost inhalation were not observed.

During these first 3 months 14 patients reached one of the four pre-specified endpoints (death, transplant, switch to i.v. prostanoids, or additional oral therapy). When comparing baseline data of these 14 patients with those continuing iloprost treatment, they had lower values for mixed venous (52 ± 2 vs. 59 ± 1%, P = 0.01) and arterial (87 ± 1 vs. 93 ± 1%, P = 0.01) oxygen saturation, while theRAP was higher (11 ± 1 vs. 7 ± 1 mmHg, P = 0.01). Of 54 patients who performed a cardiopulmonary exercise test at baseline, nine patients reached an endpoint during the first 3 months. These patients had a lower exercise time (207 ± 46 vs. 368 ± 30 s, P = 0.02) and peak VO₂ (8.2 ± 0.5 vs. 11.8 ± 0.6 mL/kg/min, P = 0.007) at baseline, when compared with the remaining patients.

First 12 months

At year 1, 32 patients were still on inhaled iloprost mono-therapy. Between 3 and 12 months, two patients had been transplanted, four patients died and nine were switched to i.v. therapy. In three cases, beraprost was added and two patients received bosentan. Only two patients discontinued iloprost inhalation for other reasons: failure to improve in one patient and discontinuation of reimbursement in another.

Overall, 35 patients reached one of the four prospectively defined endpoints within the first 12 months of follow-up. When compared with the other patients at baseline, these 35 individuals had lower values for CI (1.6 ± 0.1 vs. 2.0 ± 0.1 L/min/m², P = 0.003) and SVo2 (53.3 ± 1.4 vs. 61.1 ± 1.6%, P < 0.001) while the RAP was higher (9.9 ± 0.8 vs. 6.1 ± 0.5 mmHg, P < 0.001). In patients who performed a cardiopulmonary exercise test at baseline, 21 patients reached an endpoint during the first 12 months. These patients had a lower peak VO₂ at baseline (9.5 ± 0.6 vs. 12.4 ± 0.7 mL/kg/min, P = 0.004), when compared with the remaining patients.

Months 12–60

At 2 years, 14 patients continued iloprost inhalation as mono-therapy, one patient had died, three patients had been transplanted, and seven had been switched to i.v. iloprost. In four patients, beraprost was added and one received bosentan. Two patients were lost to further follow-up.

At 3 years, eight patients continued inhalation, one patient had been transplanted, two were switched to i.v. therapy, and one discontinuation of reimbursement occurred. In two patients, beraprost was added. After 4 years of therapy, six patients still inhaled iloprost as single active treatment and two had been switched to i.v. iloprost. At 5 years, five patients continued inhalation. One patient had died from cancer.

Intention to treat analysis

In an intention to treat analysis including all patients initially started on inhaled iloprost as mono-therapy, event-free survival at 3 months and at 1, 2, 3, 4, and 5 years was 81% (95% CI 3–90), 53% (95% CI 42–64), 29% (95% CI 18–39), 20% (95% CI 10–29), 17% (95% CI 8–27), and 13% (95% CI 3–23), respectively (Figure 1).

Mortality

For the entire group of 76 patients overall survival at 3 months and at 1, 2, 3, 4, and 5 years was 93% (95% CI 88–99), 79% (95% CI 69–88), 70% (95% CI 60–81), 59% (95% CI 48–71), 59% (95% CI 48–71) and 49% (95% CI 33–65), respectively. For comparison, the expected survival according to the NIH formula was calculated survival at 1, 2, 3, 4,
and 5 years was 68, 55, 46, 38, and 32%, respectively (Table 5).

Cox proportional-hazards analysis

Baseline haemodynamic data

**Event-free survival.** In univariate Cox proportional-hazards analysis, SvO₂ (%) HR 0.951, 95% CI 0.928–0.975, χ²-value 14.9, P < 0.0001, RAP (mmHg, HR 1.125, 95% CI 1.057–1.119, χ²-value 12.8, P < 0.0001), CI (L/min/m², HR 0.450, 95% CI 0.274–0.740, χ²-value 11.6, P < 0.0001), CO (L/min, HR 0.720, 95% CI 0.557–0.930, χ²-value 6.8, P = 0.009), and PVR (dyne s cm⁻², HR 1.000, 95% CI 1.000–1.001, χ²-value 6.6, P = 0.01) were predictors of event-free survival.

Multivariable forward stepwise Cox proportional-hazards analysis of all these variables but CI and CO (because of collinearity with SvO₂) revealed SvO₂ (%) HR 0.964, 95% CI 0.61–6.1, P = 0.013) and RAP (mmHg, HR 1.075, χ²-value 3.94, P = 0.047) to be independent predictors of event-free survival. Backward stepwise analysis showed identical results. Once we identified these significant predictors, we sequentially included the other covariates that were not selected by the stepwise algorithm to see if they might change the regression coefficients of SvO₂ and RAP and improve precision. However, they did not show any impact on regression coefficient of either SvO₂ or RAP but slightly decreased precision, therefore, they were not included in our final model.

**Death and transplantation.** When survival is defined as non-occurrence of death and transplantation SvO₂ (%) HR 0.921, 95% CI 0.892–0.952, χ²-value 25.0, P < 0.0001, CI (L/min/m², HR 0.277, 95% CI 0.139–0.553, χ²-value 16.2, P < 0.0001), PVR (dyne s cm⁻², HR 1.000, 95% CI 1.000–1.001, χ²-value 12.8, P < 0.0001), CO (L/min, HR 0.565, 95% CI 0.401–0.796, χ²-value 12.2, P < 0.0001), RAP (mmHg, HR 1.136, 95% CI 1.051–1.229, χ²-value 10.0, P = 0.0016), and heart rate (beats/min, HR 1.030, 95% CI 1.007–1.052, χ²-value 6.8, P = 0.009) were significant predictors of prognosis on univariate Cox proportional-hazards analysis. Only SvO₂ was an independent predictor on multivariable forward stepwise analysis that included all these parameters apart from CI and CO. Again, we sequentially included the other covariates that were not selected by the stepwise algorithm. They did not show any impact on regression coefficient of SvO₂ but slightly decreased precision and were not included in our final model.

**Baseline spiroergometric data.** Among spiroergometric data, exercise duration (s, HR 0.98, 95% CI 0.996–1.000, χ²-value 5.06, P = 0.025) and peak VO₂ (mL/kg/min, HR 8.857, 95% CI 0.767–0.956, χ²-value 9.90, P = 0.002) were predictors of event-free survival.

**3-months follow-up**

**Event-free survival.** Among haemodynamic data obtained at 3 months, RAP (mmHg, HR 1.184, 95% CI 1.098–1.277, χ²-value 18.4, P < 0.0001), SvO₂ (%) HR 0.929, 95% CI 0.898–0.961, χ²-value 17.2, P < 0.001), CI (L/min/m², HR 0.259, 95% CI 0.101–0.664, χ²-value 9.3, P = 0.002), and heart rate (beats/min, HR 1.034, 95% CI 1.012–1.058, χ²-value 8.4, P = 0.004) were predictors of event-free survival in a univariate Cox proportional-hazards-analysis. On multivariable forward stepwise analysis, RAP (mmHg, HR 1.140, χ²-value 9.4, P = 0.002) and SvO₂ (%) HR 0.945, 95% CI 0.898–0.961, 8.4, P = 0.004) were found to be independent predictors of prognosis. Again, we sequentially included the other covariates that were not selected by the stepwise algorithm. They did not show any impact on regression coefficient of RAP or SvO₂ but slightly decreased precision and were not included in our final model.

**Death and transplantation.** SvO₂ (%) HR 0.921, 95% CI 0.898–0.961, χ²-value 17.6, P < 0.0001), CI (L/min/m², 0.128, 95% CI 0.039–0.423, χ²-value 1.5, P < 0.001), CO (L/min, HR 0.453, 95% CI 0.251–0.818, χ²-value 8.6, P = 0.003), RAP (mmHg, HR 1.106, 95% CI 1.025–1.193, χ²-value 6.3, P = 0.01), and PVR (dyne s cm⁻², HR 1.001, 95% CI 1.000–1.001, χ²-value 4.9, P = 0.027) were predictors of survival (when defined as non-occurrence of death and transplantation) on univariate Cox proportional-hazards analysis. The multivariable forward stepwise analysis showed only SvO₂ to be a significant and independent predictor of prognosis. Again, we sequentially included the other covariates that were not selected by the stepwise algorithm. They did not show any impact on regression coefficient of SvO₂ but slightly decreased precision and were not included in our final model.

### Table 5 Overall survival in comparison to estimated survival (NIH)

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Cumulative survival of the study population, % (95% CI)</th>
<th>NIH estimated survival, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79 (69–88)</td>
<td>68 (58–79)</td>
</tr>
<tr>
<td>2</td>
<td>70 (60–81)</td>
<td>55 (44–66)</td>
</tr>
<tr>
<td>3</td>
<td>59 (48–71)</td>
<td>46 (35–57)</td>
</tr>
<tr>
<td>4</td>
<td>59 (48–71)</td>
<td>38 (27–49)</td>
</tr>
<tr>
<td>5</td>
<td>49 (33–65)</td>
<td>32 (22–43)</td>
</tr>
</tbody>
</table>

Kaplan–Meier cumulative survival of the study population compared with the estimated cumulative survival according to the NIH survival probability formula, log-rank P = 0.28.
Discussion

This study describes the clinical course of a large group of patients with symptomatic IPAH with inhaled iloprost as initial mono-therapy. During a follow-up period of up to 5 years, only a minority of these patients continued this initial approach. At 12 months, 42% (32/76) of our patients were clinically stable with continued inhaled iloprost as mono-therapy. The remaining patients showed significant disease progression and nine patients died within this period. In most of these patients, other forms of treatment had to be added (bosentan \( n = 2 \), beraprost \( n = 7 \)), they were switched to i.v. prostanoïd treatment \( n = 14 \) or transplanted \( n = 2 \).

More favourable results have been reported by Hoeper et al.\(^{10}\) for a group of 31 IPAH patients initially treated with inhaled iloprost and followed for up to 1 year. None of the 31 patients died during follow-up and a subgroup of 24 patients continued iloprost inhalation for at least 12 months. For that group of 24 patients, significant improvements in symptoms, haemodynamics, and exercise capacity were reported, although a subgroup of patients appeared to have less benefit with iloprost mono-therapy. Preliminary data from an open-label multicentre study of 63 patients with primary \( n = 40 \) or secondary \( n = 23 \) pulmonary hypertension treated with inhaled iloprost for up to 2 years suggest sustained efficacy in those patients continuing iloprost inhalation. In that study, 37 (59%) patients continued iloprost inhalation at 2 years.

For chronic oral prostanoïd therapy with beraprost in patients with pulmonary arterial hypertension, the available data suggest an initial positive effect on symptoms and exercise capacity during the first 3–6 months of treatment.\(^{24,25}\) Thereafter, this benefit was lost with continued mono-therapy.\(^{25}\)

When patients with PAH are treated with the endothelin receptor antagonist, bosentan, as mono-therapy, significant improvements of symptoms and exercise capacity have been reported for treatment periods of up to 16 weeks.\(^{8}\) An open-label extension study of 29 patients treated with bosentan for at least 12 months following the initial study showed sustained benefit with respect to exercise capacity in 16 patients at 6 months and haemodynamic stabilization in 11 patients at 15 ± 4 months.\(^{26}\) Preliminary long-term data from a larger group of 169 IPAH patients (NYHA functional class III/IV) treated with bosentan suggest sustained clinical efficacy because 70% of them received bosentan mono-therapy at 2 years.\(^{27}\)

So far, only continuous i.v. prostanoïd therapy has been shown to improve survival in patients with IPAH.\(^4\) Because no prospectively controlled mortality data are available for other forms of IPAH therapy, potential effects on survival are usually estimated by calculating survival according to the NIH formula.\(^{22}\) Overall survival in our study was 79 and 59% at 1 and 3 years, respectively. The expected survival, when calculated by the NIH formula, would have been 68 and 46% at these time points (Table 5). With i.v. prostanoïds, survival rates at 1 and 3 years of 85–88 and 63% have been reported, respectively.\(^{1,2}\) Preliminary data from an open-label multicentre study of inhaled iloprost report an overall survival rate of 85% at 2 years in a group of 63 patients.\(^{23}\) The 2 years survival rate of 91% for the subgroup of IPAH patients was higher than the expected survival for this group of 63%, when calculated according to the NIH-formula. Another preliminary report on the effects of first-line bosentan therapy in IPAH patients found survival rates of 96 and 86% at 1 and 3 years,\(^{27}\) respectively. The expected survival for that group according to the NIH formula would have been 69 and 48% at these time points.

Haemodynamics

As it has recently been described for IPAH patients treated with i.v. epoprostenol,\(^1\) haemodynamic data at baseline were important predictors of outcome in our group of patients treated with inhaled iloprost as well. Among several prognostic indicators identified by univariate analysis among baseline haemodynamics, \( \text{SvO}_2 \) and RAP were significant predictors of event-free survival in multivariable analysis. When survival was defined as freedom from death and transplantation, \( \text{SvO}_2 \) was a significant predictor of event-free survival in multivariable analysis. These findings underscore the importance of CO as a key parameter reflecting right ventricular pump function and thereby disease severity in patients with pulmonary hypertension. In contrast, in the group of IPAH patients treated with i.v. epoprostenol by Sitbon et al., \(^1\) CI at baseline was not related to survival as in the series reported by McLaughlin et al.\(^2\)

As suggested by Sitbon et al.,\(^1\) it might be especially important to assess changes in haemodynamics and functional capacity after 3 months of therapy. Our data support this concept and extend it to inhaled iloprost treatment. Our patients were re-studied after 3 months of therapy which could be performed in 48/54 patients on iloprost mono-therapy at this time. With the exception of a minor but statistically significant deterioration of parameters related to CO pre-inhalation haemodynamics were not different from baseline. This finding is not in agreement with data from the AIR-study, which demonstrated constant CO pre-inhalation in the iloprost group.\(^7\) However, the failure to obtain haemodynamic data in six clinically stable patients at 3 months may have resulted in a selection bias towards a haemodynamically sicker population in our study.

Exercise-related parameters

As we previously reported, a peak \( \text{VO}_2 < 10.4 \text{mL/kg/min} \) and a peak systolic blood pressure \( < 120 \text{mmHg} \) each strongly predict a severely compromised prognosis in patients with symptomatic IPAH.\(^3\) The current data extend these findings to patients treated with inhaled iloprost. Exercise time and peak \( \text{VO}_2 \) both related to NYHA class and predicted event-free survival at 12 months.

Study limitations

When assessing the association between haemodynamic parameters and event-free survival as defined in this study (non-occurrence of death, transplantation, switch to i.v. therapy, or addition of oral therapy) there might be a bias since haemodynamic criteria are part of the treatment algorithm. However, the decision to switch a patient to i.v. therapy or add oral treatment was never based on hemodynamic parameters obtained from the pre-scheduled invasive studies at baseline or after 12 weeks. Instead, patients were re-studied invasively in case of clinical deterioration independent from pre-scheduled studies (as described in the
than epoprostenol. For these reasons, we switched our addition, iloprost has a longer half-life and is less costly the entire study. With newer inhalation devices, a more efficacious attempt to minimize technical variability, patients in this study used the identical inhalation device throughout the entire study. With newer inhalation devices, a more efficacious disease progression cannot successfully be prevented. In this study, adherence to therapy is now available. The fact that in 8/76 patients the assigned iloprost treatment had to be discontinued within the first 3 months upon patient request (missing subjective improvement) certainly weakens follow-up data, but probably reflects a real-life situation. Only in a controlled study, adherence to therapy can reliably be assessed.

Epoprostenol is certainly the most commonly used drug for i.v. prostanooid treatment in patients with severe IPAH. Nevertheless, iloprost showed comparable clinical efficacy in smaller studies and has been recommended as an alternative i.v. treatment in this patient group. In addition, iloprost has a longer half-life and is less costly than epoprostenol. For these reasons, we switched our patients to i.v. iloprost in case of clinical deterioration.

Due to the multicentre design of our study, cardiopulmonary exercise testing could not be performed in all patients. Therefore, the importance of exercise related variables could only be analysed in a subgroup of patients. A control group would have strengthened the results of this study. However, the type of treatment (inhaled) and the often malignant course of the disease make it very difficult to withhold active treatment for extended time periods in these patients for ethical and practical reasons.

At the time this study began, no single drug was approved for the treatment of IPAH in Germany. Even i.v. prostanooids, which have been shown to improve symptoms and mortality, are still not approved in our country. Therefore, this study set out to investigate the clinical value of iloprost mono-therapy in IPAH patients. During >5 years of follow-up, several new drugs became available for patients with IPAH and bosentan was the first drug being approved for the treatment of IPAH in Germany. With these evolving therapeu-etic options, treatment strategies had to be adapted in our patients and an increasing number of patients received bosentan or i.v. iloprost, when needed. Furthermore, initial data document the potential benefits of combination therapy for these patients. In a group of 20 IPAH patients treated with inhaled or oral prostanooids, Hooper et al. added bosentan therapy and found significant improvements in symptoms and exercise capacity following 3 months of combined therapy. For these reasons, our initial strategy to keep patients as long as possible on inhaled iloprost as mono-therapy might be outdated. The future treatment of patients with symptomatic IPAH is probably composed as a stepwise approach tailoring the treatment options available to the needs of the individual patient with combination therapy being a common approach.

Despite these limitations, we think these outcome data describing the clinical efficacy of inhaled iloprost as monotherapy provide some useful clinical information for physicians treating this demanding group of patients.

References

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