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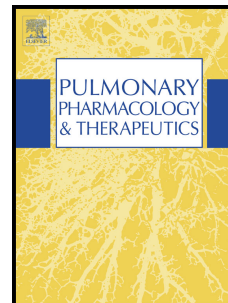
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## Intravenous Epoprostenol versus *High Dose* Inhaled Iloprost for Long-term Treatment of Pulmonary Hypertension

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**Abstract**

Background: Intravenous prostacyclin (iv PGI) and inhaled Iloprost (inh ilo) are established therapies in pulmonary arterial hypertension (PAH), however comparative data are lacking.

Methods and Patients: We performed a long-term open label comparison trial of iv PGI or **high dose** inh ilo in 24 patients with severe PAH: 12 patients (9 female, 40 +/- 14 years, 10 idiopathic PAH, 2 PAH in connective tissue disease CTD) received iv PGI, whereas 12 patients (7 female, 43 +/- 12 years, 5 IPAH, 6 CTD, 1 porto-pulmonary hypertension) were commenced on inh ilo with a median dose of 120 µg / 24 hours. Hemodynamic parameters and 6 minute walking distance (6MWD) at baseline did not differ between both groups.

Results: After 3 months therapy, patients on iv PGI showed a significant increase in 6 MWD from 220 to 280 meters ( $p < 0.01$ ), whereas patients on **high dose** inh ilo increased 6 MWD from 200 to 275 meters ( $p < 0.05$ ). The event free follow up was 23 [1-76] months in the iv PGI group, and 16 [7-38] months in the **high dose** inh ilo group ( $p < 0.05$ ). Patients with a 6MWD  $\geq$  300 meters after 3 months therapy had a significantly longer event free follow up [16 vs. 35 months;  $p < 0.004$ ]

Conclusion: In this patient population with severe pulmonary hypertension of different etiologies, event free follow up on treatment with iv PGI is significantly longer compared to **high dose** inh ilo. The 6MWD after 3 months treatment might be predictive for long term outcome.

Key Words: pulmonary hypertension, epoprostenol, high dose Inhaled iloprost, long-term treatment

## 1. Introduction

Administration of prostacyclin or its analogues is currently one of the main therapeutic principles in pulmonary arterial hypertension (1).

Intravenous epoprostenol (iv PGI<sub>2</sub>) is established therapy for severe pulmonary hypertension of different etiologies. Over the last 20 years, the effects of iv PGI<sub>2</sub> on hemodynamic parameters, clinical performance, and survival have been repeatedly documented with a mean increase in 6MWD of 47 meters after 3 months treatment, while patients with idiopathic pulmonary arterial hypertension (PAH) respond best to iv PGI therapy (2-6). However iv PGI<sub>2</sub> therapy is hampered by several disadvantages including the invasiveness and associated risks (1, 7, 8). Furthermore its long term effectiveness on disease progression beyond 1 year treatment has not been studied (9)

Inhaled Iloprost (inh ilo) is also an approved for therapy of severe pulmonary arterial hypertension (PAH) with the advantage of noninvasive drug application. It has been shown to improve symptoms, exercise capacity, and hemodynamic parameters in patients with severe pulmonary hypertension in a randomized controlled trial and several uncontrolled trials; however there are only few data on long term use beyond one year treatment (10-13).

Although several new therapies are available for pulmonary hypertension, studies comparing the different treatment options in pulmonary hypertension are very limited and there is no head to head clinical study comparing the treatment with prostacyclin analogues (14).

The present study compares the effects of primary treatment with either iv PGI<sub>2</sub> or inh ilo in 26 patients with severe pulmonary hypertension. The end-points were hemodynamic and functional parameters after 3 months treatment, and long term outcome.

## 2. Methods and Patients

### 2.1. Initial Assessment

In this long-term observation, 26 consecutive patients with newly diagnosed severe pulmonary hypertension were assessed. None of the patients had previously received specific pulmonary vasoactive treatment. Fifteen patients suffered from idiopathic PAH. Eight patients had PAH due to connective tissue disease (CTD) and one patient from porto- pulmonary hypertension due to viral hepatitis. Two patients with chronic thromboembolic pulmonary hypertension not amenable for pulmonary thromboendarterectomy (CTEPH) and severe pulmonary hypertension in mild pulmonary fibrosis were excluded from further analyses as they suffered from non PAH- PH.

In total 24 patients (16 female, 8 male, median age 40, 16-67 years) were included.

All patients underwent a functional and haemodynamic assessment including 6 minute walking distance (6MWD) and right heart catheterization. None of the patient had an acute significant vasodilator response to inhaled nitric oxide according to current guidelines (1, 15). All patients were in WHO stage III-IV with indication for specific pulmonary vasoactive therapy (1).

Baseline demographic, haemodynamic and functional parameters did not differ between both treatment groups (table 1)

### 2.1. Initiation of Therapy

At time of initiation of treatment, iv PGI as well as inh ilo was approved treatment for severe PH. The follow up was carried out within the regular clinical care schedule.

For administration of iv PGI<sub>2</sub> (Flolan), a Hickman central venous catheter was inserted in the subclavian vein. Iv PGI was infused using a battery driven syringe pump with automatic auditory alarm (MS16A Graseby Dynamics, Bushey, U.K.). Dose of iv PGI<sub>2</sub> was gradually

increased to the maximum tolerated dose. Further dose increase was according to patients' symptoms and clinical condition (1).

Inh ilo was delivered via an ultrasonic jet nebuliser (Multisonic compact® , Schill Company, Probstzella, Germany) with an efficacy of 86%, expressing the percentage of dosage delivered at the mouthpiece (15). Patients were started on treatment as described previously (16). In summary, patients inhaled 3mls of iloprost dilution over 5-8 minutes with gradual increase depending on the patient's symptoms up to a maximum dose of 20 µg iloprost / inhalation. Inhalation was repeated every 3 hours with a 9 hour night time break. In total, there were 7 inhalation sessions per day, and the patients received 120 µg iloprost mouthpiece dose per 24 hours (**high dose inh ilo**), as previously described (17). This inhalation regimen was approved by the local ethics committee. Patients were trained to handle the medication and the intravenous and inhalation devices at the ward.

Eighteen patients were started on treatment with iv PGI<sub>2</sub>. Within 1 week, 5 patients were subsequently changed to **high dose** inh ilo because of severe catheter related infections (n=4, among them 2 pts with CTD), or inability to handle the continuous iv infusion devices (n=1). Eight patients were primarily started on **high dose** inh ilo. Six patients refused iv PGI<sub>2</sub> therapy. One patient was on chronic ambulatory hemodialysis due to renal involvement in systemic Lupus erythematosus, and another patient had severe pulmonary hypertension in mild pulmonary fibrosis.

## 2.2. Follow up

After 3 months treatment patients underwent a repeat of 6MWD and hemodynamic measurements. Iv PGI treatment was continued during right heart catheterization, whereas in patients on treatment with **high dose** inh ilo, haemodynamics were measured 1 - 2 hours after last administration of inh ilo. An intermediate analysis was performed after 12 months

concerning functional capacity and survival. During the whole observation period patients remained in regular clinical follow up every 3 - 6 months. We recorded need for additional medical therapy, atrial septostomy or transplantation due to clinical worsening. Clinical worsening was defined as described previously (13), i.e. deterioration in their condition with refractory systemic hypotension with systolic blood pressure less than 85 mm Hg, signs of progressive right ventricular failure, secondary organ failure, a reduction of 6 minute walking distance > 30% or a deterioration of in haemodynamic parameters.

### 2.3. Statistics

As data were not normally distributed, values are displayed as median (min-max). To test for statistical differences, we used the Mann Whitney u-test, Wilcoxon rank sum test, and Chi square test ( $\chi^2$ ). For comparing survival, Kaplan Meier Survival Analysis was performed (18).

## 3. Results

### 3.1. *Iv PGI* group

Twelve patients were commenced on treatment with iv PGI<sub>2</sub> (9 female; 10 idiopathic PAH, 2 PAH in CTD; median age 38, 19-67 years). Within the first 3 months patients received a median dose of 8 ng/kg/min (7-10 ng/kg/min). Afterwards the dose of iv PGI<sub>2</sub> was further increased according to patient's symptoms and clinical condition. After 1 year the median dose was 15 ng/kg/min (10-24) ng/kg/min.

### 3.2. **High Dose** *Inh ilo* group

Twelve patients received inh ilo (7 female; 5 idiopathic PAH, 6 PAH in CTD, 1 portopulmonary hypertension, median age 43, 16-57 years) at an effective median dose at mouthpiece of 120 (90-120) µg / 24 hours.



### 3.3. Follow up

#### 3.3.1. Assessment after 3 months

After 3 months treatment, patients receiving iv PGI<sub>2</sub> showed an increase in the 6MWD from 220 [0-380] to 280 [200-400] meters (27%;  $p < 0.01$ ). The cardiac index (CI) increased from 1.6 [0.8-1.9] to 2.0 [1.3-3.1] l/min/m<sup>2</sup> (25%;  $p < 0.005$ ), whereas pulmonary vascular resistance (PVR) decreased from 1174 [847-3160] to 1078 [504-1615] dyne\*s/cm<sup>5</sup> (9%;  $p < 0.005$ ) (Table 2A).

Patients on treatment with **high dose** inh ilo showed an increase of the 6MWD from 200 [100-480] to 275 [100-500] meters (37%;  $p < 0.05$ ), and a decrease in PVR from 1227 [481-2069] to 1012 [341-1785] (17%;  $p=0.38$ ). The CI remained stable at 1.7 l/min/m<sup>2</sup> (Table 2B).

#### 3.3.2. Assessment after 12 months

After 12 months 20 patients were alive on continuous treatment. In the iv PGI<sub>2</sub> group 1 patient had died and 2 patients had undergone lung transplantation. In the remaining 10 patients 6MWD increased to 295 [100-400] meters ( $p < 0.01$  from baseline) with a median dose of 12.8 ng/kg/min (10-21 ng/kg/min). In the **high dose** inh ilo group 3 patients had died within one year. The 10 patients on continuing treatment achieved a 6MWD of 280 [20-450] meters ( $p < 0.05$  from baseline).

#### 3.3.3. Long term follow up

The median time of follow up was 20 [1-76] months after starting prostaglandin analogue therapy. During this period, 5 patients underwent successful heart lung transplantation after 15 [1-27] months, among them 3 patients treated with iv PGI<sub>2</sub> and 2 patient on treatment with **high dose** inh ilo.

Six patients (2 iv PGI<sub>2</sub>, 4 inh ilo) deteriorated on monotherapy after a median of 38 (16-72) months. They could be stabilized on combination treatment with bosentan (n=3), sildenafil (n=2) and iv PGI<sub>2</sub> in one patient, respectively. Three patients in the iv PGI<sub>2</sub> group and one patient on inh ilo underwent successful atrial septostomy (19).

Twelve patients died after 18 [3-64] months prostaglandin analogue treatment, among them 5 in the iv PGI<sub>2</sub> and 6 in the **high dose** inh ilo group. Ten patients died due to progressive right heart failure despite escalation of medical therapy in all of them. Four patients could not be stabilized even with atrial septostomy (19). One patient treated with **high dose** inh ilo died from renal failure due to underlying diagnosis of sLE. Another patient in the **high dose** inh ilo group died due to cardiac arrhythmia.

Comparing both treatment groups, the event free follow up was 21 [1-76] months in the iv PGI<sub>2</sub> group, and 16 [7-38] months in the **high dose** inh ilo group [p=0.049] (Figure 1).

Patients with a 6 MWD > 300 meters at baseline had a longer event free follow up compared to patients with a 6MWD < 300 meters prior to prostaglandin analogue therapy but this was not statistically significant [34 (10-40) versus 16 (1-75) months; p= 0.4].

Patients with a 6MWD > 300 meters after 3 months prostaglandin analogue therapy had a statistically significant longer event free follow up compared to patients walking < 300 meters [35 (5-75) vs. 16 (1-64) months; p=0.02] (Figure 2).

#### 4. Discussion

This long term observational study compares monotherapy with either intravenous prostacyclin or **high dose** inhaled iloprost in patients with severe PAH and provides data on long term follow up to 6 years of treatment.

Both treatments resulted in a significant functional improvement after 3 months and stabilization of functional capacity after 12 months, respectively. **However, only in the iv PGI<sub>2</sub> group there was also a significant improvement in the haemodynamic parameters after 3 months, a prognostic relevant goal to achieve in the treatment of PAH patients.**

These effects of either iv PGI<sub>2</sub> or **high dose** inh ilo on 6 MWD and haemodynamics are comparable with results of previously published trials (2-6, 11).

The decision about establishing patients on treatment with **high dose** inh ilo was made to limit transpulmonary shunt blood flow (12), according to patient' preferences, or in early complications of iv PGI<sub>2</sub> therapy (especially due to infectious complications). We experienced a rate of early line infections of 15%, which is comparable with previous studies (2).

Although both treatment groups did not differ concerning baseline hemodynamics and functional parameters, the underlying diseases were not equally distributed. In the iv PGI<sub>2</sub> group 10 patients had idiopathic PAH (77%), whereas in the **high dose** inh ilo group 5 patients suffered from idiopathic PAH (38%). While patients with idiopathic PAH respond best to prostaglandin analogue treatment, patients with PAH due to CTD have a worse prognosis (1, 3, 17). The improvement in prognosis is well documented in patient with idiopathic PAH on treatment with iv PGI<sub>2</sub> (1, 5, 15, 20). For inh ilo, a benefit concerning event free follow up is currently published over a period of 3 months (13). In our study, a selection bias concerning etiology of PAH needs to be considered for the event free long term follow up, which was significantly lower in the **high dose** inh ilo group (16 months) compared to the iv PGI<sub>2</sub> group (23 months).

The dose of ivPGI has been uptitrated in respect to patients' symptoms and clinical stability (1).

The dose range of iv PGI<sub>2</sub> was comparable with dosage used in previous studies (2).

**However, a dose depending treatment effect has been shown for prostacyclin and prostacyclin analogues in the therapy of PAH. The use of higher dosages of iv PGI<sub>2</sub> as applied in our observation, been reported in the long term treatment of PAH patients (21, 22).**

In this study we used an inhalation regimen with a maximum dose of 120 µg Iloprost per day.

**This dose is significantly higher than the currently used dosage of inhaled iloprost in the US and Europe.** Previously, we could show that inhalation of this high dose of iloprost is safe and effective in the long term treatment of patients with PAH and PH of other origin (17).

**Nevertheless, the results obtained in this long term observation can only be related to the use of high dose inhaled iloprost.**

Besides haemodynamics, assessment of prognosis in PAH includes exercise capacity before and during therapy (5, 17, 23, 24). In our study, the 6MWD before therapy did not significantly discriminate concerning overall outcome, but patients with a 6MWD > 300 meters after 3 months treatment with prostaglandin analogue had a significant longer event free follow up (Figure 2). Functional improvement on prostaglandin analogue treatment is a useful parameter for assessment of long term outcome (5).

Therapy of PAH has changed considerably with introduction of orally active medication (1, 25, 26). Comparing the results of the recently published trials of treatment for PAH, the present study confirms the impact of intravenous epoprostenol and inhaled iloprost as an efficacious and powerful medical treatment for severe pulmonary hypertension (27, 28). Current strategies for patients' management involve clinical goals of treatment and combination therapy in PAH (29). Concomitant use of intravenous or inhaled prostaglandin analogues with endothelin

antagonists or phosphodiesterase 5 inhibitors showed favorable results in several uncontrolled studies and randomized controlled trials (30-36).

#### 4.1. Study limitations

The study has several major limitations. Firstly the lack of randomization, but also the small number of patients with heterogeneous etiology of pulmonary hypertension and their unequal distribution within the study groups should be taken into account. The higher number of patients with IPAH, which respond better to prostacyclin therapy, might influence the outcome of the study. **Otherwise, the relatively low dosage of iv PGI<sub>2</sub> and the use of high dose inh ilo needs to be taken into account when comparing both treatment groups.**

In conclusion, in this long term observation treatment with either iv PGI<sub>2</sub> or **high dose inh ilo** in severe pulmonary hypertension enables a similar functional improvement after 3 months.

However, in long term follow up iv PGI enables a significantly longer time to clinical worsening compared to **high dose inh ilo**. The 6MWD after 3 months treatment might be predictive for long term event free outcome.

#### Conflict of Interests

Frank Reichenberger nothing to declare

Ann Mainwood nothing to declare

Nicholas W Morrell nothing to declare

Jayan Parameshwar nothing to declare

Joanna Pepke-Zaba has received honoraria from Actelion Pharmaceuticals, Pfizer plc, GlaxoSmithKline, Encysive Pharmaceuticals, and Bayer Schering from speaking and advisory board meetings.

## Reference

1. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV; American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004; 126: 35S-62S.
2. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jöbsis MM, Blackburn SD, Shortino D, Crow JW, for The Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296-302.
3. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, Jobsis MM, Loyd JE, Murali S, Frost A, Girgis R, Bourge RC, Ralph DD, Elliott CG, Hill NS, Langleben D, Schilz RJ, McLaughlin VV, Robbins IM, Groves BM, Shapiro S, Medsger TA Jr. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; 132: 425-434.
4. Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* 1984; 8385: 1046-7.
5. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780-8
6. Higenbottam T, Butt AY, McMahan A, Westerbeck R, Sharples L. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; 80: 151-5.
7. Graham DR, Keldermans MM, Klemm LW, Semenza NJ, Shafer ML. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. *Am J Med* 1991; 91: 95S-100S.
8. Fishman AP. Epoprostenol (prostacyclin) and pulmonary hypertension. *Ann Intern Med* 2000; 132: 500-502.
9. Hoepfer MM, Gall H, Seyfarth HJ, Halank M, Ghofrani HA, Winkler J, Golpon H, Olsson KM, Nickel N, Opitz C, Ewert R. Long-term outcome with intravenous iloprost in pulmonary arterial hypertension. *Eur Respir J*. 2009; 34:132-7.
10. Olschewski H, Ghofrani A, Schmehl T, Winkler J, Wilkens H, Hoepfer MM, Behr J, Kleber FX, Seeger W. Inhaled Iloprost to Treat Severe Pulmonary Hypertension. *Ann Intern Med* 2000; 132: 435-443.

11. Hoepfer MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J, Hamm M, Fabel H. Long-term treatment of primary pulmonary hypertension with aerosolized Iloprost, a prostacyclin analogue. *N Engl J Med* 2000; 342: 1866-1870.
12. Olschewski H, Ghofrani HA, Walrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, Seeger W. Inhaled prostacyclin and Iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med* 1999; 160: 600-607.
13. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoepfer MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002; 347: 322-9.
14. Wilkins MR, Paul GA, Strange JW, Tunariu N, Gin-Sing W, Banya WA, Westwood MA, Stefanidis A, Ng LL, Pennell DJ, Mohiaddin RH, Nihoyannopoulos P, Gibbs JS. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *Am J Respir Crit Care Med*. 2005; 171: 1292-7
15. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G; American College of Chest Physicians. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004; 126: 78S-92S.
16. Gessler T, Schmehl T, Hoepfer MM, Rose F, Ghofrani HA, Olschewski H, Grimminger F, Seeger W. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. *Eur Respir J* 2001; 17: 14-9.
17. Reichenberger F, Mainwood A, Doughty N, Fineberg A, Morrell NW, Pepke-Zaba J. Effects of nebulised iloprost on pulmonary function and gas exchange in severe pulmonary hypertension. *Respir Med*. 2007; 101: 217-22.
18. Goodman T. Towards evidence – based medical statistics. *Ann Intern Med*. 1999; 130: 995-1013.
19. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. *Thorax*. 2003; 58: 797-800.
20. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, Mandayam S, Ginzton LE, Brundage BH. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol* 1997; 30: 343-9.
- 21. Oudiz RJ, Farber HW. Dosing considerations in the use of intravenous prostanoids in pulmonary arterial hypertension: an experience-based review. *Am Heart J*. 2009; 157: 625-35**
- 22. Gombert-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *Eur Respir J*. 2008; 31: 891-901.**



23. D'Alonzo GE, Barst RJ, Ayres SM, Bergowsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Berton MG, Kernis JT, Levy Ps, Pietra RM, Reid LM, Reeves JT, Rich S, Vreim CE, Williams GW, Wu M. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med* 1991; 115: 343-349.
24. Miyamoto S, Nagaya N, Atoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical Correlates and Prognostic Significance of Six minute Walk Test in Patients with Primary Pulmonary Hypertension. *Am J Respir Crit Care Med* 2000; 161: 487-492.
25. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002; 346: 896-903.
26. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005; 353: 2148-57.
27. Galie N, Manes A, Branzi A. Medical therapy of pulmonary hypertension. The prostacyclins. *Clin Chest Med* 2001; 22: 529-37.
28. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004; 351: 1425-36.
29. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J*. 2005; 26: 858-63.
30. Wilkens H, Guth A, Konig J, Forestier N, Cremers B, Hennen B, Bohm M, Sybrecht GW. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 1218-22.
31. Ghofrani HA, Wiedemann R, Rose F, Olschewski H, Schermuly RT, Weissmann N, Seeger W, Grimminger F. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; 136: 515-22.
32. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as longterm adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; 42: 158-64.
33. Hoeper MM, Taha N, Bekjarova A, Gatzke R, Spiekerkoetter E. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostaglandin analogues. *Eur Respir J*. 2003; 22: 330-4.
34. Humbert M, Barst RJ, Robbins IM, Channick RN, Galie N, Boonstra A, Rubin LJ, Horn EM, Manes A, Simonneau G. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J*. 2004; 24: 353-9.



35. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, Badesch DB, Barst RJ, Hsu HH, Rubin LJ. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2006; 174: 1257-63.

36. Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008; 149: 521-30.

Table 2 A 6 MWD and haemodynamic parameters before and after 3 months treatment with iv PGI<sub>2</sub>

	6MWD metres		CI l/min/m <sup>2</sup>		CVSO <sub>2</sub> %		mPAP mm Hg		RAP mm Hg		PVR dyne*s/cm <sup>5</sup>	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
<b>Median</b>	<b>220</b>	<b>280</b>	<b>1.6</b>	<b>2.0</b>	<b>56</b>	<b>65</b>	<b>58</b>	<b>58</b>	<b>11</b>	<b>10</b>	<b>1174</b>	<b>1078</b>
<b>min – max</b>	0-380	200-400	0.8-1.9	1.3-3.1	42-67	49-71	42-86	39-74	1-20	0-20	847-3160	504-1615
<b>Wilcox.</b>	p < 0.01		p < 0.005		p < 0.03		p = 0.7		p = 0.5		p < 0.005	

Table 2 B 6 MWD and haemodynamic parameters before and after 3 months treatment with high dose inh ilo

	6MWD metres		CI l/min/m <sup>2</sup>		CVSO <sub>2</sub> %		mPAP mm Hg		RAP mm Hg		PVR dyne*s/cm <sup>5</sup>	
	pre	post	pre	post	pre	post	Pre	post	pre	post	pre	post
<b>median</b>	<b>200</b>	<b>270</b>	<b>1.7</b>	<b>1.7</b>	<b>57</b>	<b>60</b>	<b>55</b>	<b>50</b>	<b>13</b>	<b>9</b>	<b>1227</b>	<b>1012</b>
<b>min- max</b>	0-480	0-500	1.1-2.8	1.4-3.1	46-77	44-82	40-79	32-70	0-23	3-32	481-2069	341-1785
<b>Wilcox</b>	p < 0.05		p = 0.64		p = 0.21		P = 0.11		p = 0.43		p = 0.38	

Table 1 Demographic, haemodynamic and functional parameter at baseline in both treatment groups in median (min- max)

	<b>iv PGI2 group</b>	<b>high dose inh ilo group</b>	Mann Whitney Test
Age (years)	38 (19 - 67)	43 (16 – 57)	p=0,33
Gender	9 female / 3 male	7 female / 5 male	$\chi^2 = 0,99$
Etiology of PH IPAH PAH in CTD Porto- PH	10 2	5 6 1	$\chi^2 = 0,24$
NYHA class III / IV	9 / 3	9 / 3	
6 minute walking test	220 (0- 380)	200 (0 - 480)	p =0,35
mPAP (mmHg)	58 (42-86)	55 (40 - 79)	p =0,71
CI (l/min/qm)	1.6 (0.8 – 1.9)	1.7 (1.1- 2.3)	p =0,42
PVR	1098 (855- 2848)	1027 (533- 3408)	p =0,2
FVC (%pred)	86 (82 – 93)	83 (80 – 92)	p =0,18
TLC (%pred)	94 (92 – 102)	93 (90 - 103)	p =0,2
DLCO (%pred)	73 (66 – 84)	70 (64 - 82)	p =0,24

Figure 1 Comparison of event free follow up on treatment with iv PGI<sub>2</sub> or high dose inh ilo treatment, respectively. (p=0.049)

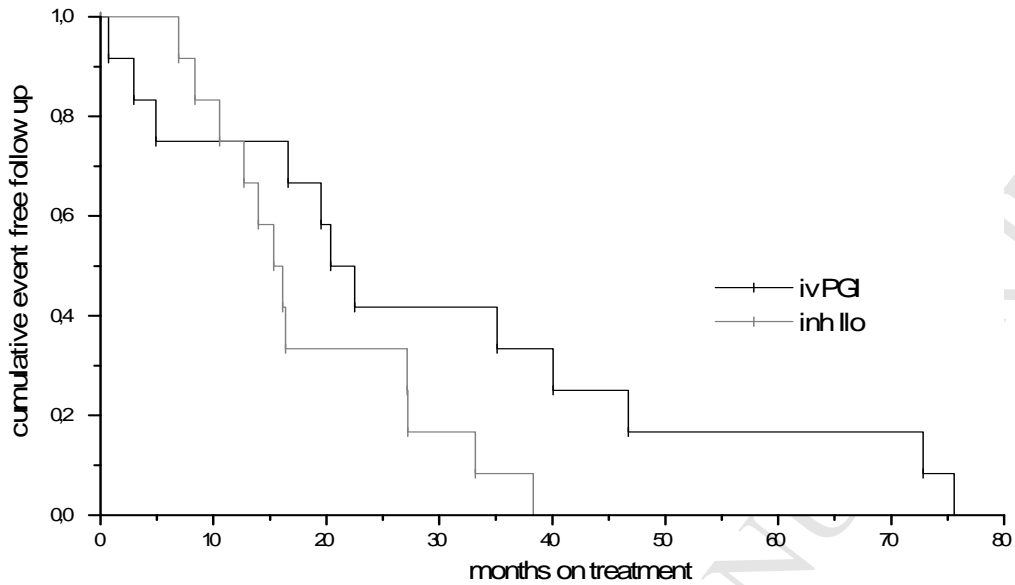


Figure 2 Comparison of event free follow up according to 6 minute walking distance after 3 months treatment with iv PGI or high dose inh ilo, respectively (p=0.02)

