**Original Article**

# Rapid and high-dose titration of epoprostenol improves pulmonary hemodynamics and clinical outcomes in patients with idiopathic and heritable pulmonary arterial hypertension

Short title: Rapid and high-dose epoprostenol improved I/HPAH hemodynamics

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## Abstract

***Background:*** Intravenous epoprostenol is an effective treatment for idiopathic and heritable pulmonary arterial hypertension. We aimed to clarify factors that determine the survival of patients with severe pulmonary hypertension who received epoprostenol treatment.

***Methods:*** This is a retrospective observational study consisting of 46 patients with idiopathic and heritable pulmonary arterial hypertension in World Health Organization (WHO) functional class III or IV and undergoing intravenous epoprostenol treatment. We compared the following factors between survivors and non-survivors: clinical characteristics, exercise capacity, hemodynamics, interval between diagnosis and treatment initiation, concomitant pulmonary arterial hypertension-targeted drugs, maximum dose of epoprostenol, and the speed of up-titration. We defined a rapid increase group as those receiving epoprostenol $\geq$20 ng/kg/min at 3 months and $\geq$45 ng/kg/min at 1 year of treatment.

***Results:*** Thirty-two patients (70%) survived and 14 patients died during an average follow-up period of 2,100 days. Mean pulmonary artery pressure, concomitant pulmonary arterial hypertension-targeted drugs, and the maximum epoprostenol dose were comparable between the two subsets of patients. WHO functional class III was more common than class IV, and the 6-min walking distance was longer in the survivor than the non-survivor group. The survivors typically showed a rapid increase in epoprostenol dose during the first year of treatment. This rapid increase group was associated with a continuous reduction of mean pulmonary artery pressure during the follow-up period, whereas the slow increase group showed no reduction in mean

pulmonary artery pressure after 6 months of treatment. The survival rate was also significantly better in the rapid increase group compared with the slow increase group (100% vs. 51%, $p$=0.022).

***Conclusions:*** In idiopathic and heritable pulmonary arterial hypertension patients, a rapid increase in epoprostenol dose soon after the initiation of treatment appears to be important to achieve a continuous reduction in mean pulmonary artery pressure and to improve survival.

## Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disease that deteriorates over time. Recently, prostaglandins, endothelin receptor antagonists (ERAs), and phosphodiesterase 5 (PDE-5) inhibitors have been approved for use in the treatment of PAH, and reported to improve prognosis in treated patients [1-4]. Among them, the intravenous infusion of epoprostenol sodium, a derivative of prostaglandin $I_2$, is considered to be the most potent therapeutic agent for PAH. Prostaglandin $I_2$ promotes intracellular cyclic AMP production, and inhibits thromboxane A2 production and the calcium influx into cells, causing powerful vasodilation, inhibiting platelet aggregation, and attenuating the proliferation of vascular smooth muscle cells [5, 6].

Intravenous epoprostenol was shown in a multicenter, prospective, randomized trial to improve exercise tolerance, reduce pulmonary vascular resistance, and improve survival in patients with PAH [7]. Similarly, a meta-analysis of controlled clinical studies found that only intravenous epoprostenol out of multiple PAH-targeted drugs improved patient prognosis [8]. Recent guidelines recommend epoprostenol treatment for patients with severe PAH that is identified as World Health Organization (WHO) functional class III and IV [9]. As yet, however, there are no guidelines for the optimal protocol of intravenous epoprostenol.

The previous recommended dose of epoprostenol was 25–40 ng/kg/min [10]. However, we reported that treatment with 100 ng/kg/min of epoprostenol for an average of 3.8 years is associated with a substantial reduction in mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance by 29% and 68%, respectively, in patients with idiopathic and heritable pulmonary arterial hypertension (I/HPAH) [11]. Furthermore, we reported an improved survival of I/HPAH patients with 1-, 5-, and

10-year survival rates of 98%, 96%, and 78%, respectively [4]. In this previous study cohort, 75% of patients received epoprostenol. The average epoprostenol dose at the time of hemodynamic improvement was approximately 80 ng/kg/min. Hemodynamic parameters improved significantly after treatment, with a substantial reduction observed in mean PAP and pulmonary vascular resistance by 44% and 67%, respectively, which might reflect the high prescription rates of PAH-targeted drugs.

To avoid systemic hypotension, the infusion rate of epoprostenol is gradually increased until the appropriate therapeutic dose is reached. However, it remains unknown whether the speed of up-titration can affect pulmonary hemodynamics and clinical outcomes. Thus, we conducted this retrospective clinical study to clarify whether speed of increase in epoprostenol dose affects clinical outcomes and pulmonary hemodynamics.

## Methods

### *Study population*

This is a retrospective observational study. The initial study population comprised patients with I/HPAH who were admitted to the National Hospital Organization Okayama Medical Center and Okayama University Hospital, Japan, from May 1999 to December 2011. A total of 61 patients with I/HPAH were admitted during this period (Fig. 1), and 15 were excluded who had undergone lung transplantation (Supplemental Table). Thus, the remaining 46 patients were used for analysis.

### *Therapeutic strategy of I/HPAH*

Our goal of PAH treatment is to reduce the mean PAP as much as possible with a combination of oral PAH-targeted drugs and intravenous epoprostenol [12]. Patients were initially prescribed oral PAH-targeted drugs, but if these did not result in an adequate reduction in mean PAP, we administered a continuous infusion of epoprostenol via a central venous route. Epoprostenol was usually initiated at doses of 0.5–2 ng/kg/min, and was increased by 0.5–2 ng/kg/min every 1–2 days, as tolerated. The rate at which the dose can be increased varied between patients, and depended on the clinician's decision and on how well the drug was tolerated. After an initial level of 10 ng/kg/min was achieved, we further increased the dose as high as possible, to achieve a mean PAP of less than 40 mmHg. Some patients received doses as high as >100 ng/kg/min for sustained clinical and hemodynamic benefits. However, if severe side effects such as thrombocytopenia occurred, the speed of increase in epoprostenol dose was reduced, depending on the severity. We measured pulmonary hemodynamics with right heart catheterization within 1 week, and around 6 months, 1 year, and 2 years after the initiation of treatment where possible.

*Data collection*

We followed-up the patients after the initiation of intravenous epoprostenol treatment. The follow-up period for monitoring patient survival ended in December 2013. The primary endpoint for survival analysis was death related to pulmonary hypertension. One patient who died from a road traffic accident was censored at the time of death in survival analysis (included in the survivor group) and other data of this patient were included in all analyses. Patient records were used to collect clinical data,

including concomitant PAH-targeted drugs, WHO functional class, 6-min walking distance, pulmonary hemodynamics, and brain natriuretic peptide (BNP) levels. We also checked the dose of epoprostenol at 7 days, 1, 3, and 6 months, and 1, 1.5, and 2 years after the initiation of the treatment.

*Statistical analysis*

Numerical data were expressed as mean ± standard deviation (SD). Student's *t*-test or Welch's *t*-test was used to analyze differences between continuous variables, while Fisher's exact test analyzed differences between categorical variables. A linear mixed model was used to compare the epoprostenol dose administered to survivor and non-survivor groups, and to compare mean PAP data between the rapid increase and slow increase groups. We analyzed patient survival using the Kaplan–Meier method. Differences between survival curves were assessed using the log-rank test. Statistical analysis was performed using the IBM SPSS Statistics 17.0 package (SPSS Inc., Chicago, IL). Statistical significance was defined as $p<0.05$.

**Results**

*Baseline characteristics*

We analyzed 46 consecutive patients with I/HPAH who received intravenous epoprostenol treatment. The mean age at the initiation of epoprostenol treatment was 28 ± 9 years, and 34 (74%) patients were female. Thirty-five (76%) patients had idiopathic PAH and 11 (24%) had heritable PAH. WHO functional class III and IV were observed in 24 (52%) and 22 patients (48%), respectively. The baseline 6-min walking distance was 297±121 m, the BNP level was 370 ±340 pg/mL, and the mean PAP was 63±15

mmHg. The mean duration of epoprostenol treatment was 2,110 days (range, 2–5,347 days).

*Clinical characteristics and treatment between survivors and non-survivors*

Within the follow-up period, 32 patients survived (survivors), and 14 patients died (non-survivors) (Fig. 1). Table 1 compares baseline characteristics and treatment regimens between survivors and non-survivors. There were no significant differences in age, gender, plasma BNP level, hemodynamics, interval between diagnosis and treatment initiation, or PAH-targeted drugs at the initiation of epoprostenol between the two groups. However, the proportion of WHO functional class IV and the heart rate were significantly higher, and the 6-min walking distance significantly shorter in the non-survivors compared with the survivors. The duration of intravenous epoprostenol treatment was significantly shorter in the non-survivor group than in the survivors, but the maximum dose of epoprostenol achieved was comparable between the two groups.

*Titration of epoprostenol*

Figure 2 shows the titration pattern of the epoprostenol dose in each patient until 2 years after the initiation of treatment. The up-titration of epoprostenol was successfully performed in each patient; however, the speed of increase in epoprostenol dose varied significantly among patients.

We compared the epoprostenol dose at seven time points until 2 years after the initiation of treatment between the survivors and non-survivors (Fig. 3). The dose was comparable between the two groups at 7 days and 1 month after the initiation of therapy. After 3 months, it was significantly higher in the survivors than the non-survivors (22.9

± 9.3 vs 14.4 ± 5.7 ng/ml/min, respectively, $p<0.05$), and remained significantly higher until 1.5 years after treatment. Mean differences between epoprostenol doses in survivors and non-survivors were 8.5, 9.7, 14.4, and 14.6 ng/kg/min at 3 months, 6 months, 1 year, and 1.5 years, respectively. The mean difference in dose between the two groups decreased between 1.5 years to 2 years after treatment initiation, indicating that the dose rapidly increased soon after the initiation of treatment in the survivors, whereas it was accelerated in some of the non-survivors after 1 year of treatment. Thus, the rapid increase in epoprostenol early after the initiation of therapy seems to be associated with an imported survival among patients with I/HPAH.

*Impact of up-titration speed on survival and mean PAP*

At 3 months after the initiation of treatment, 18 (56%) of 32 survivors reached an epoprostenol dose of $\geq$ 20 ng/kg/min, but only one (7%) of 14 non-survivors attained this dose. After 1 year, 18 (56%) of the survivors, but none of the non-survivors, reached an epoprostenol dose of $\geq$45 ng/kg/min. We defined the rapid increase group as those patients who received $\geq$20 ng/kg/min and $\geq$45 ng/kg/min of epoprostenol at 3 months and 1 year after treatment, respectively. The other patients were defined as the slow increase group. For this analysis, we included 39 patients with at least two mean PAP measurements during follow-up, of which one was performed within 7 days and the other was performed within 3 years of treatment. Seven patients were excluded because of insufficient mean PAP data (Fig. 1). Sixteen (41%) patients were therefore included in the rapid increase group (including one patient who died from a traffic accident), and 23 (59%) in the slow increase group. We compared baseline characteristic and treatment regimens between the two groups (Table 2) and observed

no differences in age, gender, IPAH or HPAH, WHO functional class, heart rate, 6-min walking distance, plasma BNP level, hemodynamics, interval between diagnosis and treatment initiation, or concomitant PAH-targeted drugs. The maximum epoprostenol dose achieved was also comparable between the two groups, despite the longer duration of treatment in the slow increase group. There were 14 survivors and 9 non-survivors in the slow increase group. We further compared characteristic and treatment regimens between these two groups (Table 3). There were significant differences in plasma BNP level at baseline and duration of epoprostenol therapy.

We further studied the impact of up-titration speed of epoprostenol on mean PAP. We compared average mean PAP in four periods after the initiation of epoprostenol treatment: within 7 days, 7 days to 6 months, 1 to 2 years, and 2 to 3 years. Because limited data were obtained between 6 months and 1 year, this period was excluded from further analysis. The mean PAP was shown to reduce significantly until 6 months after treatment in both groups (Fig. 4A). A further reduction in mean PAP was observed after 6 months of treatment in the rapid increase group, but not in the slow increase group even following an increase in epoprostenol dose.

Because the baseline mean PAP varied significantly among patients, we also assessed temporal changes in the mean PAP ratio, which was expressed as the ratio of mean PAP at each time point to the mean PAP within 7 days of treatment (Figure 4B). The mean PAP ratio decreased until 6 months after treatment in both groups. After 1 year of treatment, the mean PAP ratio significantly decreased in the rapid increase group but not the slow increase group. Thus, the mean PAP was significantly lower in the rapid increase compared with the slow increase group at 1 to 2 years as well as 2 to 3 years.

Kaplan–Meier survival curves for the rapid increase and slow increase groups are shown in Figure 5. All 16 patients in the rapid increase group survived during the observation period. Among the 23 slow increase group patients, nine (39%) died. This difference in mortality reached significance (log-rank test, $p$=0.022).

**Discussion**

Intravenous epoprostenol is a standard treatment in patients with severe PAH [9]. Our retrospective observational study revealed no significant difference in the maximum epoprostenol dose or concomitant PAH-targeted drugs between the survivors and the non-survivors. However, the survivor group was typically associated with a rapid increase in epoprostenol dose within 1 year after the initiation of treatment. This rapid up-titration regimen of epoprostenol was associated with a continuous decrease in mean PAP and with an improved prognosis in patients with I/HPAH compared with the slow up-titration regimen. To our knowledge, this is the first report to clarify that the speed of increase in epoprostenol dose in the early stages of treatment is an important predictor of survival in patients with severe PAH, together with their baseline functional state.

Intravenous epoprostenol is associated with an improvement in pulmonary hemodynamics and in patient survival rates [8]. However, as yet, no standard dosing regimens for high-dose epoprostenol treatment have been proposed. In our retrospective study, epoprostenol dose curves of survivors showed a rapid increase soon after the initiation of treatment compared with the dose curves of non-survivors. Most survivors achieved an epoprostenol dose of $\geq$20 ng/kg/min after 3 months of treatment, and $\geq$45 ng/kg/min after 1 year. No patient in the rapid increase group died during the follow-up

period regardless of baseline clinical characteristics, exercise capacity, or concomitant PAH-targeted drugs. We aimed to increase the epoprostenol dose as much as possible to reduce mean PAP, and ultimately no difference in achieved epoprostenol dose at the end of follow-up between the rapid increase and slow increase groups was recorded. Therefore, it appears that an early exposure to a high epoprostenol dose soon after the initiation of treatment is important for improving the survival of patients with I/HPAH rather than the final dose achieved.

The significance of early exposure to epoprostenol is supported by the results of a previous clinical study by Badagliacca et al [13]. This study found that patients with PAH showed a worse prognosis if the start of intravenous epoprostenol was delayed. The recent SUPER-2 study also showed the importance of early exposure to the PDE-5 inhibitor sildenafil citrate for treating patients with PAH [14]. This study demonstrated that patients assigned to a placebo for the first 12 weeks of the study period did not achieve the same improvement in prognosis as those assigned to sildenafil in the entire study period. Therefore, it should be considered that PAH-targeted drugs including intravenous epoprostenol should be started as early as possible after the diagnosis of PAH, and that the dosage should be increased rapidly.

In our previous study, we demonstrated that the mean PAP achieved with PAH-targeted drugs was the most important prognostic factor of the survival of patients with I/HPAH [4]. Among I/HPAH patients, the survival rate was significantly higher in those with a mean PAP <42.5 mmHg achieved using PAH-targeted drugs than those with a mean PAP $\geq$42.5 mmHg. Interestingly, the 10-year survival rate of those with a mean PAP <42.5 mmHg was 100%. This implies that we should aim to reduce the mean PAP as much as possible in PAH patients to improve survival.

The dose of epoprostenol also appears to be important in reducing mean PAP. In the previous study cohort with 75% of patients on epoprostenol treatment, the average epoprostenol dose at the time of hemodynamic improvement was approximately 80 ng/kg/min [4]. With the high dose epoprostenol, a substantial reduction was observed in mean PAP by 44%. In patients administered an epoprostenol dose of 100 ng/kg/min as monotherapy, the mean PAP declined by 29% [11]. Our present study demonstrated that rapid up-titration in the early stages of epoprostenol treatment is a key factor in reducing mean PAP. In the rapid increase group of this study, the epoprostenol dose was continuously increased in the early stages of the follow-up period, which was associated with a further reduction of mean PAP from 1 to 3 years after treatment. The amount of reduction in mean PAP differed between the rapid and slow increase groups, although a similar maximum epoprostenol dose was achieved during the follow-up period in both groups. The reason behind the continuous reduction of mean PAP following rapid up-titration remains unknown, but it may explain the improved survival rate of the rapid increase group compared with the slow increase group.

**Limitations**

Our study had several limitations. Its potential was limited by the small study size which reflected the rare nature of I/HPAH and the fact that intravenous epoprostenol is only administered to severely ill patients. Patients in this study were also restricted to those treated in only two institutions, which raises the possibility of selection and interpretation bias. This study comprised patients who were treated with intravenous epoprostenol from 1999 to 2011. Oral PAH-targeted drugs other than prostacyclin have come to market in Japan since 2005 and our treatment strategy changed after that. Currently, most patients with I/HPAH are administered ERAs and PDE-5 inhibitors

before epoprostenol treatment. Therefore, the dose of epoprostenol may be changed with concomitant treatment.

**Clinical implications**

When patients with I/HPAH require intravenous epoprostenol, it should be administered immediately and its dose increased quickly according to our dosing regimen: ≥20 ng/kg/min at 3 months and ≥45 ng/kg/min at 1 year. A delay in treatment or up-titration may reduce the beneficial impact of epoprostenol on pulmonary vasculature, although the mechanisms behind this remain unclear. If cell proliferation occurs in the intima and the media of pulmonary arteries with disease progression, it is possible that the vasodilatory, anti-platelet, anti-proliferative, and pro-apoptotic effects of epoprostenol will attenuate the prgression. Our preliminary findings support the need for larger international prospective multicenter controlled studies to clarify the optimal epoprostenol treatment dosing regimens.

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**Disclosures**

Drs. Tokunaga and Ogawa have no conflict of interest.

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## References

[1] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010;122:156-63.

[2] Lee WT, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ, Johnson MK. Predicting survival in pulmonary arterial hypertension in the UK. Eur Respir J. 2012;40:604-11.

[3] Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012;142:448-56.

[4] Ogawa A, Ejiri K, Matsubara H. Long-term patient survival with idiopathic/heritable pulmonary arterial hypertension treated at a single center in Japan. Life Sci. 2014;118:414-9.

[5] Armstrong JM, Lattimer N, Moncada S, Vane JR. Comparison of the vasodepressor effects of prostacyclin and 6-oxo-prostaglandin F1alpha with those of prostaglandin E2 in rats and rabbits. Br J Pharmacol. 1978;62:125-30.

[6] Whittle BJ, Moncada S, Vane JR. Comparison of the effects of prostacyclin (PGI2), prostaglandin E1 and D2 on platelet aggregation in different species. Prostaglandins. 1978;16:373-88.

[7] Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334:296-301.

[8] Ryerson CJ, Nayar S, Swiston JR, Sin DD. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. Respir Res. 2010;11:12.

[9] Galie N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013;62:D60-72.

[10] McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation. 2006;114:1417-31.

[11] Akagi S, Nakamura K, Miyaji K, Ogawa A, Kusano KF, Ito H, et al. Marked hemodynamic improvements by high-dose epoprostenol therapy in patients with idiopathic pulmonary arterial hypertension. Circ J. 2010;74:2200-5.

[12] Matsubara H, Ogawa A. Treatment of idiopathic/hereditary pulmonary arterial hypertension. J Cardiol. 2014;64:243-9.

[13] Badagliacca R, Pezzuto B, Poscia R, Mancone M, Papa S, Marcon S, et al. Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: the impact of late referral. J Heart Lung Transplant. 2012;31:364-72.

[14] Rubin LJ, Badesch DB, Fleming TR, Galie N, Simonneau G, Ghofrani HA, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. Chest. 2011;140:1274-83.

**Figure Legends**

**Figure 1** Participant flow chart.

IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; PAP, pulmonary arterial pressure.

**Figure 2** Continuous dose curves of epoprostenol treatment.

The horizontal axis shows the number of years after the start of epoprostenol treatment; the vertical axis shows the dose for each time point. Epoprostenol dose curves of survivors (n = 32) are shown in blue; the dose curves of non-survivors (n = 14) are shown in red.

**Figure 3** Mean epoprostenol doses in the survivor group and non-survivor group.

The mean ± SD of epoprostenol treatment doses in the survivor group (blue) and the non-survivor group (red) at each time point after the start of treatment are shown. Mean doses at each time point are indicated beside the circles. Significant differences were observed between the survivor group and non-survivor group at 3 months up to 1.5 years. (7 d, seventh day; 1 m, 1 month; 3 m, 3 months; 6 m, 6 months; 1 y, 1 year; 1.5 y, 1 and a half years; 2 y, 2 years; *, $p<0.05$; ***, $p<0.001$)

**Figure 4** Changes in mean pulmonary arterial pressure (PAP) in the rapid increase and slow increase groups.

The time after the start of epoprostenol treatment was divided into five periods as follows: 7-day period, 6 months, continuously throughout the 1st year, continuously throughout the 2nd year, and continuously throughout the 3rd year after the start of

epoprostenol treatment. Because limited data were obtained between 6 months and 1 year, this period was excluded from further analysis. Average mean PAPs for each time point in the rapid increase group (green) and slow increase group (pink) are shown (**A**). Right heart catheterization was performed at 3.6±2.1, 21.4±26.9, 564±82 and 890±110 days in the rapid increase group and 3.2±2.3, 31.7±33.7, 523±110 and 886±113 days in the slow increase group. The mean PAP within each time point was compared between the two groups. The panel (**B**) shows the mean PAP ratios (ratio between the mean PAP at each time point and the mean PAP at the initial 7-day period). Mean PAP ratios within each time point were compared between groups. (7 d, seventh day; 6 m, 6 months; 1 y, 1 year; 2 y, 2 years; 3 y, 3 years; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$)

**Figure 5** Kaplan–Meier analyses of cumulative survival in the rapid increase and slow increase groups.

The horizontal axis shows the number of days after the start of epoprostenol treatment, with the survival curves of the rapid increase and slow increase groups. The values for the rapid increase group are shown in green, and those for the slow increase group in pink. In the rapid increase group, all patients survived, and a log-rank test comparison of survival rates between the two groups revealed a significantly favorable prognosis for the rapid increase group ($p=0.022$).

Figure

# Figure 1

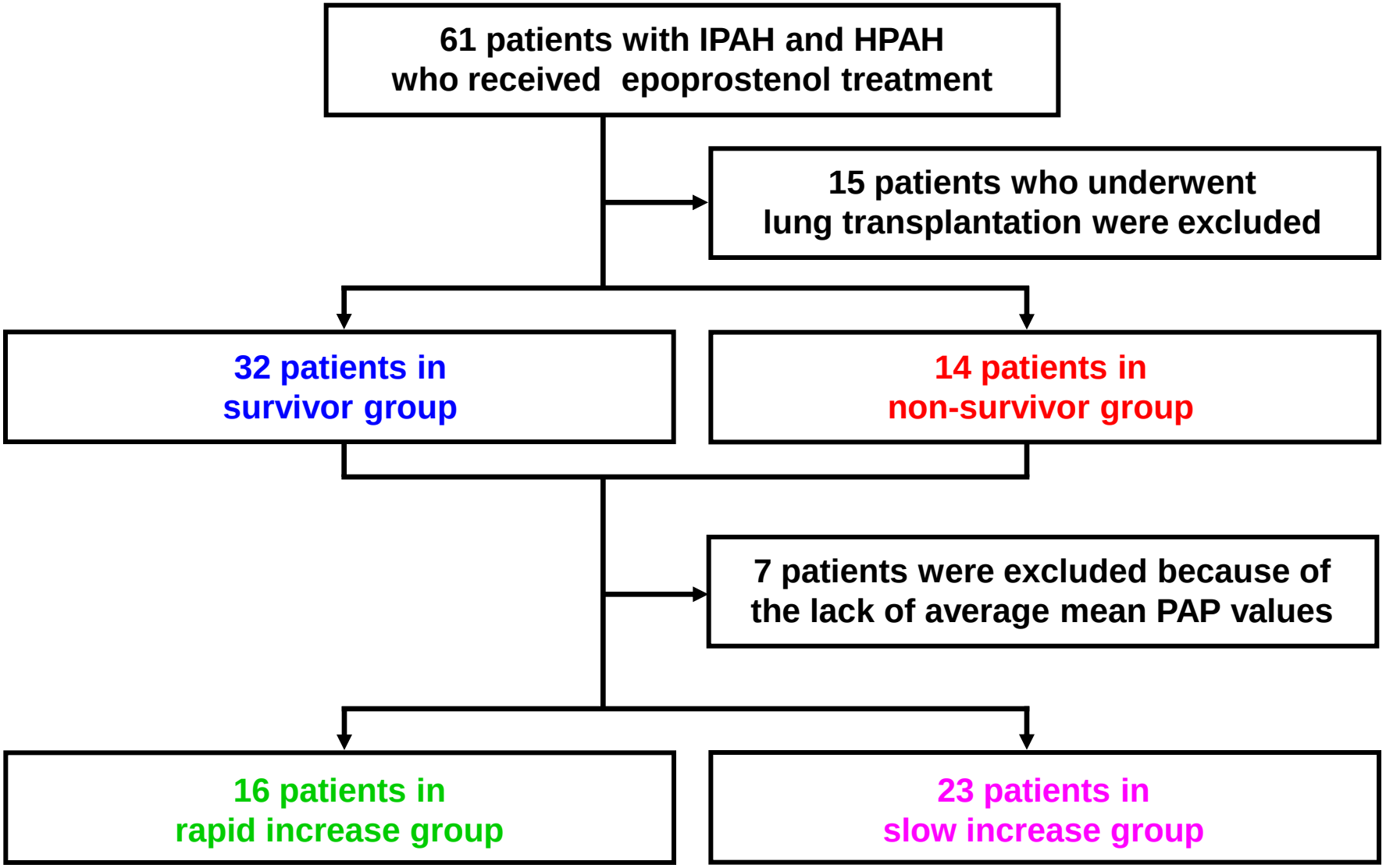


Figure 2

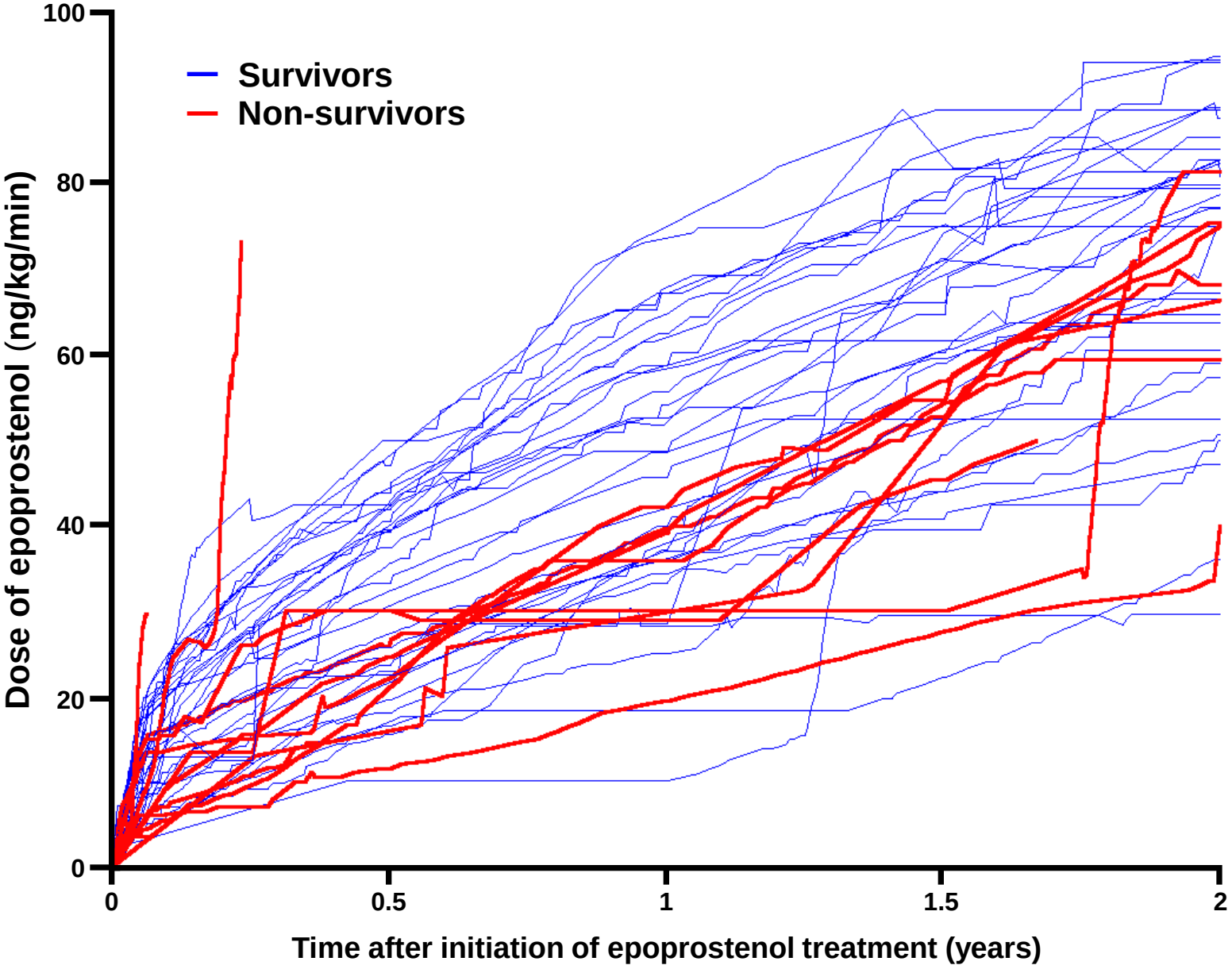
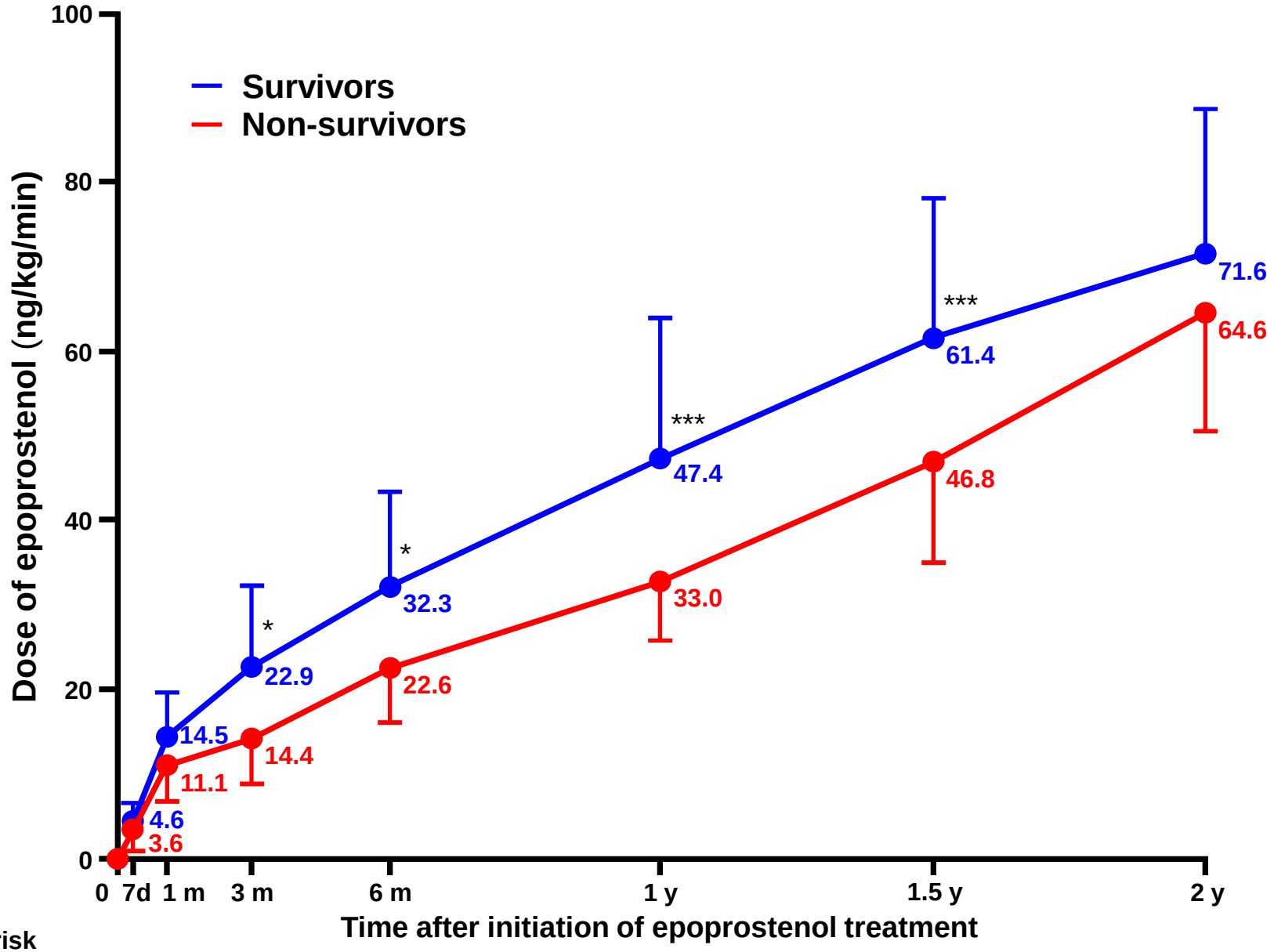

Survivors
Non-survivors
Dose of epoprostenol (ng/kg/min)
100
80
60
40
20
0
0
0.5
1
1.5
2
Time after initiation of epoprostenol treatment (years)

Figure 3




| Patient at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Survivors | 32 | 32 | 32 | 32 | 32 | 32 | 32 | 32 |
| Non-survivors | 14 | 13 | 11 | 11 | 9 | 9 | 8 | 8 |

Figure 4

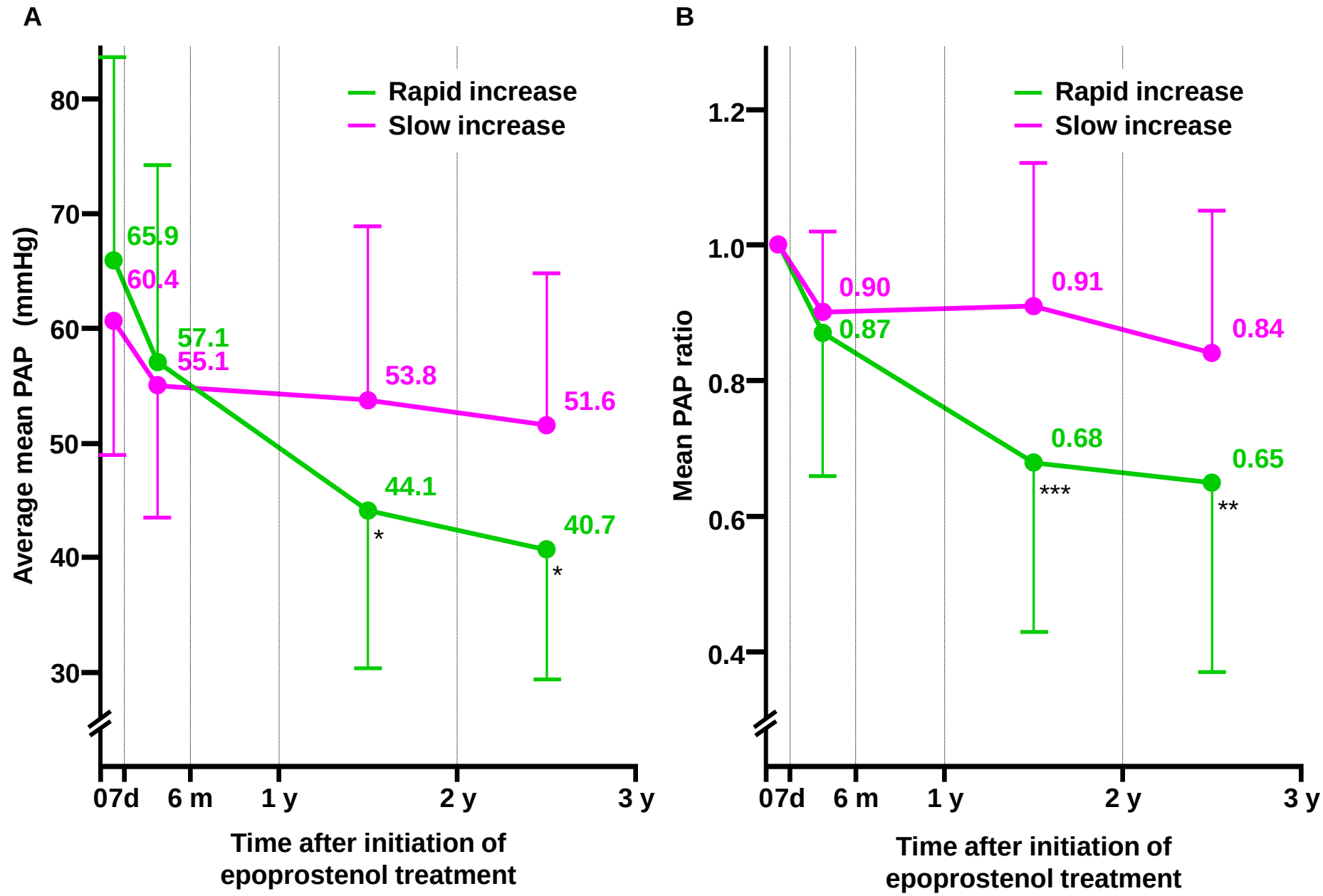
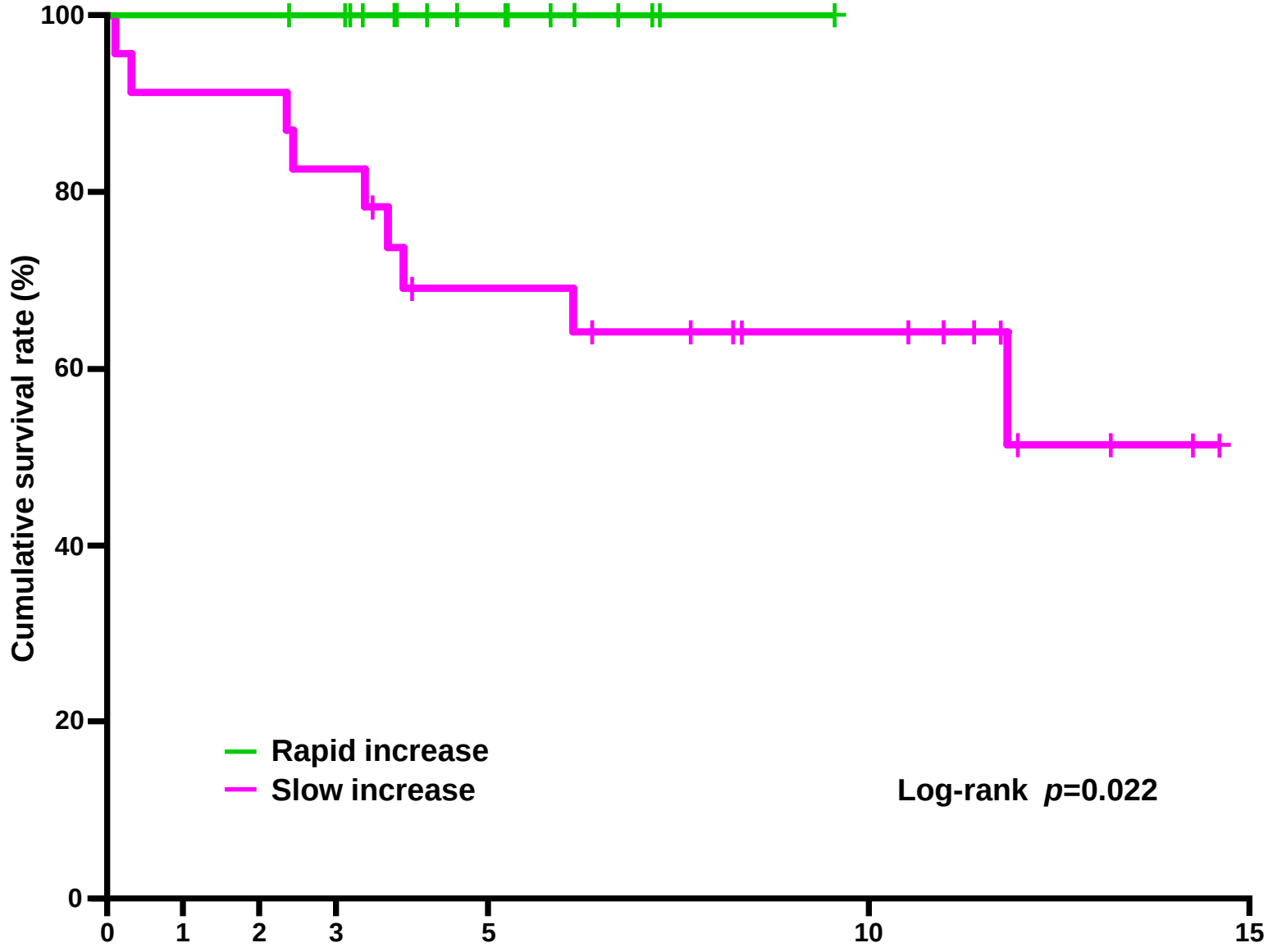

A
Rapid increase
Slow increase
Average mean PAP (mmHg)
80
70
60
50
40
30
65.9
60.4
57.1
55.1
53.8
51.6
44.1
40.7
*
*
07d
6 m
1 y
2 y
3 y
Time after initiation of epoprostenol treatment
B
Rapid increase
Slow increase
Mean PAP ratio
1.2
1.0
0.8
0.6
0.4
0.90
0.91
0.84
0.87
0.68
0.65
***
**
07d
6 m
1 y
2 y
3 y
Time after initiation of epoprostenol treatment

Figure 5




Patients at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Rapid increase | 16 | 16 | 16 | 15 | 8 | |
| Slow increase | 23 | 21 | 21 | 19 | 14 | 9 |

## Tables

**Table 1** Characteristics and treatment regimen of survivors and non-survivors.

| | | **Survivors** n=32 | **Non-survivors** n=14 | ***p* value** |
|---|---|---|---|---|
| **Baseline** | | | | |
| Age, years | | 28 ± 9 | 31 ± 9 | 0.301 |
| Female, n (%) | | 24 (75) | 10 (71) | 1.000 |
| BMI, kg/m$^2$ | | 21.5±4.6 | 21.7±4.1 | 0.849 |
| HPAH, n (%) | | 10 (31) | 1 (7) | 0.133 |
| WHO FC, n (%) | III | 21 (66) | 3 (21) | 0.01 |
| | IV | 11 (34) | 11 (79) | |
| HR, bpm | | 79 ± 17 | 93 ± 13 | 0.010 |
| 6MWD, m | | 337 ± 85 | 206 ± 144 | 0.006 |
| BNP, pg/ml | | 334 ± 370 | 454 ± 250 | 0.272 |
| mPAP, mmHg | | 63 ± 15 | 62 ± 14 | 0.850 |
| CO, l/min | | 3.5 ± 1.1 | 2.7 ± 1.4 | 0.066 |
| PVR, dyne·sec·cm$^{-5}$ | | 1,414 ± 579 | 1,779 ± 746 | 0.107 |
| Diagnosis-oral PAH-targeted drugs, days | | 222 ± 475 | 413 ± 680 | 0.279 |
| Diagnosis-epoprostenol, days | | 473 ± 698 | 1010 ± 979 | 0.080 |
| Concomitant PAH-targeted drugs, n (%) | | | | |

| | | | |
|---|---|---|---|
| Endothelin receptor antagonist | 15 (47) | 7 (50) | 1.000 |
| PDE-5 inhibitor | 10 (31) | 4 (29) | 1.000 |
| **Post treatment** | | | |
| Duration of epoprostenol therapy, days | 2,609 ± 1,325 | 968 ± 1,190 | <0.001 |
| Maximum dose of epoprostenol (ng/kg/min) | 105.2 ± 39.3 | 78.9 ± 67.3 | 0.191 |

Data given as n (%) or mean±SD. 6MWD, 6-min walking distance; BMI, body mass index; BNP, B-type natriuretic peptide; CO, cardiac output; Diagnosis-epoprostenol, interval between diagnosis and the start of epoprostenol treatment; Diagnosis-oral PAH-targeted drugs, interval between diagnosis and the start of any oral PAH-targeted drug; HPAH, heritable pulmonary arterial hypertension; HR, heart rate; PVR, pulmonary vascular resistance; WHO FC, World Health Organization functional class; mPAP, mean pulmonary arterial pressure; PDE-5, phosphodiesterase 5.

**Table 2** Characteristics of the rapid increase and slow increase groups.

| | | **Rapid-increase n=16** | **Slow-increase n=23** | ***p* value** |
|---|---|---|---|---|
| **Baseline** | | | | |
| Age, years | | 28 ± 8 | 28 ± 9 | 0.910 |
| Female, n (%) | | 12 (75) | 16 (70) | 1.000 |
| BMI, kg/m$^2$ | | 21.1±4.3 | 22.3±4.9 | 0.445 |
| HPAH, n (%) | | 6 (38) | 4 (17) | 0.264 |
| WHO FC, n (%) | III | 12 (75) | 12 (52) | 0.192 |
| | IV | 4 (25) | 11 (48) | |
| HR, bpm | | 80 ± 12 | 81 ± 18 | 0.844 |
| 6MWD, m | | 340 ± 102 | 304 ± 108 | 0.308 |
| BNP, pg/ml | | 306 ± 242 | 294 ± 237 | 0.878 |
| mPAP, mmHg | | 66 ± 18 | 60 ± 12 | 0.218 |
| CO, l/min | | 3.8 ± 1.2 | 3.1 ± 1.1 | 0.115 |
| PVR, dyne·sec·cm$^{-5}$ | | 1,373 ± 626 | 1,498 ± 551 | 0.514 |
| Diagnosis-oral PAH-targeted drugs, days | | 108 ± 243 | 313 ± 593 | 0.148 |
| Diagnosis-epoprostenol, days | | 342 ± 556 | 577 ± 796 | 0.315 |
| Concomitant PAH-targeted drugs, n (%) | | | | |
| Endothelin receptor antagonist | | 10 (63) | 9 (39) | 0.200 |

| | | | |
|---|---|---|---|
| PDE-5 inhibitor | 8 (50) | 5 (22) | 0.090 |
| **Post treatment** | | | |
| Duration of epoprostenol therapy, days | 1,834 ± 728 | 2,711 ± 1,674 | 0.033 |
| Maximum dose of epoprostenol (ng/kg/min) | 98.3 ± 27.1 | 109.0 ± 50.8 | 0.398 |

Abbreviations are as stated in Table 1.

**Table 3** Characteristics and treatment regimen of survivors and non-survivors in the slow increase group.

| | | **Survivors n=14** | **Non-survivors n=9** | **P value** |
|---|---|---|---|---|
| **Baseline** | | | | |
| Age, years | | 28 ± 10 | 28 ± 6 | 0.943 |
| Female, n(%) | | 10 (71) | 6 (67) | 1.000 |
| BMI, $kg/m^2$ | | 22.2±5.0 | 22.3±5.0 | 0.965 |
| HPAH, n (%) | | 4 (29) | 0 (0) | 0.127 |
| WHO FC, n (%) | III | 9 (64) | 3 (33) | 0.214 |
| | IV | 5 (36) | 6 (67) | |
| HR, bpm | | 76 ± 20 | 89 ± 11 | 0.096 |
| 6MWD, m | | 334 ± 72 | 257 ± 141 | 0.095 |
| BNP, pg/ml | | 209 ± 214 | 427 ± 217 | 0.027 |
| mPAP, mmHg | | 60 ± 11 | 60 ± 14 | 0.960 |
| CO, l/min | | 3.2 ± 0.8 | 2.9 ± 1.5 | 0.522 |
| PVR, $dyne \cdot sec \cdot cm^{-5}$ | | 1,462 ± 540 | 1,553 ± 596 | 0.708 |
| Diagnosis-oral PAH-targeted drugs, days | | 367 ± 654 | 228 ± 508 | 0.597 |
| Diagnosis-epoprostenol, days | | 534 ± 727 | 644 ± 936 | 0.754 |
| Concomitant PAH-targeted drugs, n (%) | | | | |
| Endothelin receptor antagonist | | 4 (29) | 5 (56) | 0.383 |

| | | | |
|---|---|---|---|
| PDE-5 inhibitor | 2 (14) | 3 (33) | 0.343 |
| **Post treatment** | | | |
| Duration of epoprostenol therapy, days | 3,569 ± 1,297 | 1,377 ± 1,299 | 0.001 |
| Maximum dose of epoprostenol (ng/kg/min) | 108.4 ± 45.5 | 110.1 ± 61.1 | 0.938 |

Abbreviations are as stated in Table 1.