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# Could We Maintain the Initial Efficacy of Triple Sequential Combination Therapies with Selexipag Against Progressive Deterioration Risk in Patients with Pulmonary Arterial Hypertension: Insights from a Single-Center Study?

ORIGINAL INVESTIGATION

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## ABSTRACT

**Background:** This study assessed the efficacy and tolerability of the oral prostacyclin receptor agonist selexipag as part of sequential triple combination therapy in patients with pulmonary arterial hypertension (PAH).

**Methods:** The study retrospectively analyzed 127 of 1160 PAH patients from a single-center registry who received sequential triple therapy including selexipag. Clinical, echocardiographic, and hemodynamic variables and multiparametric risk scores (MRS) were evaluated to assess changes in risk and outcomes.

**Results:** The mean age was 43.2 ± 16.4 years, and 84.3% were female. Prior to selexipag initiation, Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0 risk strata were: 15% first, 31.5% second, 44.1% third, and 9.4% fourth; European Society of Cardiology/European Respiratory Society low-, intermediate-, and high-risk rates were 20.5%, 61.4%, and 18.1%, respectively. Mean REVEAL Lite 2.0 score was 6.3 ± 2.7. Maximal selexipag dosing reached 1600 µg BID in 18.1% of patients, while 64.6% remained at ≤1000 µg BID. Patients were grouped into low-, intermediate-, and high-dose cohorts. Median follow-up was 727.5 days (interquartile range (IQR) 224-985). Selexipag was discontinued in 15% of patients. Across dosing cohorts, initial improvements in functional class, 6-minute walk distance, right ventricular and pulmonary echocardiographic parameters, and MRSs during the first year attenuated thereafter, except for N-terminal pro-brain natriuretic peptide and Tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure ratio. Lower baseline REVEAL Lite 2.0 score predicted low-risk status at final assessment ($P = .017$). Three-year survival was 72.5%, 85.7%, and 75.1% in low-, medium-, and high-dose cohorts ($P > .05$). Mortality was independently predicted by baseline Swedish PAH Registry, REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores.

**Conclusion:** Earlier escalation to triple therapy with selexipag may improve outcomes. Baseline risk—but not achieved selexipag dose—was associated with survival. A possible decline in treatment effect after 1 year warrants further investigation.

**Keywords:** EUPHRATES, pulmonary arterial hypertension, Selexipag

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by progressive obliteration of small pulmonary arteries, resulting in increased pulmonary vascular resistance (PVR) and pulmonary arterial pressures (PAP), and eventually leading to right-heart failure and death.[1-4] The endothelin, nitric oxide, and prostanoid pathways have been shown to be involved in the development of PAH, and several parenteral, inhaled, or oral PAH-specific drugs targeting these pathways have been developed.[1-4] Among these, the non-prostanoid drug selexipag and its 37-fold more potent metabolite ACT-333679 are selective agonists of the prostacyclin (IP) receptor, 1 of the 5 prostanoid receptors. Stimulation of the IP receptor leads to vasodilation, decreased smooth muscle cell proliferation, and

inhibition of platelet aggregation and inflammation within the pulmonary arteries.[5]

The efficacy and safety of selexipag in patients with PAH have been evaluated in the GRIPHON randomized controlled trial, the SelexiPag: tHe usErs dRug rEgistry (SPHERE) and EXPOSURE multicenter registries, single-center studies, and meta-analyses.[6-23] Currently, selexipag is indicated for PAH to delay disease progression and to reduce the risk of PAH-related hospitalization.[1-5]

This single-center study aimed to evaluate the efficacy and tolerability of selexipag as part of triple sequential combination therapy in patients with PAH.

## METHODS

The study group comprised a subgroup of 127 patients with PAH who were receiving sequential combination therapy with selexipag, extracted from 1160 patients with pulmonary hypertension recruited in the single-center EvalUation of Pulmonary Hypertension Risk Factors AssociaTEd with Survival (EUPHRATES) study.

The diagnostic algorithms, hemodynamic confirmation, clinical sub-classification of pulmonary hypertension (PH), and definitions of incident and prevalent PAH have been based on the recommendations of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) 2015 and 2022 PH guidelines, according to the time of selexipag initiation.[1,2] For the hemodynamic definition of PH by right heart catheterization, cut-off values of mean PAP (PAMP) >25 mm Hg and >20 mm Hg were adopted before and after the ESC/ERS 2022 PH guidelines, respectively.[1,2] For the diagnosis of pre-capillary pulmonary hypertension, pulmonary arterial wedge pressure ≤15 mm Hg and PVR >3 and >2 Wood units were used as criteria before and after the ESC/ERS 2022 PH guidelines, respectively.[1,2]

During the follow-up period after the initiation of selexipag, longitudinal changes in World Health Organization functional class (FC), 6-minute walk distance (6MWD), blood biochemistry and cell counts, N-terminal pro-brain natriuretic peptide (NT-proBNP), echocardiographic measures of pulmonary circulation and right heart function, and multiparametric risk scores (MRSs) were evaluated. For risk assessment, the 3-strata risk prediction model from the 2022 ESC/ERS guidelines for PAH, adapted from the Swedish PAH Registry (SPAHR),[24] the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry,[25] 4 strata-risk model of COMPERA 2.0, and the French Pulmonary Hypertension Network (FPHN) registry low-risk models,[26] as well as the REVEAL 2.0 registry, its abridged 6-component REVEAL Lite 2.0, and REVEAL ECHO scores, were used both at the time of selexipag initiation and at follow-up visits.[27,28,29] All patients under regular follow-up were informed, and written informed consent was obtained from each patient. The study protocol was reviewed and approved by the Institutional Ethics Committee (Ethics committee approved in July 12, 2013, approval number: 2013.3/4). This study was conducted in accordance with the Declaration of Helsinki.

### Statistical Analysis

The normality of continuous variables was assessed using Shapiro–Wilk's test and histogram. Numerical variables were expressed as mean ± standard deviation or median and interquartile ranges (IQR: 25$^{th}$-75$^{th}$) according to distribution. Discrete data were shown as percentages and absolute numbers. For continuous data comparison according to survival status, the *t*-test or Mann–Whitney *U*-test were used; for discrete data comparison according to survival status, the Pearson chi-square test were used. For longitudinal changes, continuous data comparison was made using analysis of variance or Kruskal–Wallis's test according to the normality of data, and pairwise comparison was performed using Tukey HSD or Bonferroni multiple comparison test.

The cumulative risk of all-cause mortality was displayed using Kaplan–Meier plots. Differences between groups, including dose and baseline risk strata, were assessed using the log-rank test, and risk tables were presented below the plots. Selexipag dose was categorized as low (200 or 400 µg twice daily), medium (600, 800, or 1000 µg twice daily), and high (1200, 1400, or 1600 µg twice daily). To evaluate the independent association of selexipag dose with mortality, Cox proportional hazards regression models were constructed. Due to the limited number of events, only selexipag dose (low, medium, high) and baseline risk scores were included in the models to avoid overfitting. Hazard ratios (HRs) with 95% CIs were reported. Proportional hazards assumptions were checked using Schoenfeld residuals.

All statistical analyses were performed using R software v. 4.0.2 with the "survival," "survminer," "ggplot2," and "Hmisc" packages (Vienna, Austria). A 2-sided *P* value <.05 was considered statistically significant.

## RESULTS

Patient characteristics and background therapies prior to the addition of selexipag are shown in Table 1. The mean age of the patients was 43.2 ± 16.4 years, and 84.3% were

### HIGHLIGHTS

- Sequential triple combination therapy including selexipag demonstrated marked early improvement in clinical risk profile in patients with pulmonary arterial hypertension (PAH).
- Selexipag was well-tolerated, and treatment continuation was not limited by adverse effects in the majority of patients.
- The initial therapeutic benefits showed attenuation beyond the first year, underscoring the progressive nature of PAH despite aggressive escalation.
- Baseline clinical risk status was the key determinant of long-term outcomes, while response magnitude and maintenance did not correlate with selexipag dose.
- Early implementation of triple therapy may be crucial for optimizing long-term risk trajectory and functional stabilization in advanced PAH.

**Table 1. Demographics, Clinical, Echocardiographic and Hemodynamic Characteristics and Treatment Patterns in Study Population**

| | n = 127 patients |
|---|---|
| Demographics, clinical and laboratory | |
| Age (years) | 43.2 (16.4) |
| Female sex, n (%) | 107 (84.3) |
| Idiopathic PAH, n (%) | 58 (45.7) |
| PAH associated with CHD, n (%) | 58 (45.7) |
| Eisenmenger Syndrome, n (%) | 32 (25.2) |
| Prevalent systemic-to-pulmonary shunt, n (%) | 6 (4.7) |
| PAH with small shunt defect, n (%) | 1 (0.8) |
| PAH with corrected congenital shunt, n (%) | 19 (15) |
| Drug-associated PAH, n (%) | 1 (0.8) |
| Hereditary PAH, n (%) | 2 (1.6) |
| PAH associated with CTD, n (%) | 8 (6.3) |
| WHO Functional Class II, n (%) | 24 (18.9) |
| WHO Functional Class III, n (%) | 84 (66.1) |
| WHO Functional Class IV, n (%) | 19 (15) |
| 6-minute walk distance (m) | 330 (238-403) |
| NT-ProBNP levels (ng/L) | 486 (171-946) |
| Echocardiographic measures | |
| Pericardial effusion, n (%) | 10 (7.9) |
| LVEF, % | 63.9 (3.25) |
| D-shaped septum, n (%) | 104 (81.9) |
| PA diameter, cm | 3.52 (0.79) |
| RA area, $cm^2$ | 23.3 (7.89) |
| IVC diameter, cm | 1.99 (0.42) |
| TAPSE, cm | 1.98 (0.46) |
| RV TDI, cm/sec | 12.4 (2.79) |
| TR grade not traceable, n (%) | 1 (0.8) |
| TR grade 1, n (%) | 46 (36.2) |
| TR grade 2, n (%) | 47 (37) |
| TR grade 3, n (%) | 20 (15.7) |
| TR grade 4, n (%) | 13 (10.2) |
| TR Vmax, m/sec | 4.3 (3.4-4.93) |
| TAPSE/PASP ratio | 0.25 (0.17-0.38) |
| Right heart catheterization | |
| PASP, mm Hg | 93.8 (27.3) |
| PAMP, mm Hg | 59.2 (19.6) |
| PVR, Wood unit | 10 (6-16) |
| ESC/ERS 2022 Risk Model (3-component) | |
| Low risk, n (%) | 26 (20.5) |
| Intermediate risk, n (%) | 78 (61.4) |
| High risk, n (%) | 23 (18.1) |
| COMPERA 1.0 (3-component) | |
| Low risk, n (%) | 37 (29.1) |
| Intermediate risk, n (%) | 69 (54.3) |
| High risk, n (%) | 21 (16.5) |
| COMPERA 2.0 (4-component) | |
| 1, n (%) | 19 (15) |
| 2, n (%) | 40 (31.5) |
| 3, n (%) | 56 (44.1) |
| 4, n (%) | 12 (9.4) |
| FPHN—non-invasive risk model | |
| 0 (%) | 89 (70.1) |
| 1 (%) | 19 (15) |
| 2 (%) | 13 (10.2) |
| 3 (%) | 6 (4.7) |
| REVEAL 2.0 score | 8.45 (1.9) |
| REVEAL Lite 2.0 score | 6.3 (2.7) |
| REVEAL—Echo score | |
| Low risk (%) | 62 (48.8) |
| Intermediate risk (%) | 48 (37.8) |
| High risk (%) | 17 (13.4) |
| Back-ground PAH therapies | |
| Monotherapy | |
| Bosentan, n (%) | 1 (0.8) |
| Double combination therapy | 118 (92.9) |
| Bosentan + Riociguat, n (%) | 1 (0.8) |
| Bosentan + Sildenafil, n (%) | 20 (15.7) |
| Bosentan + Tadalafil, n (%) | 11 (8.6) |
| Ambrisentan + Sildenafil, n (%) | 2 (1.6) |
| Ambrisentan + Tadalafil, n (%) | 3 (2.3) |
| Macitentan + Riociguat, n (%) | 6 (4.7) |
| Macitentan + Sildenafil, n (%) | 17 (13,4) |
| Macitentan + Tadalafil, n (%) | 58 (45.6) |
| Triple combination therapy—switch to selexipag | 8 (6.3) |
| Ambrisentan + Tadalafil + inhaled Iloprost, n (%) | 1 (0.8) |
| Macitentan + Sildenafil + inhaled Iloprost, n (%) | 2 (1.6) |
| Macitentan + Tadalafil + inhaled Iloprost, n (%) | 5 (3.9) |
| Daily Selexipag dose, ug | |
| 400, n (%) | 14 (11) |
| 800, n (%) | 19 (15) |
| 1200, n (%) | 13 (10.2) |
| 1600, n (%) | 18 (14.2) |
| 2000, n (%) | 18 (14.2) |
| 2400, n (%) | 14 (11) |
| 2800, n (%) | 8 (6.3) |
| 3200, n (%) | 23 (18.1) |
| Follow-up time, days | 682 (224-985) |
| Clinical worsening before therapy, n (%) | 34 (26.7) |
| Clinical worsening after therapy, n (%) | 29 (22.8) |
| Patients discontinued therapy, n (%) | 19 (15) |
| Long-term mortality, n (%) | 19 (15.1) |

female. Idiopathic PAH (IPAH) was observed in 45.7% of patients, while hereditary PAH and PAH associated with congenital heart disease, connective tissue disease (CTD), and drugs were documented in 1.6%, 45.7%, 6.3%, and 0.8% of patients, respectively. Background combination therapies were as follows: macitentan and tadalafil in 58 (45.6%), macitentan and sildenafil in 17 (13.4%), macitentan and riociguat in 6 (4.7%), bosentan and tadalafil in 11 (8.6%), bosentan and sildenafil in 20 (15.7%), bosentan and riociguat in 1 (0.8%), ambrisentan and tadalafil in 3 (2.3%), and ambrisentan and sildenafil in 2 (1.6%) of the 127 patients (Table 1).PAH, pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease; WHO, World Health Organization; NT-proBNP, N-terminal pro–B-type natriuretic peptide; LVEF, left ventricular ejection fraction; PA, pulmonary artery; RA, right atrium; IVC, inferior vena cava; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; TDI, tissue Doppler imaging; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; PAMP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; ESC, European Society of Cardiology; ERS, European Respiratory Society; FPHN, French Pulmonary Hypertension Network.

## Baseline Parameters Before Selexipag Addition to Dual Therapy

The FC was II, III, and IV in 18.9%, 66.1%, and 15% of patients, respectively. Median 6MWD was 330 m (IQR 238-403), and median serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level was 486 ng/L (IQR 171–946) (Table 1). Tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular tissue Doppler velocity (RV TDI), right atrial area, and pulmonary arterial diameter were 1.98 ± 0.46 cm, 12.4 ± 2.79 cm/sec, 23.3 ± 7.89 $cm^2$, and 3.52 ± 0.79 cm, respectively. Invasively measured pulmonary arterial systolic and mean pressures (PASP and mPAP) were 93.8 ± 27.3 mm Hg and 59.2 ± 19.6 mm Hg, respectively. Median PVR was 10 Wood units (IQR 6-16).

Before the addition of selexipag to background therapies, COMPERA 2.0 first, second, third, and fourth risk strata were noted in 15%, 31.5%, 44.1%, and 9.4% of patients, and ESC/ERS low-, intermediate-, and high-risk status were noted in 20.5%, 61.4%, and 18.1% of patients, respectively. The REVEAL Lite 2.0 score was 6.3 ± 2.7. Non-invasive FPHN scores of 0, 1, 2, and 3 were documented in 70.1%, 15%, 10.2%, and 4.7% of patients, respectively. The REVEAL ECHO score showed low risk in 48.8%, intermediate risk in 37.8%, and high risk in 13.4% of patients (Table 1).

Maximally tolerated selexipag doses were 1600 µg BID in 18.1% of patients, 1400 µg BID in 6.3%, 1200 µg BID in 11%, and ≤1000 µg BID in 64.6% (Table 2). Consistent with definitions in the GRIPHON study, patients were categorized as low-dose, intermediate-dose, and high-dose cohorts in 26%, 38.6%, and 35.4% of cases, respectively. Median and mean follow-up periods were 682 days (IQR 224-985) and 683 ± 481 days, respectively.

## The Evolution of Measures and Risk Scores

The progressive improvements in FC, NT-proBNP, PASP, right atrial area and pressure estimates, pulmonary artery and inferior vena cava diameters, pericardial effusion grade assessed by echocardiography, and MRSs evaluated using COMPERA, FPHN, REVEAL Lite 2.0, and REVEAL ECHO models during the first 12 months of selexipag treatment were found to be attenuated thereafter (Supplementary Figures 1 and 2).

Regardless of dose status, 6MWD showed significant improvement at 12 months compared with baseline ($P$ = .022), followed by attenuation thereafter (Figure 1A), while NT-proBNP levels demonstrated significant reduction at the final assessment ($P$ = .018) (Figure 1B). All dose cohorts exhibited significant improvements in TAPSE at 6 and 12 months compared with baseline ($P$ = .040 and $P$ = .027, respectively), with high- vs. low-dose associated with a greater increase at 6 months (Figure 1C). Increases in RV TDI were consistent across the 3 dose cohorts, although high- vs. low-dose was linked to a greater increase at 6 months ($P$ = .037) (Figure 1D). Comparable reductions in PASP were observed at 6 and 12 months ($P$ = .037 and $P$ = .009, respectively), followed by subsequent increases (Figure 1E). Significant reductions in mPAP were noted at 12 months across all cohorts ($P$ = .049), and low- vs. medium-dose associated with a more pronounced reduction ($P$ = .031). However, mPAP increased in all cohorts after 12 months (Figure 1F). The TAPSE/PASP ratio showed a marked but non-significant trend toward increase from baseline to the final assessment, consistent across all 3 dose cohorts ($P$ > .05) (Figure 1G). Similarly, FC status improved up to 12 months across all dose cohorts, followed by attenuation of this trend (Figure 1H).

**Table 2. Kaplan–Meier Estimated 1-, 3-, and 5-Year Survival According to Selexipag Dose Cohorts, Including Number at Risk and Events**

| 1, 3, 5 year Survival—Dose | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| Levels | time | Number at Risk | Number of Events | Survival, % | Lower, % | Upper, % |
| Low dose (200-400 mcg) | 12 | 16 | 3 | 89.8 | 79.3 | 100.0 |
| Low dose (200-400 mcg) | 36 | 3 | 2 | 72.5 | 52.6 | 100.0 |
| Medium dose (600-1000 mcg) | 12 | 36 | 2 | 95.3 | 89.1 | 100.0 |
| Medium dose (600-1000 mcg) | 36 | 10 | 3 | 85.7 | 74.6 | 98.4 |
| High dose (1200-1600 mcg) | 12 | 35 | 2 | 95.0 | 88.5 | 100.0 |
| High dose (1200-1600 mcg) | 36 | 12 | 6 | 75.1 | 61.2 | 92.2 |

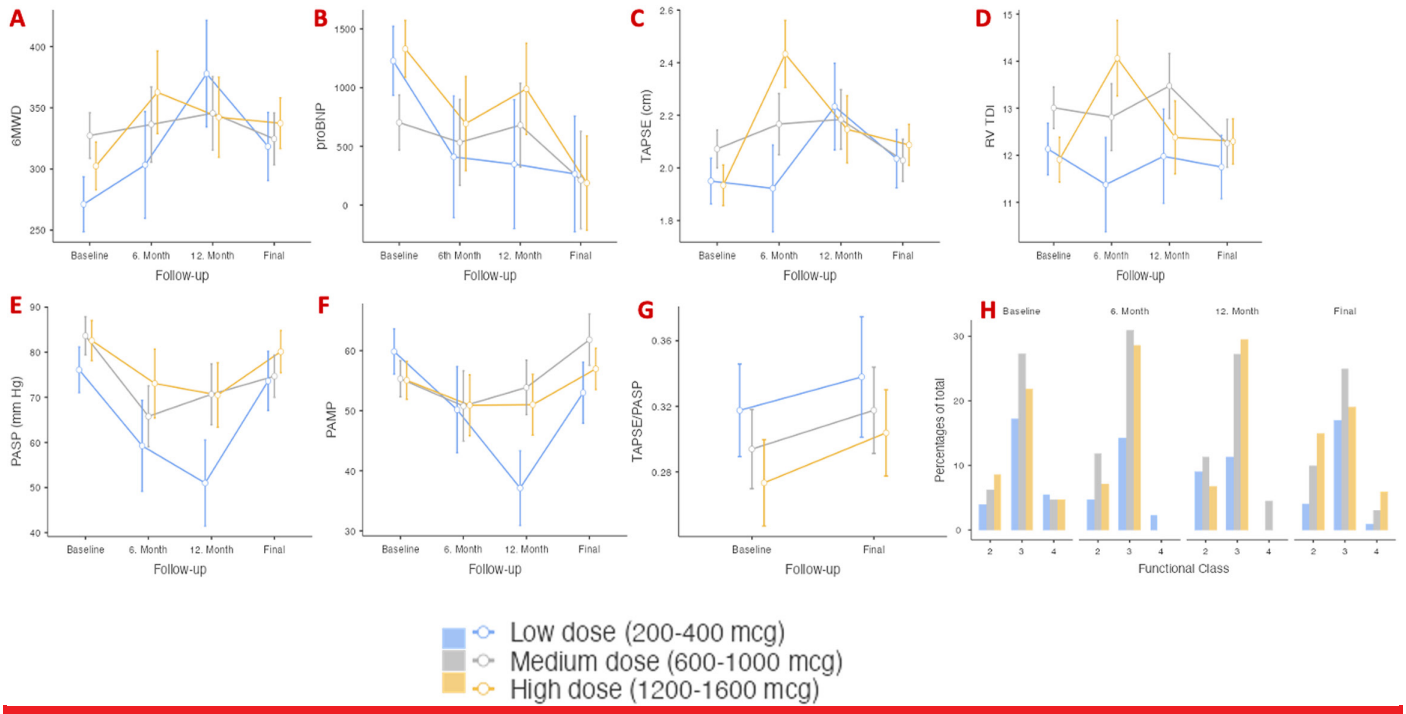


**Figure 1. Longitudinal changes in functional, biochemical, and echocardiographic parameters according to selexipag dose cohorts. (A) Six-minute walk distance (6MWD), (B) N-terminal pro–brain natriuretic peptide (NT-proBNP), (C) tricuspid annular plane systolic excursion (TAPSE), (D) right ventricular tissue Doppler imaging velocity (RV TDI), (E) pulmonary arterial systolic pressure (PASP), (F) pulmonary arterial mean pressure (mPAP), (G) TAPSE/PASP ratio, and (H) World Health Organization functional class (FC). Data are presented at baseline, 6 months, 12 months, and final follow-up.**

The 19 patients (15%) discontinued selexipag due to side effects. The most common adverse events (AEs) were headache; pain in the jaw, muscles, or legs; diarrhea; nausea; vomiting; and flushing. Clinical worsening and all-cause mortality were documented in 29 (22.8%) and 19 (15.1%) patients, respectively. During the follow-up period, 5 of the 19 patients who discontinued selexipag died.

Table 2 demonstrated survival estimates in 3 maximally tolerable selexipag dose cohorts. The 12-month and 36-month survival were 89.8% (79.3%-100%) and 72.5% (52.6%-100%) in low-dose cohort, 95.3% (89.1%-100%) and 85.7% (74.6%-98.4%) in medium-dose cohort, and 95% (88.5%-100%) and 75.1 % (61.2%-92.2%) in high-dose cohort, respectively.

Figure 2A shows that Kaplan–Meier survival estimates were comparable among the 3 dose cohorts. Baseline multiparametric risk status at the time of selexipag initiation, as assessed by the 4-component COMPERA 2.0 (Figure 2C), but not by the 3-component COMPERA 1.0 (Figure 2B) or FPHN (Figure 2D), was associated with significant differences in Kaplan–Meier survival estimates.

Forest plots revealed that COMPERA 1.0, COMPERA 2.0, and FPHN scores were not significantly associated with mortality after adjustment for dose groups, (Figure 3A-C). In contrast, the SPAHR score at baseline remained significantly associated with mortality after adjustment for dose groups (HR 6.41; 95% CI 2.49-16.49; $P < .001$) (Figure 3D).

REVEAL Lite 2.0 risk status was associated with significant survival differences in Kaplan–Meier estimates ($P = .0014$) (Figure 4A). Forest plots demonstrated that baseline REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores were significantly associated with mortality after adjustment for dose groups in 3 separate models (Figures 4B-D). The HRs for REVEAL 2.0 and REVEAL Lite 2.0 were 1.22 (95% CI 1.03-1.46, $P = .024$) and 1.48 (95% CI 1.25-1.75, $P < .001$), respectively. For the REVEAL Echo score, the HR increased incrementally with higher risk strata, from 6.01 (95% CI 1.09-33.15, $P = .040$) at score 3, to 8.09 (95% CI 1.46-44.72, $P = .017$) at score 4, and to 26.34 (95% CI 3.39-204.86, $P = .002$) at score 5 (Figure 4D). Moreover, initial REVEAL Lite 2.0 score was an independent predictor of low-risk status at the final assessment according to REVEAL Lite 2.0 (HR: 0.74; 95% CI 0.57-0.95, $P = .017$).

Follow-up showed that none of the risk scores, as assessed by COMPERA 2.0, FPHN, or REVEAL Lite 2.0 models at 6 months of selexipag triple combination therapy, were significantly associated with survival differences, although there was a trend toward worse outcomes in the high-risk cohorts of each model (Figures 5A-C).

## DISCUSSION

The results of single-center follow-up data appear to be consistent with previously reported studies regarding the efficacy and tolerability of selexipag-based triple sequential combination therapy, the maximally tolerated doses achieved, and the patterns of discontinuation in patients with PAH. Regardless of the maximally tolerated selexipag dose, progressive improvements in FC, 6MWD, echocardiographic measures of pulmonary and right ventricular

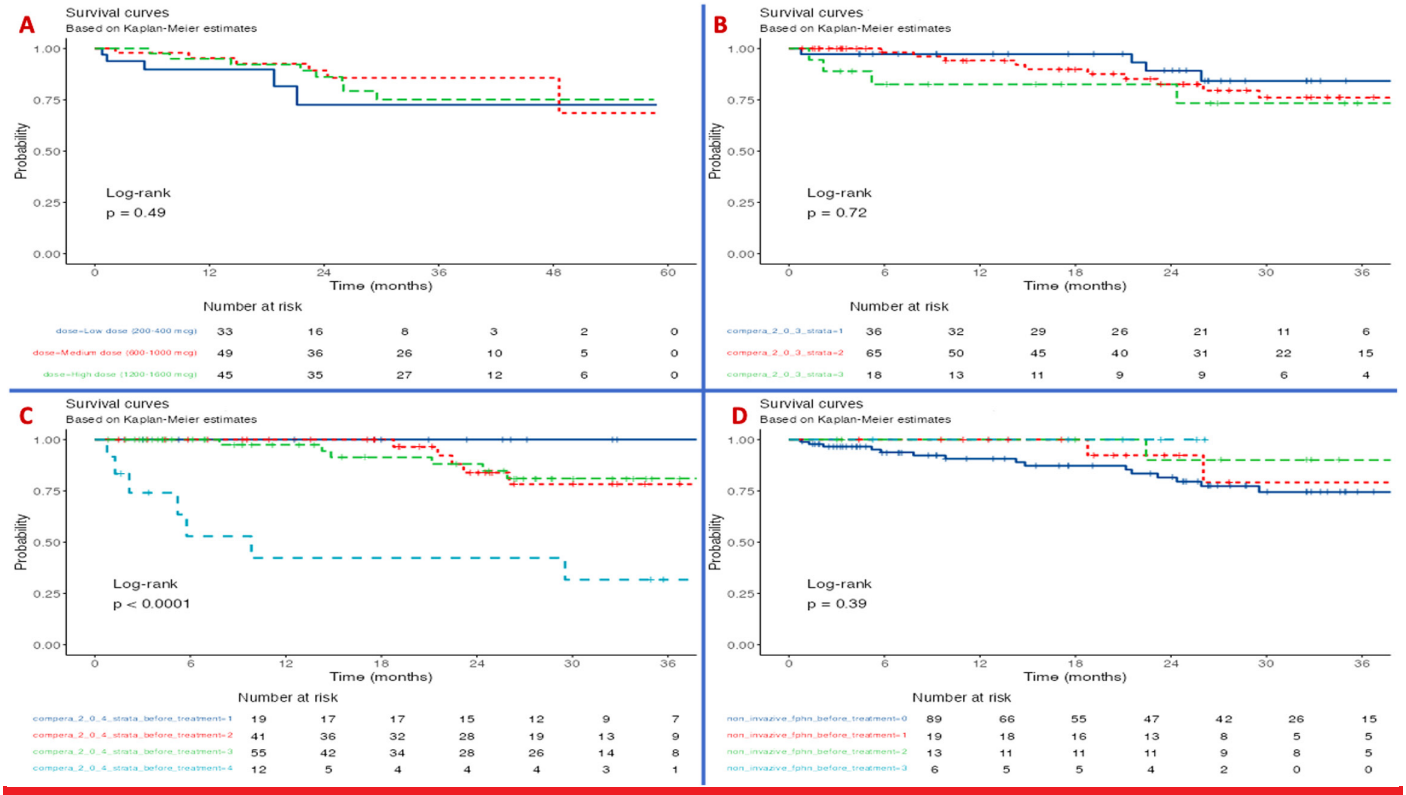


**Figure 2. Kaplan–Meier survival estimates according to selexipag dose and baseline risk status. (A) Survival estimates were comparable among low-, medium-, and high-dose cohorts. (B) Baseline risk stratification using 3-component COMPERA 1.0 showed no significant difference in survival estimates. (C) Four-component COMPERA 2.0 was associated with significant differences in survival estimates. (D) FPHN risk assessment showed no significant difference in survival estimates.**

hemodynamics, and MRSs during the first 12 months of treatment were uniformly attenuated thereafter, except for NT-proBNP levels and TAPSE. There were no differences in 3-year survival estimates among the 3 different maximally tolerated dose cohorts. Mortality was found to be associated with baseline SPAHR, REVEAL 2.0, REVEAL Lite 2.0, and REVEAL Echo scores at the time of initiating selexipag add-on therapy, but not with selexipag doses or other MRSs at baseline or at the first 6-month follow-up. However, a low final REVEAL Lite 2.0 score could be predicted by the REVEAL Lite 2.0 score at the initiation of selexipag therapy.

The GRIPHON randomized clinical trial showed that selexipag use was associated with a consistent 40% reduction in morbidity and mortality across subgroups and in mono-, dual-, and triple-combination therapies, regardless of the maximally tolerated dose attained.[6] The open-label extension phase of the GRIPHON study provided outcome data, as well as safety and tolerability profiles of selexipag over a 7-year follow-up period. Kaplan–Meier survival estimates at 1, 3, 5, and 7 years for patients randomized to selexipag were 92.0%, 79.3%, 71.2%, and 63.0%, respectively.[7] The most frequently reported AEs were related to well-known prostacyclin-related effects and/or underlying disease.[7,14] A greater benefit from earlier initiation of selexipag on background endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE5i) combination therapy has been shown in 2 sub-analyses of the GRIPHON data.[8,9] Consistent with these results, a retrospective study by Tsang et al[19] found that initiation of selexipag within 12 months of PAH diagnosis, compared with no selexipag therapy during that period, was associated with a lower rate of all-cause hospitalizations and reduced all-cause and PAH-related total medical costs, but showed no significant difference in PAH-related hospitalization rates or risk of disease progression.[17] In the SPHERE (NCT03278002) prospective, real-world registry including patients with PAH treated with selexipag, newly initiated (≤60 days) and previously initiated (>60 days) selexipag cohorts were compared.[10] At the initiation of selexipag, 55.6% of patients were in FC III/IV, and 57.3% were classified as intermediate- or high-risk according to the REVEAL 2.0 score.[10] Over a median titration period of 8.1 weeks, the lowest, intermediate, and highest (≥1200 µg) maintenance doses were achieved in 15%, 31%, and 41% of patients, respectively.[10] This dose range was comparable to those in the GRIPHON trial, in which the reported rates of lowest, intermediate, and highest maintenance doses were 23%, 31%, and 43%, respectively.[6,10] The FC and REVEAL 2.0 risk status were reported to improve in 25% and 21% of patients, respectively, while remaining stable in 61% and 57% of patients.[10] The 18-month survival rates were 89.4%, 84.2%, and 94.5%, and discontinuation rates for AEs were 22%, 32%, and 11.9%, in the overall, newly, and previously initiated patient groups, respectively.[10] Importantly, discontinuation for AEs, hospitalization, and survival were comparable regardless of maximally tolerable selexipag doses attained,[10] and were consistent with

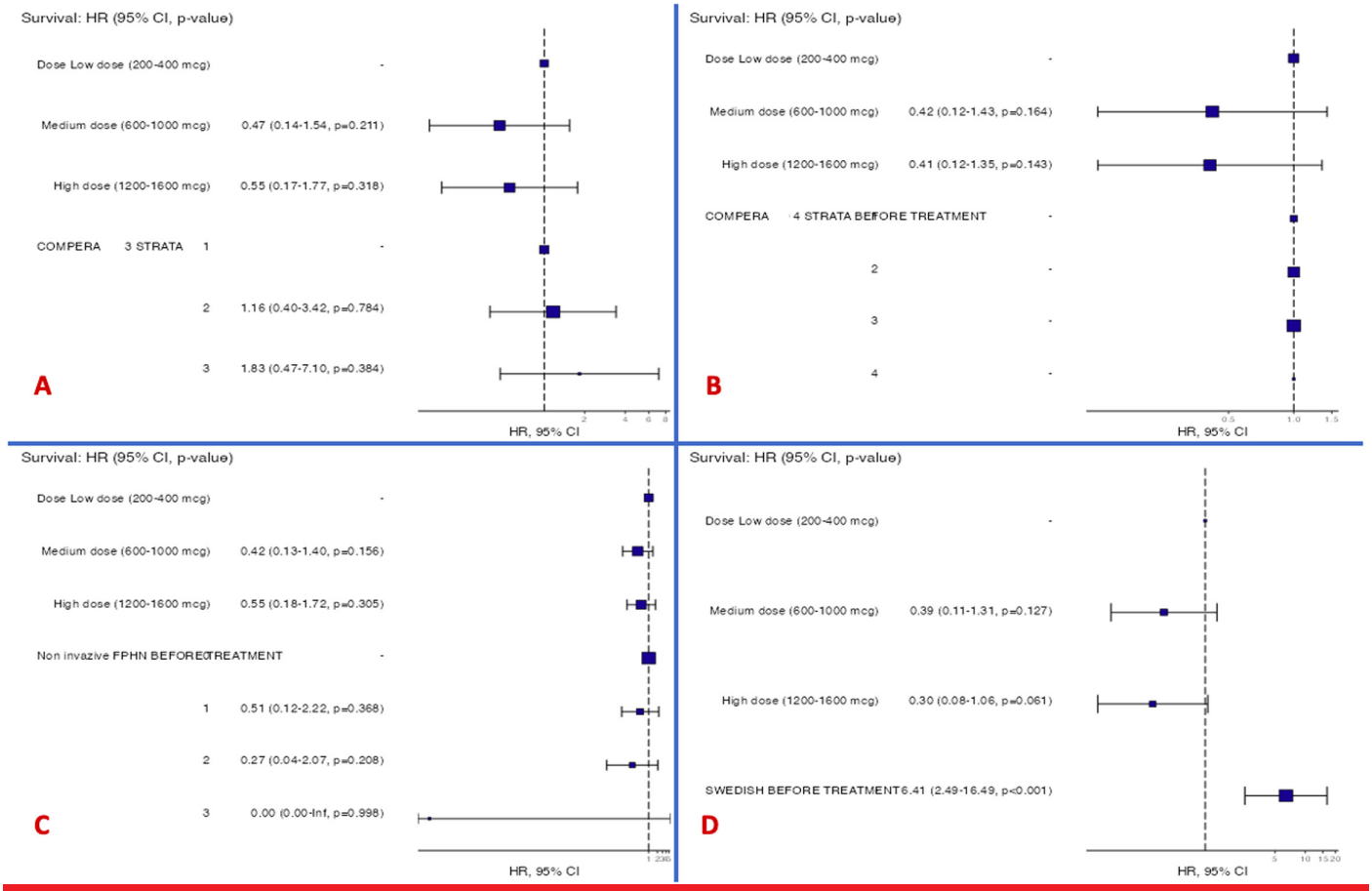


**Figure 3. Forest plot of baseline risk scores for mortality after adjustment for dose groups. (A) COMPERA 1.0, (B) COMPERA 2.0, and (C) FPHN scores were not significantly associated with mortality after adjustment. (D) The Swedish (SPAHR) score remained significantly associated with mortality after adjustment for dose groups (HR 6.41; 95% CI 2.49-16.49; *P* < .001).**

GRIPHON and the US prescribing information for prostacyclin therapies.[6,10,15] The main limitations of SPHERE seem to have originated from its observational nature and the potential bias that might be associated with the previously initiated selexipag cohort in which immortal time bias was possible and no data were collected between treatment initiation and study enrollment.[10] Moreover, results of SPHERE suggest that the adoption status of guideline recommendations in real-world clinical practice remains unsatisfactory.

EXPOSURE (EUPAS19085) is an ongoing, multicenter, prospective, observational study of patients with PAH who are initiating a new PAH-specific therapy in Europe or Canada.[11-14] Although half of incident patients were on combination therapy, this rate seems to be insufficient in the presence of the 70% rate of intermediate-high- or high-risk status in the study population. Utilization of selexipag across risk groups ranged from 74% to 81%. The survival rates in EXPOSURE were comparable between the incident and prevalent patients. Survival estimates were 98%, 98%, 93%, and 80% at 1 year and 98%, 92%, 81%, and 67% at 2 years, in 4 risk strata from low to high, respectively.[11-14] Similar to those in SPHERE, the low rates of selexipag initiation in the EXPOSURE trial also suggest a gap between real-life practice and guidelines recommendations for treatment escalations.[10-14]

In a subgroup analysis of EXPOSURE, rates of selexipag including triple combinations were similar, and titration duration, maximally tolerable doses, and discontinuation rates were comparable between Idiopathic Pulmonary Arterial HypertensionIPAH and CTD-PAH patients.[13] However, the proportion of triple-combination therapy including selexipag decreased from 81% to 53% in IPAH and to 56% in CTD-PAH cohorts at 12 months of selexipag treatment. Time to all-cause hospitalizations and time to all-cause death curves showed relatively better 36-month outcomes in IPAH compared with CTD-PAH.[13] Moreover, in a recently published paper from the EXPOSURE study, pre-specified comparative survival analyses based on propensity score weighting between patients who newly initiated selexipag vs. other PAH-specific therapies revealed that the mortality rate ratio was significantly lower for selexipag-treated patients (0.55; 95% CI 0.31-0.99).[14]

In this study, the majority of patients at intermediate risk status, and the mean and median time delay for the combination of selexipag with background therapies were 1705 ± 1363 days and 1424 days (IQR 541-2523), respectively. Selexipag was titrated over a median of 8 weeks, with 200 µg twice-daily increments every 2 weeks in the absence of AEs attributable to the drug. Maximally tolerable doses

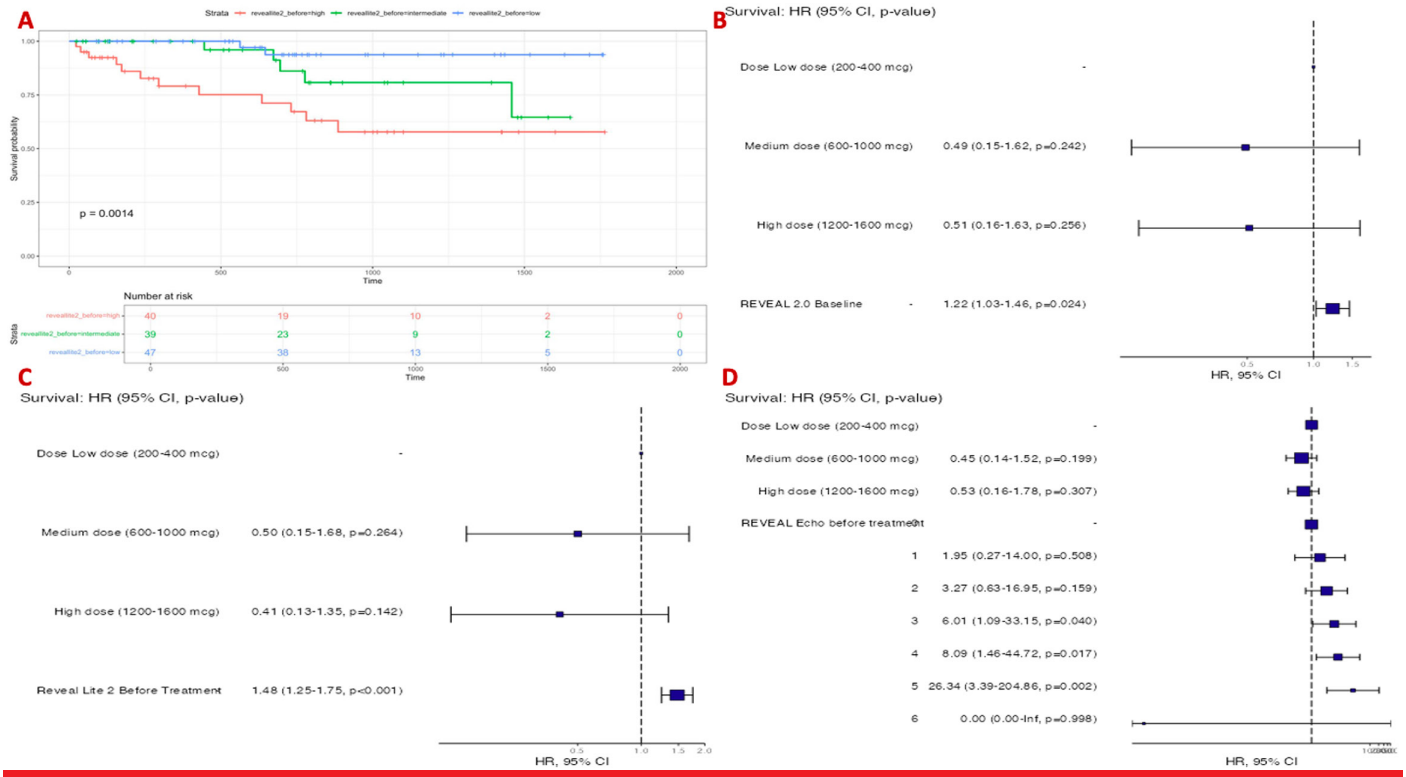


**Figure 4. Kaplan–Meier and forest plot analyses for REVEAL risk models. (A) Kaplan–Meier survival curves according to baseline REVEAL Lite 2.0 risk status. (B-D) Forest plot analyses demonstrating the association of baseline REVEAL 2.0 (B), REVEAL Lite 2.0 (C), and REVEAL Echo (D) scores with mortality after adjustment for dose groups. The REVEAL Echo score showed an incremental increase in hazard ratios with higher scores, indicating a dose–response relationship between risk category and mortality.**

were maintained at lowest, intermediate, and highest dose stratum in 11.7%, 70.4%, and 17.9%, respectively. In comparison to those in SPHERE and GRIPHON studies, the rate of the highest dose was lower, but the discontinuation rate was also lower. Side effects were not different from previously reported series. The study revealed that the marked improvements in FC, 6MWD, NT-proBNP, echocardiographic measures, and risk status as assessed by MRSs during the first 12 months of selexipag treatment were followed by an attenuation of these benefits in a nearly uniform pattern. However, this trend was not seen for NT-proBNP and TAPSE, and the statistically significant decrease from baseline to final analysis was maintained in these 2 measures regardless of the selexipag dose. The non-significant trend toward increase in TAPSE/PASP ratio was also consistent across all 3 dose cohorts. These results seem to implicate the progressive deteriorating nature of the disease rather than a potential risk for loss in the efficacy of selexipag at the mid-term period. In consistency with GRIPHON sub-analyses and real-life data[30], the lower risk status according to SPAHR, REVEAL 2.0, REVEAL lite 2.0, and REVEAL-Echo models at the start of selexipag was found to be independently associated with improved survival in the study. Moreover, a lower REVEAL Lite 2.0 score at the start of selexipag begets a lower final REVEAL Lite 2.0 score. Despite a signal implying a relation between the risk status attained at the sixth month of selexipag and survival, this trend did not achieve statistical significance.

Early addition of selexipag to double PAH therapy has been evaluated in Komodo Health payer-complete dataset, and all-cause hospitalizations, PAH-related hospitalizations,

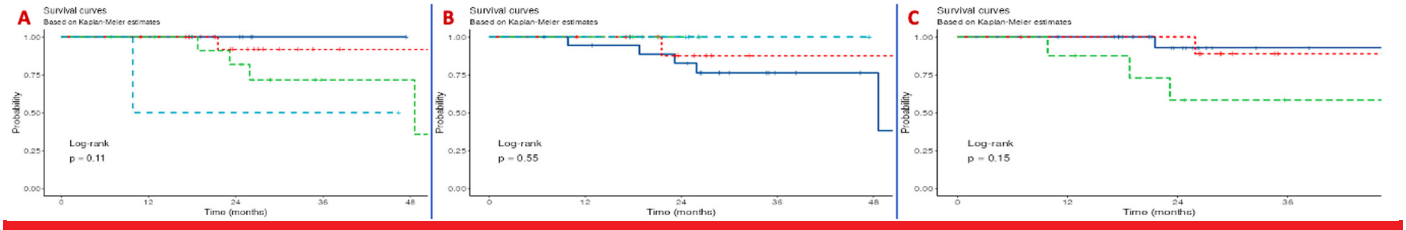


**Figure 5. Kaplan–Meier survival estimates of selexipag triple combination therapy according to baseline risk status. (A) COMPERA 2.0, (B) FPHN, and (C) REVEAL Lite 2.0 risk models. No statistically significant differences in survival were observed between risk strata, although high-risk cohorts showed a trend toward worse outcomes.**

and PAH-related progression were found to be significantly improved if selexipag was added within 6 months as compared to dual therapies without selexipag.[17] These benefits were more pronounced when selexipag was added within the first 3 months, and a treatment gap of no more than 45 days was allowed. However, these benefits were not documented in those whom selexipag was added to dual therapies after 12 months.[17]

In a retrospective study including 192 patients with PAH from 10 centers, different oral sequential triple combination therapies based on selexipag improved FC, number of low-risk parameters, 6MWD, PASP, RV functions, eccentricity index, and in NT-proBNP after 6 months of treatment.[18] However, selexipag combined with background macitentan vs. ambrisentan, or riociguat vs. tadalafil or sildenafil were not associated with any difference in 6-month event-free survival and all-cause survival.[18] Selexipag initiation within 12 months of PAH diagnosis demonstrated reductions in all-cause hospitalization rate and medical costs,[19] and improved prognosis in PAH.[20]

The efficacy and safety of selexipag against oral treprostinil, beraprost, or placebo have been evaluated in 3 recent meta-analyses.[21-23] In the first meta-analysis based on 7 randomized controlled studies and 6 cohort studies, selexipag was reported to be associated with improvements in the 6MWD, NT-proBNP, cardiac index, and WHO-FC.[21] Selexipag dose status was not associated with a difference in 6MWD benefit, but highest doses related to more reduction in PVR. Moreover, the increase in 6MWD and decrease in PVR became more pronounced with selexipag treatment longer than 6 months.[21] In another recent meta-analysis based on selexipag-including randomized controlled trials, selexipag was safe and was associated with significant improvements in the mPAP, NT-proBNP, cardiac index, FC, and hospitalization for worsening of PAH.[22] In the last meta-analysis based on data from 8 randomized controlled studies including 3023 patients receiving oral treprostinil, selexipag, or beraprost and placebo, the risk of clinical worsening was significantly reduced with selexipag and oral treprostinil, but not with beraprost.[23]

Current results from a nation-wide SIMURG registry and a single-center EUPHRATES study demonstrated a trend towards better clinical, echocardiographic, and hemodynamic presentations and improved survival in the overall PH population, PAH subgroups, and group IV PH across the 3 consecutive time periods, i.e., before 2016, between 2016 and 2019, and after 2019, that might be attributed to more proactive management strategies favoring earlier initiation of targeted combinations including selexipag.[31-35]

In an upcoming 2 × 2 randomized crossover trial including patients with PAH established on guideline-recommended dual therapy and implanted with CardioMEMS (a wireless pulmonary artery sensor) and ConfirmRx (an insertable cardiac rhythm monitor), triple combinations with ERA, riociguat, and selexipag or ERA, PDEi, and selexipag regimens will be compared.[36] In this very complex design, the primary endpoint will be the change in RV systolic volume measured by magnetic resonance imaging from baseline to maximal tolerable dose with each therapy. Moreover, secondary endpoints including physiological measures, hemodynamics, physical activity, quality of life, and side effects will assess whether remote technology facilitates early evaluation of clinical efficacy and compare intra-patient efficacy of the 2 treatment strategies.[36]

### Study Limitations

The size of the patient population, retrospective analysis, and non-randomized nature of this study are the main limitations. The absence of routine periodical right heart catheterization during follow-up might limit reflections on the impact of the triple sequential combinations with selexipag on pulmonary and right-heart hemodynamics. However, nearly uniform changes in all measures and MRSs, regardless of the selexipag dose status, should be meaningful. Longer follow-up periods might provide more comprehensive evidence for efficacy and safety concerns of selexipag. Most importantly, the cumulative data suggest a delay in the initiation of selexipag. However, reimbursing the upfront combinations with ERA and PDE5i in the country can also be expected to shorten the time to escalations to triple combinations and may augment clinical benefit. The last limitation was related to the low rate of triple combinations including parenteral prostacyclins in high-risk status at baseline or follow-up, despite the proven benefits. This might be related to the unwillingness of some patients to use parenteral prostacyclin and transient problems in cooperation between the social security agency and the pharmaceutical industry.

## CONCLUSIONS

The results highlighted the critical importance of earlier escalation to selexipag, including triple combinations in PAH, and a better risk status at baseline, but not maximally tolerable selexipag doses attained, seem to be associated with better survival. However, a trend for the attenuation in the efficacy after the first year of selexipag therapies should also be taken into consideration. This trend seems to be consistent with the progressive nature of PAH and may implicate earlier quadruple combinations including sotatercept even in stable patients or the need for switching to parenteral prostacyclins in the case of clinical deterioration.

**Ethics Committee Approval:** The study protocol was reviewed and approved by the Koşuyolu Training and Research Hospital Ethics Committee (Ethics committee approved in July 12, 2013, approval number: 2013.3/4).

**Informed Consent:** Written informed consent was obtained from each patient.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – H.C.T., C.K.; Design – H.C.T., B.K.; Supervision – C.K., İ.H.T.; Resources – C.K., S.T.; Materials – Ç.B., D.S.; Data Collection and/or Processing – Ş.Z.A., M.K., A.K., Ş.N.Ç., A.V., C.E., F.B.E., F.D., Z.B., A.S.; Analysis and/or Interpretation – B.K., B.Ke., A.H., A.Ka.; Literature Search – H.C.T., S.T.; Writing – H.C.T., C.K.; Critical Review – C.K., İ.H.T., N.Ö.

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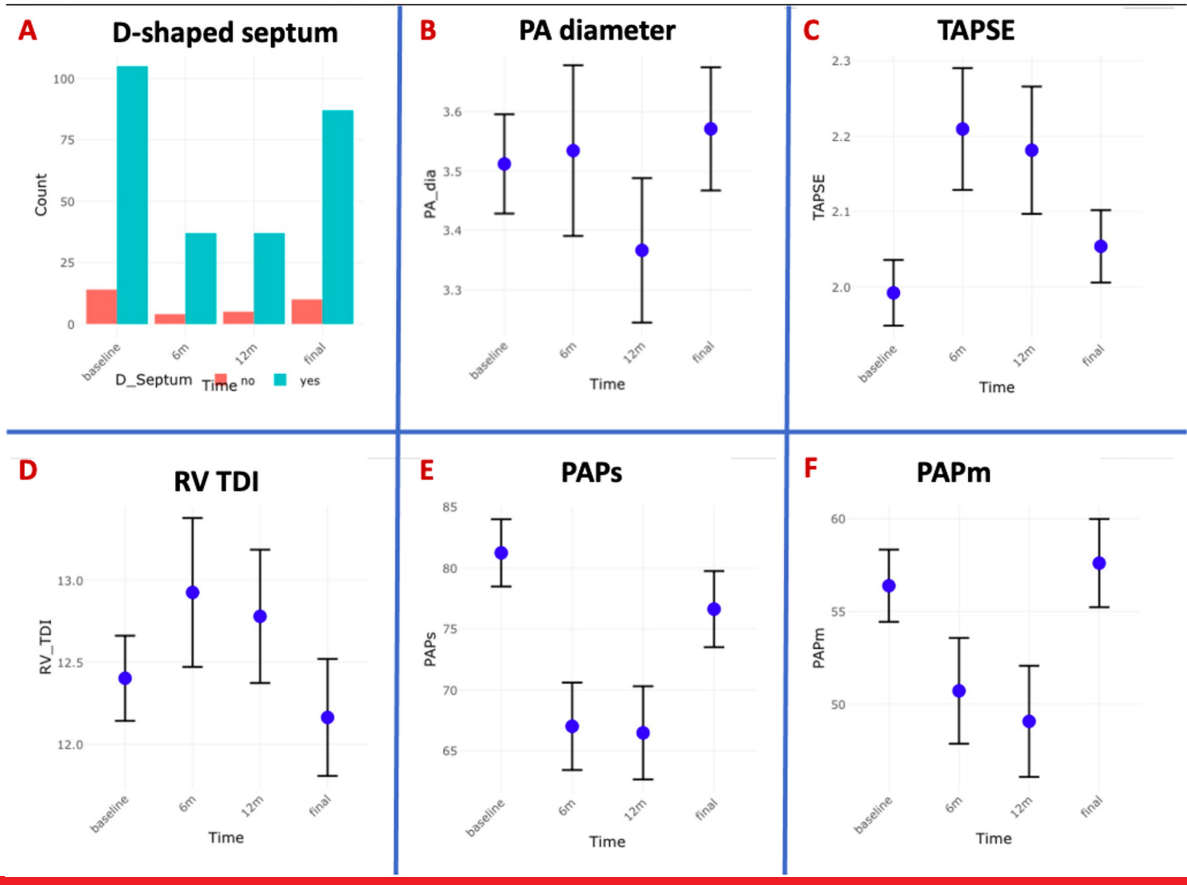
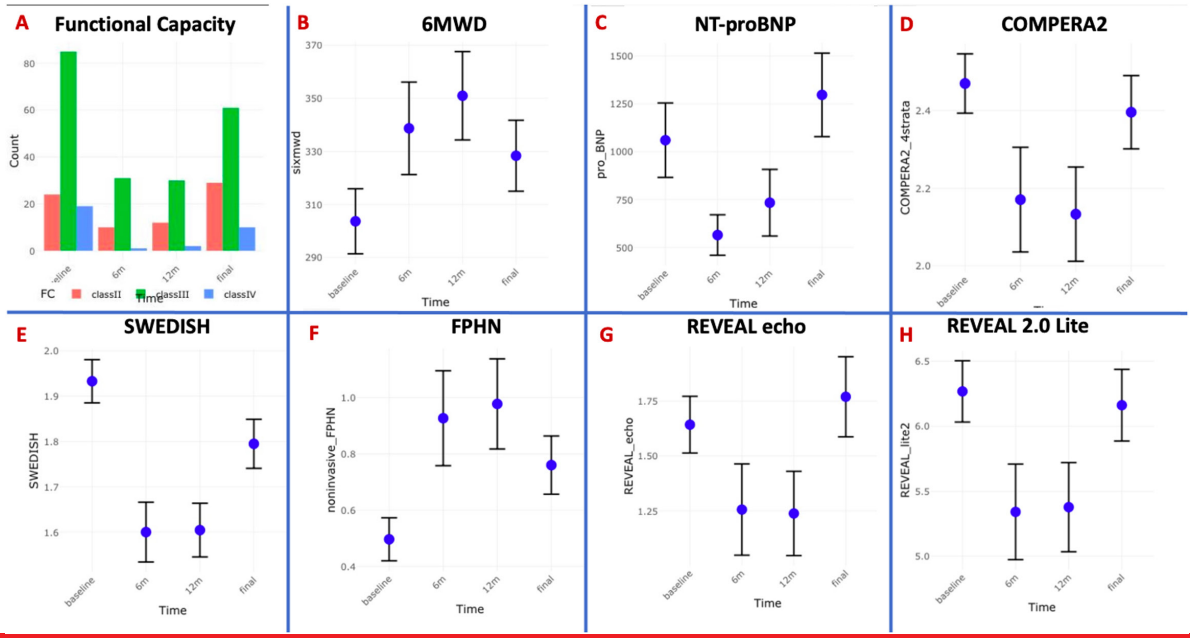



**Supplementary Figure 1.** a. Baseline and follow up bar plot for D-shaped septum. b. Baseline and follow up plot for pulmonary artery diameter. c. Baseline and follow up plot for TAPSE. d. Baseline and follow up plot for RV-TDI. e. Baseline and follow up plot for echocardiography estimated PAPs. f. Baseline and follow up plot for estimated PAMP.




**Supplementary Figure 2.** Baseline and follow-up assessments of clinical and risk parameters: (A) World Health Organization functional class (FC), (B) six-minute walk distance (6MWD), (C) N-terminal pro–brain natriuretic peptide (NT-proBNP), (D) COMPERA risk score, (E) Swedish PAH Registry (SPAHR) risk score, (F) non-invasive FPHN score, (G) REVEAL ECHO score, and (H) REVEAL Lite 2.0 score.