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Disease characteristics, treatments, and outcomes of patients with pulmonary arterial hypertension treated with selexipag in real-world settings from the SPHERE registry (SelexiPag: tHe usErs dRug rEgistry)

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ORIGINAL CLINICAL SCIENCE

Disease characteristics, treatments, and outcomes of patients with pulmonary arterial hypertension treated with selexipag in real-world settings from the SPHERE registry (SelexiPag: tHe usErs dRug rEgistry)

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KEYWORDS:
SPHERE registry;
Selexipag;
PAH;
REVEAL;
Risk assessment

BACKGROUND: Selexipag is an oral prostacyclin receptor agonist, indicated for pulmonary arterial hypertension to delay disease progression and reduce the risk of pulmonary arterial hypertension–related hospitalization. SelexiPag: tHe usErs dRug rEgistry (NCT03278002) was a US-based, prospective, real-world registry of selexipag-treated patients.

METHODS: Adults with pulmonary hypertension (enrolled 2016-2020) prescribed selexipag were followed for ≤18 months, with data collected at routine clinic visits. Patients were defined as newly or previously initiated if they had started selexipag ≤60 days or > 60 days, respectively, before enrollment.

RESULTS: The registry included 829 patients (430 newly initiated, 399 previously initiated; 759 with pulmonary arterial hypertension), of whom 55.6% were World Health Organization functional class (FC) 3/4; 57.3% were intermediate or high risk per Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0. In patients with pulmonary arterial hypertension, 18-month discontinuation rates for adverse events were 22.0%, 32.0%, and 11.9%, and 18-month survival rates were 89.4%, 84.2%, and 94.5% in the overall, newly, and previously initiated patient populations, respectively. From baseline to month 18, most patients had stable or improved FC and stable or improved REVEAL 2.0 risk category status. Discontinuation for adverse events, hospitalization, and survival were similar regardless of patients' individually tolerated selexipag maintenance dose. No new safety signals were identified.

CONCLUSIONS: In this real-world analysis of patients initiating selexipag, most patients had stable or improved FC and REVEAL 2.0 risk category. Similar to the GRIPHON trial, outcomes with selexipag in this real-world study were comparable across maintenance dose strata, with no new safety signals.

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Background

Pulmonary arterial hypertension (PAH) is a progressive disease with high mortality. Although treatment for PAH has substantially improved over the past 2 decades,[1] 1-year mortality is estimated at 8% to 17% and 3-year mortality at 25% to 44%.[2-5] A recent analysis reported lower 5-year mortality in patients receiving triple therapy (9%) compared with those receiving dual or monotherapy (39%),[6] and combination therapy is recommended in current PAH treatment guidelines to achieve low-risk status.[1,7]

Selexipag is an oral, selective prostacyclin (IP) receptor agonist.[1,7] It is approved for use in patients with PAH based on large-scale evidence, including the phase III, placebo-controlled GRIPHON trial, in which selexipag was given in combination with background endothelin receptor antagonist (ERA) or phosphodiesterase 5 inhibitor (PDE5i) therapy or as monotherapy.[8] Selexipag treatment resulted in a 40% reduction in risk of disease progression, regardless of whether it was part of a triple oral therapy regimen, a dual oral therapy regimen, or as monotherapy.[8] The tolerability and safety profile of selexipag in GRIPHON was consistent with the usual profile of drugs targeting the prostacyclin pathway, and adverse events (AEs) were mainly mild to moderate.[8]

Real-world evidence is becoming increasingly important to complement clinical trials; patients treated in real-world settings are by nature more diverse than trial participants.[9-11] Patient registries in PAH provide real-world data on epidemiology, patient demographics, clinical characteristics, treatment practices, and outcomes.[12] SelexiPag: tHe usErs dRug rEgistry (SPHERE) is an observational registry study of patients receiving selexipag in routine clinical practice in the United States. We have previously reported data from the first 500 patients enrolled in SPHERE, describing baseline patient demographics, disease characteristics, concomitant therapy, selexipag dosing regimens and titration, and safety.[13] Here, we report real-world outcomes from SPHERE for the first time, as well as further details of patient demographics and disease characteristics in the entire population of SPHERE.

Methods

The methodology of SPHERE (registered at www.clinicaltrials.gov [NCT03278002]) has been previously described;[13] key features are summarized here. Institutional review board or ethics committee permission, according to local and national regulations, was required for each participating site, and the study complied with the International Society for Heart & Lung Transplantation Ethics statement. Patients provided written informed consent.

Study design, patients, and treatment

SPHERE was a US-based, multicenter, prospective, real-world, observational selexipag drug registry. Adult patients (aged ≥18 years) were enrolled (November 2016 to March 2020); they were followed for up to 18 months.

Selexipag was initiated by the treating physician per routine clinical practice. Details of recommended dosing and titration and maintenance dosing definitions are provided in the Supplementary Methods. Patients were defined as newly initiated if they had started selexipag ≤60 days before enrollment, and patients were defined as previously initiated if they had started selexipag >60 days before enrollment. Patients were excluded if they had previously received selexipag in a clinical trial, previously discontinued selexipag for any reason before study enrollment, or participated in a blinded clinical trial or trial of any unapproved drug. For newly initiated patients, baseline assessments were defined as the first available measurement between the first selexipag dose and enrollment; for previously initiated patients, they were defined as the closest measurement performed around the first selexipag dose. Each patient's 1-year mortality risk category (low, intermediate, and high) was assessed at baseline using the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 risk calculator.[14]

The original protocol planned to enroll 500 patients; it was amended in January 2018 to expand enrollment to 800 patients and to include only newly initiated patients to maintain group size balance between newly and previously initiated patients.

Data collection and analysis

Data were collected using electronic case report forms at enrollment and then every 3 months at routine clinic visits. There were no study-mandated visits or procedures. Data included patient demographics, medical history, disease characteristics, New York Heart Association/World Health Organization (WHO) functional class (FC), prior PAH therapy within 12 months of enrollment or concomitant PAH therapy, selexipag dosing regimens and titration, patient outcomes (discontinuation due to an AE, discontinuation due to an AE related to PAH progression, time to first hospitalization, overall survival), and safety. AEs were collected from enrollment to the last dose of selexipag and coded using the Medical Dictionary for Regulatory Activities. AEs associated with selexipag's mode of action were collected during the titration phase only if they were defined as serious, led to selexipag discontinuation, or reflected an unusual pattern of severity according to investigator judgment. AEs leading to selexipag discontinuation were classified as related or unrelated to PAH progression using Medical Dictionary for Regulatory Activities system organ class and preferred term by medical review. Patients were followed for 18 months or until they died, withdrew consent, or entered a blinded clinical trial or trial of an unapproved drug. Patients who discontinued selexipag were followed for survival only, which was recorded up to 18 months after enrollment regardless of treatment

status. The outcomes analysis focuses mainly on patients with PAH (i.e., WHO Group 1 pulmonary hypertension [PH]).

Statistical considerations

Characteristics of the study population were described using means with standard deviations (SDs), medians with interquartile ranges or ranges (minimum, maximum), counts, or percentages. Analyses of time to discontinuation of selexipag due to an AE, time to first hospitalization, and overall survival are described using the Kaplan-Meier method, with 95% confidence interval calculated using the method of Brookmeyer & Crowley.[15] Analyses were descriptive. As SPHERE was a registry study, missing data were inevitable. No imputation for missing observations was performed.

Results

Patient disposition and baseline demographics in the total PH population

Due to the real-world nature of the study, some patients with WHO Group 2 through Group 5 PH were enrolled (i.e., non-PAH). The study included 829 patients with PH, of whom 430 (51.9%) were newly initiated on selexipag, and 399 (48.1%) were previously initiated (Table S1). Of the 829 patients, 161 (19.4%) discontinued the study. The reasons for discontinuation, including all-cause death, are shown in Figure S1. The median duration of follow-up was 17.8 months.

Most of the 829 patients in the total population had PAH (n = 759), with the most common PAH subtypes being idiopathic PAH (n = 384, 50.6%) and PAH associated with connective tissue disease (n = 205, 27.0%; Table 1). The majority of the PAH study population was female (76.5%), 72.3% were White, and 15.4% were Black or African American. At the time of selexipag initiation, the median age was 61.0 years, and the median body mass index was 28.5 kg/m^2 (Table 1). The median time from PAH diagnosis to selexipag initiation was 2.7 years in the overall population, 2.1 years in the newly initiated population, and 3.5 years in the previously initiated population (Table 1).

Disease characteristics in the PAH population

Of the 759 patients with PAH, the majority (51.0%) were FC 3 at selexipag initiation, with a higher proportion of FC 3 among newly vs previously initiated patients (Table 2). According to REVEAL 2.0, 42.7% were low risk, 30.2% were intermediate risk, and 27.1% were high risk for 1-year mortality (Table 2). Most patients (95%) were taking other PAH-specific medications before selexipag initiation, with approximately half taking dual therapy targeting the endothelin and nitric oxide pathways and one third taking monotherapy, mainly with an ERA or PDE5i (Table 3).

Table 1 Patient Demographics and Disease Characteristics in Patients with PAH

Characteristic	All patients (N = 759)	Newly initiated (n = 387)	Previously initiated (n = 372)
Age at selexipag initiation (years), median (IQR)	61.0 (49.0, 69.0)	62.0 (22.0, 89.0)	59.0 (48.0, 67.0)
Age at PAH diagnosis (years), median (IQR)	55.0 (43.0, 65.0)	57.0 (44.0, 67.0)	54.0 (42.0, 63.0)
Female, n (%)	581 (76.5)	297 (76.7)	284 (76.3)
Race or ethnicity, n (%)			
White	549 (72.3)	268 (69.3)	281 (75.5)
Black or African American	117 (15.4)	65 (16.8)	52 (14.0)
Hispanic	45 (5.9)	21 (5.4)	24 (6.5)
Asian	26 (3.4)	18 (4.7)	8 (2.2)
Native Hawaiian or Other Pacific Islander	3 (0.4)	1 (0.3)	2 (0.5)
American Indian or Alaskan Native	2 (0.3)	2 (0.5)	0
Other	10 (1.3)	8 (2.1)	2 (0.5)
Unknown	7 (0.9)	4 (1.0)	3 (0.8)
BMI at selexipag initiation, n			
Median (IQR), kg/m^2	28.5 (24.5, 34.4)	28.1 (24.5, 34.1)	28.9 (24.6, 34.5)
WHO classification of Group 1 PAH at diagnosis, n (%)			
Idiopathic	384 (50.6)	192 (49.6)	192 (51.6)
Associated			
Connective tissue disease	205 (27.0)	106 (27.4)	99 (26.6)
Congenital heart disease	40 (5.3)	14 (3.6)	26 (7.0)
Portal hypertension	24 (3.2)	13 (3.4)	11 (3.0)
HIV infection	8 (1.1)	5 (1.3)	3 (0.8)
Drug- and toxin-induced	47 (6.2)	28 (7.2)	19 (5.1)
Heritable	15 (2.0)	5 (1.3)	10 (2.7)
Other	29 (3.8)	20 (5.2)	9 (2.4)
Time from PAH diagnosis to selexipag initiation (years), median (IQR)	2.7 (1.1, 6.9)	2.1 (0.8, 5.9)	3.5 (1.4, 7.4)

BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

Selexipag dosing regimen and titration schemes

Among the 759 patients with PAH, the median duration of selexipag titration was 8.1 weeks, with 88.4% of patients (87.3% newly initiated and 89.5% previously initiated) titrating at a weekly dose of < 200 μg twice daily (Table S2). The median maintenance dose was 1,100 μg twice daily (range, 100-3,200 μg; Table S2). In total, 114 (15.0%) patients received a twice-daily maintenance dose of selexipag 200-400 μg, 238 (31.4%) received 600-1,000 μg, 310 (40.8%) received > 1,200 μg, and 97 (12.8%) received a different dose or an unrecorded dose.

Patient outcomes

Most patients with PAH had stable or improved FC vs baseline (68.5% and 20.2%, respectively, to month 6; 65.6% and 22.0% to month 12; and 61.1% and 24.9% to month 18; Tables 2 and 4). REVEAL 2.0 risk category status was also stable or improved in most patients (62.9% and 22.1%, respectively, to month 6; 59.7% and 19.6% to month 12; and 57.2% and 21.3% to month 18; Tables 2 and 4). Similar results were observed in newly and previously initiated patients (Tables 2 and 4). In total, 39.4% of patients with PAH experienced ≥1 hospitalization over 18 months' follow-up (39.7% newly initiated; 39.0% previously initiated; time to first hospitalization is shown in Figure 1A). Patients with PAH at high or intermediate risk according to REVEAL 2.0 were more likely to be hospitalized compared with low-risk patients (Figure 1B). Time to first hospitalization was similar among selexipag maintenance dose strata in patients with PAH (Figure 1C) whether patients received monotherapy, dual therapy, or triple therapy at baseline (Figure 1D). In the total PH population (N = 829), 39.5% experienced ≥1 hospitalization (40.4% newly initiated; 38.6% previously initiated).

In patients with PAH (N = 759), the 12-month and 18-month overall survival rates were 93.4% and 89.4%, respectively (Figure 2A). Patients at high or intermediate risk according to REVEAL 2.0 had poorer overall survival than low-risk patients (Figure 2B). Overall survival was similar between maintenance dose strata and number of baseline PAH therapies (Figure 2C and D). In the total PH population, the estimated overall survival rate at 18 months was 83.8% in newly initiated patients and 94.6% in previously initiated patients.

Safety and persistence to treatment

Among all patients treated with selexipag, the mean (SD) duration of treatment was 18.7 (9.5), 13.1 (6.8), and 24.7 (8.2) months in the overall, newly initiated, and previously initiated groups, respectively. The mean (SD) duration of treatment during the study period was 13.5 (6.3), 12.5 (6.7), and 14.6 (5.5) months, in the 3 groups, respectively. AEs were reported in 71.4% of the overall, 74.7% of the newly initiated, and 67.9% of the previously initiated population (Table 5). Of patients identified as high, intermediate, or low risk at baseline, 79.0%, 71.0%, and 66.8%, respectively, reported ≥1 AE. Higher rates of AEs leading to death, AEs leading to discontinuation, and AEs related to

Table 2 WHO Functional Class and Risk Assessment According to REVEAL 2.0 in Patients With PAH

Classification	All patients (N = 759)	Newly initiated[a] (n = 387)	Previously initiated[b] (n = 372)
WHO functional class			
Baseline			
1	40 (5.3)	22 (5.7)	18 (4.8)
2	224 (29.5)	101 (26.1)	123 (33.1)
3	387 (51.0)	216 (55.8)	171 (46.0)
4	35 (4.6)	17 (4.4)	18 (4.8)
Missing	73 (9.6)	31 (8.0)	42 (11.3)
6 months			
I	28 (3.7)	21 (5.4)	7 (1.9)
II	179 (23.6)	113 (29.2)	66 (17.7)
III	223 (29.4)	147 (38.0)	76 (20.4)
IV	18 (2.4)	13 (3.4)	5 (1.3)
Missing	311 (41.0)	93 (24.0)	218 (58.6)
12 months			
I	29 (3.8)	14 (3.6)	15 (4.0)
II	184 (24.2)	82 (21.2)	102 (27.4)
III	203 (26.7)	93 (24.0)	110 (29.6)
IV	17 (2.2)	11 (2.8)	6 (1.6)
Missing	326 (43.0)	187 (48.3)	139 (37.4)
18 months			
I	29 (3.8)	6 (1.6)	23 (6.2)
II	142 (18.7)	51 (13.2)	91 (24.5)
III	137 (18.1)	45 (11.6)	92 (24.7)
IV	12 (1.6)	4 (1.0)	8 (2.2)
Missing	439 (57.8)	281 (72.6)	158 (42.5)
REVEAL 2.0			
Baseline			
Low risk	324 (42.7)	165 (42.6)	159 (42.7)
Intermediate risk	229 (30.2)	104 (26.9)	125 (33.6)
High risk	206 (27.1)	118 (30.5)	88 (23.7)
6 months			
Low risk	261 (34.4)	155 (40.1)	106 (28.5)
Intermediate risk	172 (22.7)	94 (24.3)	78 (21.0)
High risk	133 (17.5)	97 (25.1)	36 (9.7)
Missing	193 (25.4)	41 (10.6)	152 (40.9)
12 months			
Low risk	237 (31.2)	108 (27.9)	129 (34.7)
Intermediate risk	180 (23.7)	86 (22.2)	94 (25.3)
High risk	129 (17.0)	60 (15.5)	69 (18.5)
Missing	213 (28.1)	133 (34.4)	80 (21.5)
18 months			
Low risk	207 (27.3)	73 (18.9)	134 (36.0)
Intermediate risk	134 (17.7)	52 (13.4)	82 (22.0)
High risk	91 (12.0)	31 (8.0)	60 (16.1)
Missing	327 (43.1)	231 (59.7)	96 (25.8)

PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; WHO, World Health Organization.
Data represent n (%).
[a]For newly initiated patients, baseline assessments were defined as the first available measurement between the first selexipag dose and enrollment.
[b]For previously initiated patients, baseline assessments were defined as the measurement taken at the first selexipag dose.

Table 3 Summary of PAH-Specific Concomitant Medications Used Before Selexipag Initiation in Patients With PAH (WHO Group 1 PH)

Characteristic	All patients (*N* = 759)	Newly initiated (*n* = 387)	Previously initiated (*n* = 372)
Taking any PAH-specific concomitant medication (ERA, sGC, PDE5i, or PGI2)	720 (94.9)	364 (94.1)	356 (95.7)
Monotherapy	234 (30.8)	127 (32.8)	107 (28.8)
ERA	73 (9.6)	41 (10.6)	32 (8.6)
PDE5i	131 (17.3)	67 (17.3)	64 (17.2)
PGI2	13 (1.7)	8 (2.1)	5 (1.3)
sGC	17 (2.2)	11 (2.8)	6 (1.6)
Dual therapy without PGI2	377 (49.7)	192 (49.6)	185 (49.7)
ERA and PDE5i	325 (42.8)	154 (39.8)	171 (46.0)
ERA and sGC	52 (6.9)	38 (9.8)	14 (3.8)
Dual therapy with PGI2	45 (5.9)	18 (4.7)	27 (7.3)
ERA and PGI2	25 (3.3)	12 (3.1)	13 (3.5)
PDE5i and PGI2	19 (2.5)	6 (1.6)	13 (3.5)
PGI2 and sGC	1 (0.1)	0	1 (0.3)
Triple therapy	64 (8.4)	27 (7.0)	37 (9.9)
ERA, PDE5i, and PGI2	60 (7.9)	26 (6.7)	34 (9.1)
ERA, PGI2, and sGC	4 (0.5)	1 (0.3)	3 (0.8)

CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase 5 inhibitor; PAH, pulmonary arterial hypertension; PGI2, prostaglandin I2 (prostacyclin); PH, pulmonary hypertension; sGC, soluble guanylate cyclase.

Data represent *n* (%).

Table 4 Change from Baseline in WHO Functional Class and REVEAL 2.0 Risk Assessment Over the Study Period in the PAH Population

Patients	WHO FC			REVEAL 2.0		
	All patients (*N* = 759)	Newly initiated (*n* = 387)	Previously initiated (*n* = 372)	All patients (*N* = 759)	Newly initiated (*n* = 387)	Previously initiated (*n* = 372)
6 months						
Patients with available data	426	283	143	566	346	220
Improved	86 (20.2)	58 (20.5)	28 (19.6)	125 (22.1)	72 (20.8)	53 (24.1)
Stable	292 (68.5)	195 (68.9)	97 (67.8)	356 (62.9)	218 (63.0)	138 (62.7)
Worsened	48 (11.3)	30 (10.6)	18 (12.6)	85 (15.0)	56 (16.2)	29 (13.2)
12 months						
Patients with available data	410	191	219	546	254	292
Improved	90 (22.0)	46 (24.1)	44 (20.1)	107 (19.6)	46 (18.1)	61 (20.9)
Stable	269 (65.6)	121 (63.4)	148 (67.6)	326 (59.7)	154 (60.6)	172 (58.9)
Worsened	51 (12.4)	24 (12.6)	27 (12.3)	113 (20.7)	54 (21.3)	59 (20.2)
18 months						
Patients with available data	293	100	193	432	156	276
Improved	73 (24.9)	24 (24.0)	49 (25.4)	92 (21.3)	29 (18.6)	63 (22.8)
Stable	179 (61.1)	64 (64.0)	115 (59.6)	247 (57.2)	94 (60.3)	153 (55.4)
Worsened	41 (14.0)	12 (12.0)	29 (15.0)	93 (21.5)	33 (21.2)	60 (21.7)

FC, functional class; NA, not available; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; WHO, World Health Organization.

Data represent *n* or *n* (%).

For newly initiated patients, baseline assessments were defined as the first available measurement between the first selexipag dose and enrollment. For previously initiated patients, baseline assessments were defined as the measurement taken at the first selexipag dose.

Percentages were calculated with the number of patients with available data as denominator.

selexipag leading to discontinuation were seen in newly vs previously initiated patients (Table 5).

For patients with PAH (*N* = 759), 22.0% discontinued selexipag due to an AE over 18 months' follow-up (32.0% newly initiated; 11.9% previously initiated; Figure 3A). Patients with baseline high risk according to REVEAL 2.0 were more likely to discontinue selexipag due to an AE than those with low risk, but there was no difference between intermediate- and low-risk patients (Figure 3B). The rates of discontinuation due to an AE were similar regardless of the number of baseline PAH therapies (Figure 3C). In the total PH population (*N* = 829), at 18 months' follow-up, 22.3% discontinued selexipag due to an AE (32.5% newly initiated; 11.9% previously initiated).

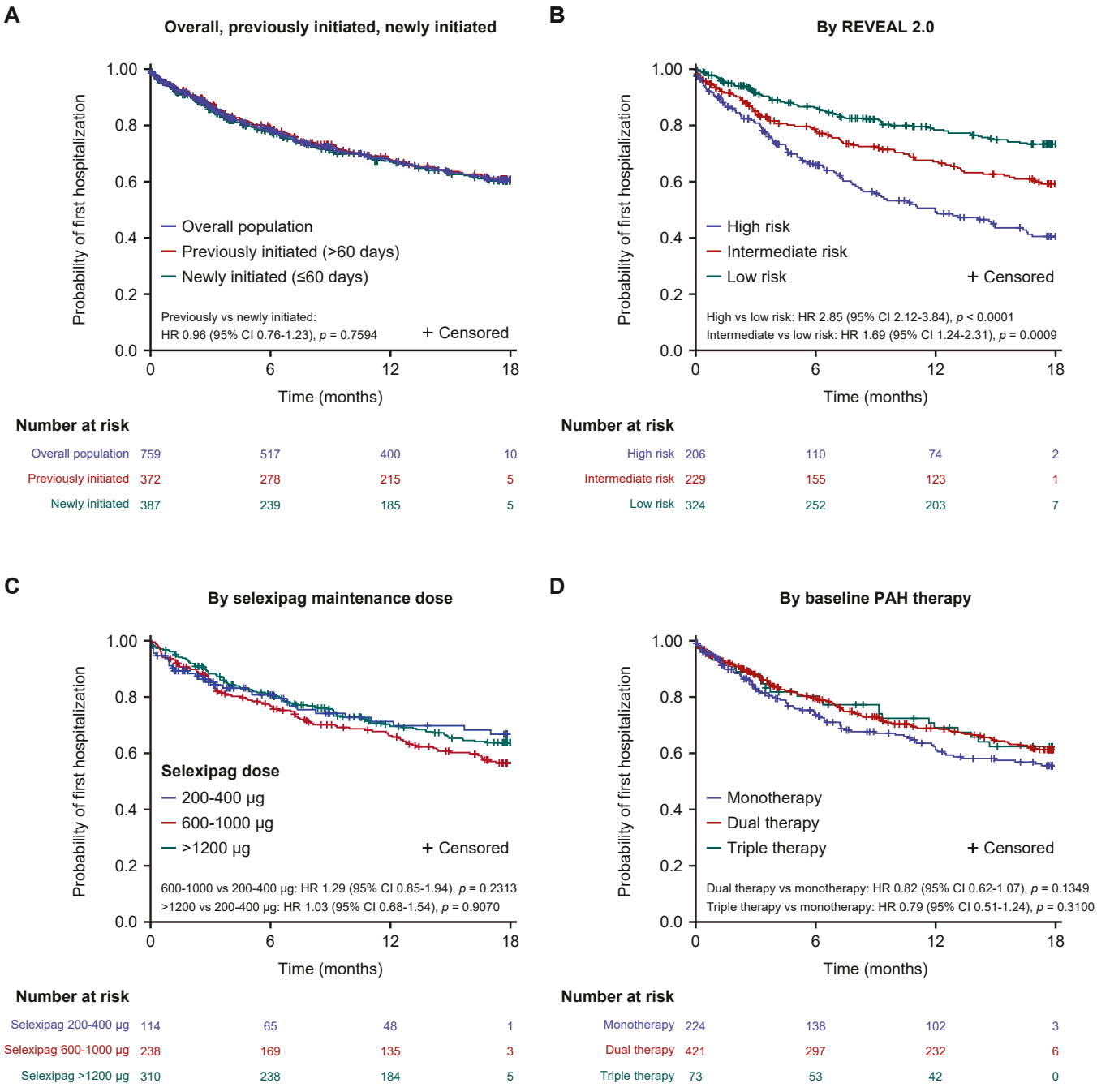

Figure 1 Time to first hospitalization among patients with PAH: (A) overall, previously initiated, newly initiated; (B) stratified by REVEAL 2.0 risk category; (C) stratified by selexipag maintenance dose; (D) stratified by baseline PAH therapy (monotherapy, dual therapy, triple therapy). CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management.

When PAH progression was classified as an AE, discontinuation of selexipag was similar regardless of maintenance dose strata (Figure 3D). Patients with PAH were more likely to discontinue selexipag due to an AE unrelated to PAH progression when receiving a maintenance dose of 200-400 µg (Figure 3E). Newly initiated patients in the low maintenance dose stratum were more likely to discontinue due to an AE unrelated to PAH progression than those in the intermediate or high maintenance dose strata (25.6%, 14.4%, and 6.1%, respectively, at 18 months).

Discussion

In accordance with selexipag's Food and Drug Administration-approved indication, most patients in SPHERE (92%) had PAH; the registry provides the largest real-world evidence data set for patients treated with selexipag in the United States and adds important insights into the use of this therapy in clinical practice in a broader population than evaluated in clinical trials. Seventy patients were enrolled in SPHERE who did not have PAH. It should be noted the clinical efficacy and safety of selexipag have not been established for non-PAH patients, and

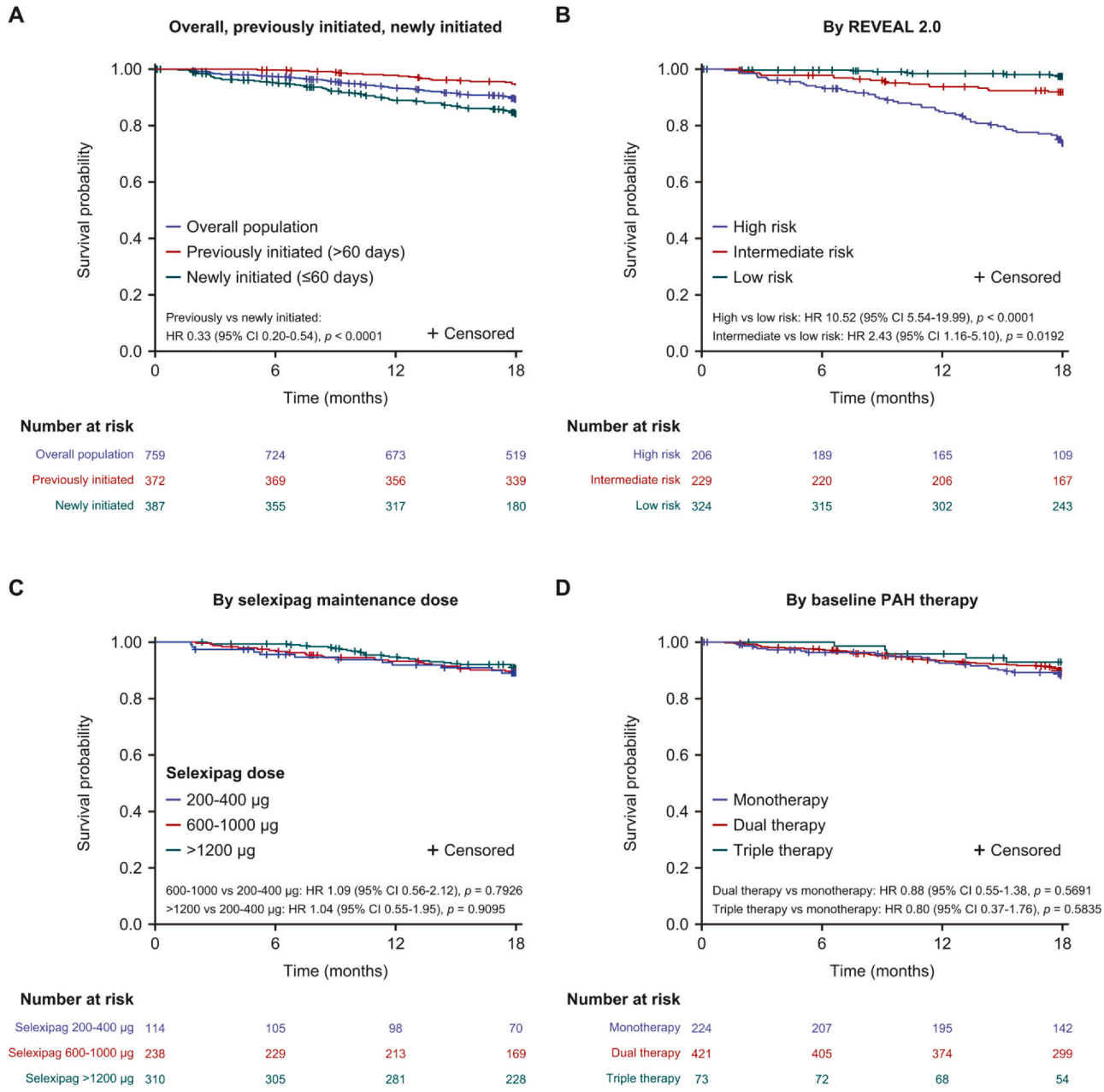

Figure 2 Overall survival among patients with PAH: (A) overall, previously initiated, newly initiated; (B) stratified by REVEAL 2.0 risk category; (C) stratified by selexipag maintenance dose; (D) stratified by baseline PAH therapy (monotherapy, dual therapy, triple therapy). Estimated 12-month overall survival rates were 93.4%, 88.9%, and 97.8% in the overall, newly, and previously initiated patient populations, respectively. Estimated 18-month overall survival rates were 89.4%, 84.2%, and 94.5% in the overall, newly, and previously initiated patient populations, respectively. CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management.

selexipag is not Food and Drug Administration-approved for the treatment of WHO Group 2 to 5 PH.

The patients enrolled in SPHERE were generally representative of patients in PH registries.[6,17-20] Most patients were female, and the average age was 61 years at selexipag initiation (55 years at diagnosis). Other recent registries have also observed that the PAH population is getting older at diagnosis.[6,17,19,20] Approximately half of the patients in SPHERE with PAH had idiopathic PAH, and a quarter had PAH associated with connective tissue disease. At selexipag initiation, approximately half of patients were FC 3 (51%) or 4 (5%)—corresponding values at diagnosis were FC 3 36% and FC 4 6.2%—and over half were classified as intermediate risk (30%) or high risk (27%) by REVEAL 2.0 at baseline. Other real-world studies have also identified a high proportion of patients in FC 3 or 4 at diagnosis: 75% in the French Pulmonary Hypertension Study and 84% of patients in Comparative Prospective Registry of Newly Initiated

Table 5 Overview of AEs in the Total Enrolled Population

AE	All patients ($N = 829$)	Newly initiated ($n = 430$)	Previously initiated ($n = 399$)
Any AE	592 (71.4)	321 (74.7)	271 (67.9)
SAE	304 (36.7)	155 (36.0)	149 (37.3)
AE leading to death	58 (7.0)	36 (8.4)	22 (5.5)
AE leading to hospitalization	287 (34.6)	144 (33.5)	143 (35.8)
AE leading to discontinuation	207 (25.0)	128 (29.8)	79 (19.8)
Related to selexipag	60 (7.2)	48 (11.2)	12 (3.0)
Headache	25 (3.0)	20 (4.7)	5 (1.3)
Diarrhea	14 (1.7)	13 (3.0)	1 (0.3)
Myalgia	14 (1.7)	11 (2.6)	3 (0.8)
Nausea	13 (1.6)	13 (3.0)	0
Arthralgia	6 (0.7)	6 (1.4)	0
Pain in jaw	5 (0.6)	5 (1.2)	0
Related to PAH progression	118 (14.2)	63 (14.7)	55 (13.8)
Pulmonary hypertension	19 (2.3)	11 (2.6)	8 (2.0)
Dyspnea	17 (2.1)	10 (2.3)	7 (1.8)
Right ventricular failure	16 (1.9)	9 (2.1)	7 (1.8)
PAH	14 (1.7)	7 (1.6)	7 (1.8)
Acute respiratory failure	11 (1.3)	7 (1.6)	4 (1.0)
Respiratory failure	7 (0.8)	5 (1.2)	2 (0.5)

AE, adverse event; PAH, pulmonary arterial hypertension; SAE, serious adverse event.

Data represent *n* (%).

Data are shown for patients with ≥1 AE in the category indicated. Individual AEs are included if they occurred in > 1% of patients in any group.

Therapies for Pulmonary Hypertension (COMPERA).[6,19] There have been similar observations in clinical trials; for example, in the TRITON trial, 80% of patients were in FC 3 or 4 at diagnosis,[21] and in the AMBITION trial that included patients in either FC 2 or 3, 69% were in FC 3.[22]

Current guidelines recommend frequent risk assessment of patients with PAH using tools such as WHO FC and REVEAL. Despite this recommendation, at 6 months of follow-up, 41% of patients in SPHERE had no WHO FC assessment, and 25% had no REVEAL risk assessment. Guidelines also follow a trend for increasingly aggressive therapy, recommending initial treatment with dual therapy and increased frequency of follow-up for sequential therapy or treatment escalation.[1] The addition of selexipag has been recommended for appropriate patients with FC 2 or 3 PAH already receiving dual oral therapy with an ERA and a PDE5i; selexipag is also recommended for patients on monotherapy with PDE5i or ERA.[23] SPHERE data indicate that many patients eligible for combination therapy even before initiation of selexipag might not be receiving it; despite the high proportion of patients who were FC 3 or 4, or classified as intermediate or high risk, 31% were receiving monotherapy, and 56% were receiving dual therapy with PAH-specific medications before selexipag initiation. A similar trend was seen in other registry studies. In COMPERA, 80% of patients were receiving monotherapy 3 months after diagnosis despite the high proportion who were FC 3 or 4; 3 years after diagnosis, only half of COMPERA patients were receiving combination therapy.[19] In the French Pulmonary Hypertension Study, 61% of patients initially received monotherapy, 34% received dual therapy, and 5% received triple therapy.[6] Conversely, the UK National Audit of Pulmonary Hypertension (2020-2021) reported that for patients with idiopathic, heritable, or drug-induced PAH without comorbidities, 21% were receiving monotherapy, 50% were receiving dual therapy, and 30% were receiving triple therapy,[24] and almost 70% of patients in Swedish Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension Registry were receiving combination treatment 1 year after diagnosis in 2020.[20]

The findings from SPHERE and other registries described above highlight a potential trend of undertreatment and misalignment between real-world practice and treatment guidelines, despite the widespread recognition that patients who receive early treatment have better outcomes with lower health care costs than those with more advanced disease.[25,26] Indeed, a recent pooled analysis of the GRIPHON and TRITON trials showed that early initiation of selexipag (≤6 months after PAH diagnosis) as part of triple therapy reduced the risk of disease progression by 48% and risk of all-cause death by 30% compared with control.[27] However, a retrospective study of US health care claims data for selexipag showed that most patients had remained on the same therapy the year before starting selexipag, despite high rates of emergency room visits, inpatient admissions, and increasing costs.[28] This underlines the importance of ongoing risk assessment in PAH to allow rapid escalation of therapy before clinical deterioration occurs.[28]

In SPHERE, selexipag was titrated over a median of 8.1 weeks, with almost all patients (88%) titrating more slowly than 200 μg twice daily. A total of 15% of patients received the lowest twice-daily maintenance dose (200-400 μg), 31% received the intermediate dose of 600-1,000 μg, and 41% received ≥1,200 μg. This dose distribution in real-world practice was similar to that in the GRIPHON trial, in which 23% were in the lowest maintenance dose stratum, 31% were in the intermediate dose stratum, and 43% were in the highest dose stratum.[8] Selexipag was well tolerated in SPHERE, and no new safety signals were identified. The most frequent AEs leading to discontinuation and related to selexipag were headache, diarrhea, myalgia, and nausea, which is in line with GRIPHON and the US prescribing information, and consistent with AEs commonly seen with prostacyclin therapy.[8,29] By 18 months, 22% of patients overall had discontinued

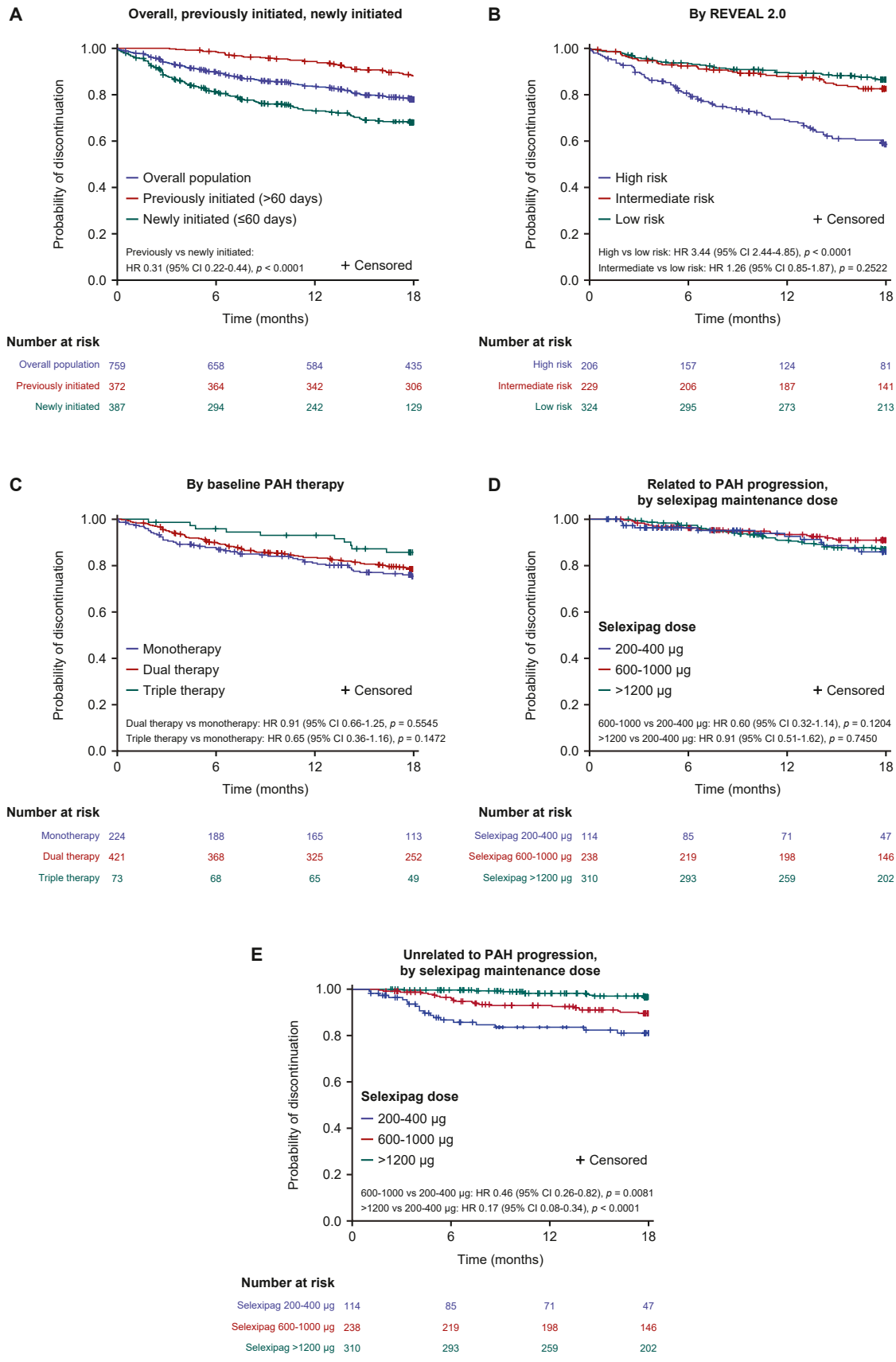

Figure 3 Time to discontinuation of selexipag: (A) due to an AE, overall, previously initiated, newly initiated; (B) due to an AE, stratified by REVEAL 2.0 risk category; (C) due to an AE, stratified by baseline PAH therapy (monotherapy, dual therapy, triple therapy); (D) due to an AE related to PAH progression stratified by selexipag maintenance dose; (E) due to an AE unrelated to PAH progression stratified by selexipag maintenance dose. AE, adverse event; CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management.

selexipag because of an AE, 32% of the newly initiated group, and 12% of the previously initiated group. It was not unexpected that AEs and discontinuations due to AEs were more common among newly than previously initiated patients; this highlights the need for increased patient monitoring and support during early treatment. Patients receiving the lowest maintenance dose (200-400 µg) were more likely to discontinue due to an AE unrelated to PAH progression than those receiving an intermediate or high maintenance dose. This might be because patients on a low maintenance dose were unable to tolerate a higher dose and therefore discontinued selexipag due to an AE rather than disease progression. Patients at high risk at baseline were more likely to discontinue selexipag due to an AE than those at low risk and were also more likely to discontinue due to an AE related to PAH (data not shown).

Current guidelines recommend achievement of low-risk status as a treatment goal. At the end of the SPHERE observation period, 25% and 21% of patients, respectively, had improved FC and REVEAL 2.0 risk status, while 61% and 57%, respectively, had stable FC and REVEAL 2.0 risk status. Although disappointing that not more patients were able to improve their status, this observation likely reflects the undertreatment and misalignment of guidelines and real-world experience, as discussed earlier. Hospitalization and overall survival in SPHERE were similar regardless of maintenance dose, as also observed in GRIPHON,[8] supporting the individualized dosing regimen of selexipag. As anticipated per risk status, patients classified as REVEAL high risk or intermediate risk had an earlier time to first hospitalization and death than low-risk patients. These data concur with a post hoc analysis of GRIPHON, which classified 41%, 26%, and 33% of patients as low, intermediate, and high risk, respectively, according to REVEAL Lite 2, and found that risk category at baseline predicted mortality/morbidity outcomes.[16] Notably, in GRIPHON, selexipag reduced mortality/morbidity compared with placebo regardless of baseline risk category (by 43% for low-, 58% for intermediate-, and 29% for high-risk patients).[16]

The main limitations of SPHERE are related to its observational nature and the potential bias introduced by including previously initiated patients for whom no data were collected between treatment initiation and study enrollment (as described previously[13]). Differences between newly and previously initiated patients (fewer AEs, fewer discontinuations, and longer survival in the previously initiated group) might be related to this survivor bias. However, inclusion of previously initiated patients allowed recruitment of more patients than would have been possible if only newly initiated patients had been included. As a drug registry (rather than a disease registry), SPHERE recruited only patients receiving selexipag, who typically take selexipag as part of a combination therapy regimen. This introduces bias in favor of combination therapy recipients. As with any observational study, missing data can impact interpretation of findings, but incomplete records are reflective of clinical practice. A protocol amendment partway through SPHERE permitted recruitment enhancement for patients newly initiated on selexipag. Thus, the overall study population differs from the first 500 patients previously reported, with approximately 50% of the overall population being newly initiated compared with approximately 30% of the first 500.[13] Nevertheless, patient demographics and disease characteristics were similar in the overall population and the first 500 patients. Due to the real-world nature of the study, patients receiving selexipag who had PH but not PAH also participated; however, for the present analysis, we have focused on patients with PAH.

In conclusion, SPHERE reports the first US-based, real-world outcomes data for selexipag, providing new insights into the clinical characteristics of patients receiving selexipag and the dosing regimens used in routine clinical practice and confirming efficacy across individualized maintenance dose strata as seen in randomized trials. Contemporary guidelines and literature recommend a more aggressive approach to risk assessment and treatment than the real-world experience chronicled in SPHERE. Despite late treatment initiation, outcomes from SPHERE reflect the efficacy and safety observed in selexipag clinical trials, presenting the opportunity to maximize therapy earlier than in current real-world practice and in accordance with guidelines. The results from SPHERE highlight the disconnect between guideline recommendations contemporaneous with SPHERE data collection[30] and real-world clinical practice. This emphasizes a need to address potential barriers to clinical adoption of the current guidelines.[1]

Disclosure statement

The authors have no conflicts of interest to disclose

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Author contributions

The authors confirm contribution to the paper as follows: study conception and design: V.M., H.W.F., K.B.H., A.R.H., M.M.C., K.M.C., N.H.K., M.C.; data collection: M.H., T.T., M.R.; analysis and interpretation of results: M.H., M.C., T.T., M.R.; draft manuscript preparation: M.H.; manuscript review and revision: V.M., H.W.F., K.B.H., A.R.H., M.M.C., K.M.C., N.H.K., M.H., M.C., T.T., M.R. All authors reviewed the results and approved the final version of the manuscript for submission.

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Data statement

The data sharing policy of the sponsor is available at https://www.janssen.com/clinical-trials/transparency. Although these data are not currently publicly available for sharing, requests for sharing can be sent to the corresponding author and will be evaluated on an individual basis.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2023.09.016.

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