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Pulmonary Arterial Hypertension-Related Morbidity Is Prognostic for Mortality

Vallerie V. McLaughlin, MD,[a] Marius M. Hoeper, MD,[b] Richard N. Channick, MD,[c] Kelly M. Chin, MD,[d] Marion Delcroix, MD,[e] Sean Gaine, MD,[f] Hossein-Ardeschir Ghofrani, MD,[g,h] Pavel Jansa, MD,[i] Irene M. Lang, MD,[j] Sanjay Mehta, MD,[k] Tomás Pulido, MD,[l] B.K.S. Sastry, MD,[m] Gérald Simonneau, MD,[n] Olivier Sitbon, MD,[n] Rogério Souza, MD, PhD,[o] Adam Torbicki, MD,[p] Victor F. Tapson, MD,[q] Loïc Perchenet, PhD,[r] Ralph Preiss, MD,[r] Pierre Verweij, PhD,[r] Lewis J. Rubin, MD,[s] Nazzareno Galiè, MD[t]

ABSTRACT

BACKGROUND Registry data suggest that disease progression in pulmonary arterial hypertension (PAH) is indicative of poor prognosis. However, the prognostic relevance of PAH-related morbidity has not been formally evaluated in randomized controlled trials.

OBJECTIVES The purpose of these analyses was to assess the impact of morbidity events on the risk of subsequent mortality using the landmark method and data from the SERAPHIN and GRIPHON studies.

METHODS For each study, the risk of all-cause death up to the end of the study was assessed from the landmark time point (months 3, 6, and 12) according to whether a patient had experienced a primary endpoint morbidity event before the landmark. Each analysis was conducted using data from all patients who were available for survival follow-up at the landmark.

RESULTS In the SERAPHIN study, on the basis of the 3-month landmark time point, patients who experienced a morbidity event before month 3 had an increased risk of death compared with patients who did not (hazard ratio [HR]: 3.39; 95% confidence interval [CI]: 1.94 to 5.92). In the GRIPHON study, on the basis of the 3-month landmark time point, there was also an increased risk with a HR of 4.48; (95% CI: 2.98 to 6.73). Analyses based on 6-month and 12-month landmarks also showed increased risk in patients who experienced morbidity events, albeit with a reduced HR.

CONCLUSIONS These results demonstrate the prognostic relevance of PAH-related morbidity as defined in the SERAPHIN and GRIPHON studies, highlighting the importance of preventing disease progression in patients with PAH and supporting the clinical relevance of SERAPHIN and GRIPHON morbidity events. (Study of Macitentan [ACT-064992] on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension [SERAPHIN]; NCT00660179; Selexipag [ACT-293987] in Pulmonary Arterial Hypertension [GRIPHON]; NCT01106014) (J Am Coll Cardiol 2018;71:752-63) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan; [b]Department of Respiratory Medicine, Hannover Medical School and German Centre for Lung Research, Hannover, Germany; [c]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [d]University of Texas Southwestern, Dallas, Texas; [e]University Hospitals Leuven, Leuven, Belgium; [f]National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin, Ireland; [g]University of Giessen and Marburg Lung Center (UGMLC), Giessen, Germany; [h]Department of Medicine, Imperial College London, London, United Kingdom; [i]Charles University, Prague, Czech Republic; [j]Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Allgemeines Krankenhaus, Vienna, Austria; [k]Respirology Division, London Health Sciences Centre, Western University, London, Ontario, Canada; [l]Cardiopulmonary Department, Ignacio Chávez National Heart Institute, Mexico City, Mexico; [m]CARE Hospitals, Hyderabad, India; [n]Hôpital de Bicêtre, Paris, France; [o]INCOR Heart Institute, University of São Paulo, São Paulo, Brazil; [p]Medical Centre for Postgraduate Education, CMKP European Health Centre, Otwock, Poland;

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Risk assessment plays a key role in the management of progressive diseases such as pulmonary arterial hypertension (PAH) (1). To achieve the best possible outcome for each patient, therapeutic decision making should be driven by the results of regular, multifactorial assessments (2,3). The European Society of Cardiology/European Respiratory Society guidelines recommend classifying patients as low, intermediate, or high risk of death based on a panel of prognostic determinants (2,3). This approach has recently been evaluated by studies from 3 European registries (4–6), which consistently demonstrated that a low-risk profile confers a survival advantage compared with other risk categories. At the same time, these studies showed that deterioration in risk category or individual risk criteria is associated with worse outcomes. A relationship between disease progression and increased risk of death is intuitive and has been observed in clinical practice (7). Moreover, it is supported by a retrospective analysis of data from the REVEAL registry (Registry to Evaluate Early And Long-term PAH Disease Management), which reported that clinical worsening events are prognostic for subsequent mortality (8). However, the prognostic relevance of PAH-related morbidity has not been formally

ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CI = confidence interval

ERA = endothelin receptor antagonist

HR = hazard ratio

PAH = pulmonary arterial hypertension

PDE-5i = phosphodiesterase type-5 inhibitor

WHO FC = World Health Organization functional class

[q]Cedars-Sinai Medical Center, Los Angeles, California; [r]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [s]Division of Pulmonary and Critical Care Medicine, University of California, San Diego Medical School, La Jolla, California; and the [t]Istituto di Malattie dell'Apparato Cardiovascolare, Università di Bologna, Bologna, Italy. Funding was by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. Dr. McLaughlin has received consultancy fees from and served as an advisory board member for Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, Gilead, Ikaria, and United Therapeutics; has served as a steering committee member for Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, and Gilead; has received personal fees from Steadymed Therapeutics and St. Jude Medical; and has received research grants from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, Eiger, Gilead, Ikaria, Novartis, and SoniVie Ltd. Dr. Hoeper has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer; has received consultancy fees from Gilead; and has received research grants from Actelion Pharmaceuticals Ltd. Dr. Channick has served as a steering committee member for Actelion Pharmaceuticals Ltd; has served on an advisory board for Actelion Pharmaceuticals Ltd and Bayer; has received consultancy fees from Bayer; and has received research grants from Actelion Pharmaceuticals Ltd and United Therapeutics. Dr. Chin has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received consultancy fees from Actelion Pharmaceuticals Ltd and United Therapeutics; and has received research grants from Actelion Pharmaceuticals Ltd, Bayer, GeNO, Gilead, NIH, SoniVie Ltd, and United Therapeutics. Dr. Delcroix has served as a steering committee member and has received research grants and consultancy, advisory board, and speaker fees from Actelion Pharmaceuticals Ltd. Dr. Gaine has served as a steering committee member for and has received research grants from Actelion Pharmaceuticals Ltd; has received speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and United Therapeutics; has received advisory board fees from Actelion Pharmaceuticals Ltd, Bayer, Novartis, Pfizer, and Daiichi-Sankyo; and has served on a data and safety monitoring board for GlaxoSmithKline, Novartis, and United Therapeutics. Dr. Ghofrani has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received advisory board and speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Novartis, and Pfizer; has received consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, Bellerophon Pulse Technologies, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Pfizer; and has received research grants from Actelion Pharmaceuticals Ltd and Deutsche Forschungsgemeinschaft. Dr. Jansa has received steering committee fees from Actelion Pharmaceuticals Ltd; has received consultancy and speaker fees from AOP Orphan, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and United Therapeutics; and has received research grants from Actelion Pharmaceuticals Ltd, AOP Orphan, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and United Therapeutics. Dr. Lang has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received speaker fees from Actelion Pharmaceuticals Ltd, Bayer, and GlaxoSmithKline; and has received research grants from Actelion Pharmaceuticals Ltd, AOP Orphan Pharmaceuticals, and Bayer. Dr. Mehta has served on a steering committee for and received advisory board fees from Actelion Pharmaceuticals Ltd; has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, AstraZeneca, and Bayer; and has received research grants from Actelion Pharmaceuticals Ltd, Bayer, Bellerophon, Gilead, Ikaria, Reata, and United Therapeutics. Dr. Pulido has served as a steering committee member for and received advisory board fees from Actelion Pharmaceuticals Ltd; has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, and GlaxoSmithKline; and has received research grants from Actelion Pharmaceuticals Ltd, Bayer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and United Therapeutics. Dr. Sastry has served as a steering committee member for and received research grants and advisory board, speaker and consultancy fees from Actelion Pharmaceuticals Ltd; has received honoraria and research grants from Cipla; and has been an investigator for clinical trials for United Therapeutics. Dr. Simonneau has served as a steering committee member for and received research grants from Actelion Pharmaceuticals Ltd and Bayer; and has received speaker and consultancy fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. Dr. Sitbon has served as a steering committee member for Actelion Pharmaceuticals Ltd; has served as an advisory board member for and received research grants from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena, Bayer, GlaxoSmithKline, Merck Sharp & Dohme, and United Therapeutics; has received speaker fees from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, and United Therapeutics; and has received writing assistance from Actelion Pharmaceuticals Ltd and GlaxoSmithKline. Dr. Souza has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received consultancy and speaker fees from Actelion Pharmaceuticals

evaluated in the setting of a randomized controlled trial.

In recent years, 4 long-term event-driven studies have been conducted in PAH (9-12). The pivotal SERAPHIN (Study of Macitentan [ACT-064992] on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension) and GRIPHON (Selexipag [ACT-293987] in Pulmonary Arterial Hypertension) trials were the largest of these studies and evaluated 742 and 1,156 patients with PAH, respectively, using composite morbidity/mortality endpoints. The SERAPHIN trial evaluated the efficacy and safety of the endothelin receptor antagonist (ERA) macitentan (11), whereas the GRIPHON trial evaluated the oral IP receptor agonist selexipag (10). In both trials, the active treatment significantly reduced the risk of experiencing a primary composite endpoint event of morbidity/mortality compared with placebo. As expected for a progressive disease such as PAH, the majority of events that contributed to the primary endpoints (i.e., first events) were morbidity events, and few patients experienced death as a first event. In the SERAPHIN trial, the vast majority of primary endpoint morbidity events were worsening of PAH (224 events, 96%). In the GRIPHON trial, which captured hospitalization as part of the primary endpoint, the most frequent primary endpoint morbidity events were PAH-related hospitalization (187 events, 53%) and PAH-related disease progression (138 events, 39%) (10,11). In both trials, all patients were followed for vital status until the end of the study.

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The SERAPHIN and GRIPHON studies provide an opportunity to assess the relationship between morbidity and long-term survival in large populations of PAH patients within a controlled setting. The objective of the current analyses was to use the landmark method (13,14) to quantify the prognostic impact of morbidity events on the risk of subsequent mortality in the SERAPHIN and GRIPHON studies.

METHODS

STUDY POPULATIONS. Patients from SERAPHIN and GRIPHON were included in the analyses. The details of the SERAPHIN and GRIPHON trials have been published previously (10,11). Both studies were conducted in accordance with the amended Declaration of Helsinki, and the protocols were reviewed by local institutional review boards with written informed consent obtained from all patients (10,11).

The SERAPHIN trial (NCT00660179) enrolled 742 patients (≥12 years old) with a diagnosis of idiopathic or heritable PAH, or PAH associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, human immunodeficiency virus infection, drug use, or toxin exposure. Patients were randomized 1:1:1 to receive placebo, macitentan 3 mg, or macitentan 10 mg. Patients were permitted to take concomitant medications including an oral phosphodiesterase type-5 inhibitor (PDE-5i), or an oral or inhaled prostanoid, provided that the dosage was stable for ≥3 months before randomization. Patients who had received treatment with an ERA within 3 months before randomization were not eligible. The diagnosis of PAH had to be confirmed by right heart catheterization with a pulmonary vascular resistance ≥320 dyn · s · cm^{-5}, and patients were required to have a 6-min walk distance (6MWD) ≥50 m and to be in World Health Organization functional class (WHO FC) II-IV at baseline (11).

The GRIPHON trial (NCT01106014) enrolled 1,156 patients (18 to 75 years of age) with similar etiologies as were enrolled in the SERAPHIN trial. Patients were

Ltd, Bayer, Bristol-Myers Squibb, Pfizer, and GlaxoSmithKline. Dr. Torbicki has served as a steering committee member for and received research grants and advisory board fees from Actelion Pharmaceuticals Ltd; has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, and Merck Sharp & Dohme; has received speaker fees from Actelion Pharmaceuticals Ltd, AOP, Bayer, and Merck Sharp & Dohme; and has received investigator honoraria from Actelion Pharmaceuticals Ltd, Bayer, Janssen, and United Therapeutics. Dr. Tapson has served as a steering committee member for Actelion Pharmaceuticals Ltd, Bayer, and United Therapeutics; has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, Bayer, Daiichi-Sankyo, EKOS/BTG, Gilead Sciences, Janssen, Reata, and United Therapeutics; has received research grants from Arena Pharmaceuticals, Arena, Bayer, EKOS/BTG, and Riata; has received speaker fees from Bayer, Gilead Sciences, and Janssen. Drs. Perchenet and Preiss are full-time employees of and stockholders in Actelion Pharmaceuticals Ltd. Dr. Verweij was at the time of the submitted work an employee of Actelion Pharmaceuticals Ltd and is now an employee of Idorsia Pharmaceuticals Ltd. Dr. Rubin has served as a steering committee member for Actelion Pharmaceuticals Ltd; and has received consultancy fees from Actelion Pharmaceuticals Ltd, Arena Pharmaceuticals, GeNO Pharmaceuticals, Gilead, Karos Pharmaceuticals, Pfizer, and SoniVie Ltd. Dr. Galiè has served as a steering committee member for Actelion Pharmaceuticals Ltd; has received research grants from Actelion Pharmaceuticals Ltd, Bayer, GlaxoSmithKline, and Pfizer; and has received speaker fees from Merck Sharp & Dohme.

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TABLE 1 Definition of Morbidity Events in SERAPHIN and GRIPHON

SERAPHIN	GRIPHON
Worsening of PAH defined as the occurrence of all 3 of the following: • A decrease in 6MWD of at least 15% from baseline, confirmed by a second 6-min walk test performed on a different day within 2 weeks • Worsening of symptoms of PAH, defined as at least 1 of the following: ▪ A change from baseline to a higher WHO FC (or no change in patients who were in WHO FC IV at baseline) ▪ Appearance or worsening of signs of right heart failure that did not respond to oral diuretic therapy • The need for additional treatment for PAH	Disease progression, defined as both of the following: • A decrease from baseline of at least 15% in the 6MWD (confirmed by means of a second test on a different day) • Worsening in WHO FC (for the patients with WHO FC II or III at baseline) or the need for additional treatment of PAH (for the patients with WHO FC III or IV at baseline)
Initiation of treatment with intravenous or subcutaneous prostanoids	Initiation of parenteral prostanoid therapy or long-term oxygen therapy*
Lung transplantation	Lung transplantation*
Atrial septostomy	Balloon atrial septostomy*
	Hospitalization*

*For worsening PAH.
6MWD = 6-min walk distance; PAH = pulmonary arterial hypertension; WHO FC = World Health Organization functional class.

randomized 1:1 to receive either placebo or selexipag. Patients were permitted to take concomitant medications including an ERA, a PDE-5i, or both, provided the dosage had been stable for ≥3 months before randomization. Patients who were taking prostacyclin analogues were not eligible for the GRIPHON trial. The diagnosis of PAH had to be confirmed by right heart catheterization at any time before screening with a pulmonary vascular resistance ≥400 dyn · sec · cm^{-5}, and patients were required to have a 6MWD of 50 to 450 m at screening (10).

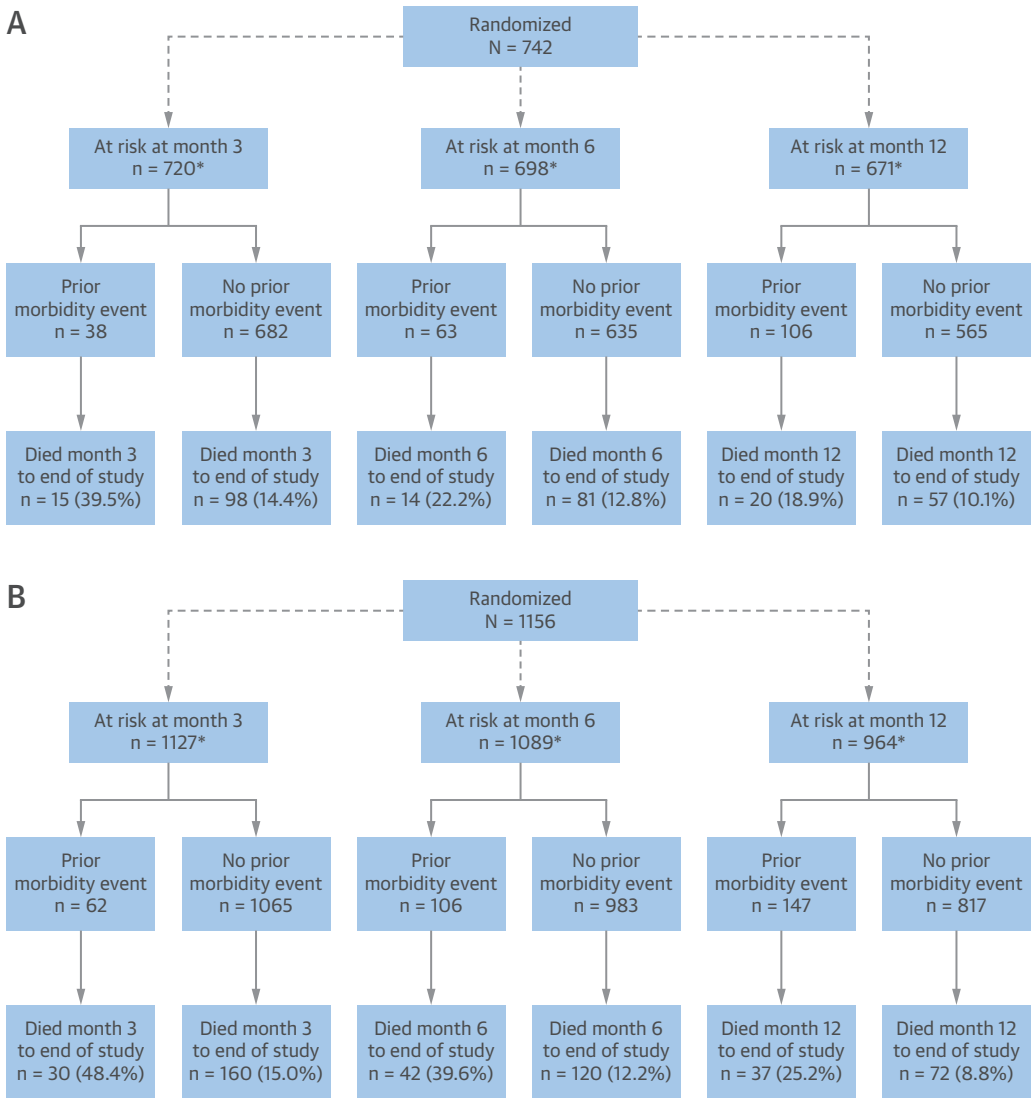
STUDY DESIGN AND OUTCOME MEASURES. The SERAPHIN and GRIPHON studies were global, double-blind, randomized, placebo-controlled, event-driven phase III studies designed to assess the safety and efficacy of macitentan and selexipag, respectively, in patients with PAH (10,11). Both studies used a composite primary endpoint of time to first morbidity or mortality event, and all events were adjudicated by blinded independent critical-event committees. The precise definition of primary-endpoint morbidity events for each of the studies is described in Table 1. The main difference between the studies was the inclusion of hospitalization for worsening of PAH in the GRIPHON trial, but not in the SERAPHIN trial.

In the SERAPHIN and GRIPHON studies, the primary endpoint was time from treatment initiation to first event. Double-blind treatment continued until a patient experienced a primary endpoint event or until premature discontinuation of double-blind treatment (e.g., due to an adverse event) or until the end of the study, which was declared after a pre-specified number of primary endpoint events had occurred. Patients who had a nonfatal primary endpoint event or who received double-blind treatment until the end of the study were eligible to receive the respective open-label investigational therapy or other commercially available PAH therapy.

STATISTICAL ANALYSES. Landmark analysis is the established method for evaluating the effect of morbidity at a particular landmark time point on survival up to the end of the study (13,14). For both the SERAPHIN and GRIPHON trials, landmark survival analyses were performed up to the end of the study, with landmark time points set at 3, 6, and 12 months. Each analysis was conducted using data from patients who were available for survival follow-up at the landmark time point. Patients were not available for the analysis if they had died, had withdrawn consent, or had been lost to follow-up before the landmark. At each landmark time point, patients were grouped according to whether or not they had already experienced a morbidity event (i.e., a nonfatal primary endpoint event) and were followed for all-cause death from the landmark time point until the end of the study. The association between a morbidity event and mortality was evaluated using the Cox regression model, with factors for prior morbidity and treatment group, and illustrated using Kaplan-Meier plots. Patients in the landmark analyses were censored for survival either at the end of the study, or at the last point of contact if patients were lost to follow-up or withdrew consent, whichever occurred first.

Interaction tests were performed to assess potential heterogeneity of the effect of prior morbidity across treatment groups. A significance level of 0.01 was employed for these tests in order to correct for multiple testing. The results for analyses using all

FIGURE 1 Patient Disposition



Patient dispositions from **(A)** SERAPHIN (Study of Macitentan [ACT-064992] on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension) and **(B)** GRIPHON (Selexipag [ACT-293987] in Pulmonary Arterial Hypertension) studies for the months 3, 6 and 12 landmark analyses. *Patients who died or were censored before the time point were excluded. SERAPHIN: 22 at month 3 (13 died, 9 censored), 44 at month 6 (31 died, 13 censored), and 71 at month 12 (49 died, 22 censored); GRIPHON: 29 at month 3 (15 died, 14 censored), 67 at month 6 (43 died, 24 censored), and 192 at month 12 (96 died, 96 censored).

3 landmark time points tested indicated no heterogeneity between the treatment arms in the SERAPHIN trial (month 3 p value for interaction, $p = 0.2971$; month 6 $p = 0.8099$; month 12 $p = 0.2425$) (Online Figure 1a) or the GRIPHON trial (month 3 $p = 0.1486$; month 6 $p = 0.4797$; month 12 $p = 0.1865$) (Online Figure 1b). The lack of heterogeneity allows the treatment groups to be combined for the analyses and increases the sample size. It should be noted that treatment is still included as a factor in the Cox regression model.

Further analyses were performed to investigate the association between the most common individual primary endpoint components (hospitalization for worsening of PAH and PAH-related disease progression) and mortality in the GRIPHON trial. Analyses were not performed on the association between other individual primary endpoint morbidity components

TABLE 2 Baseline Characteristics: SERAPHIN

	Month 3 Landmark		Month 6 Landmark		Month 12 Landmark	
	Prior Morbidity Event (n = 38)	No Prior Morbidity Event (n = 682)	Prior Morbidity Event (n = 63)	No Prior Morbidity Event (n = 635)	Prior Morbidity Event (n = 106)	No Prior Morbidity Event (n = 565)
Female	32 (84.2)	524 (76.8)	53 (84.1)	487 (76.7)	87 (82.1)	436 (77.2)
Age, yrs	50.3 ± 19.8	45.3 ± 15.8	51.2 ± 17.7	45.0 ± 15.8	46.9 ± 18.0	45.1 ± 15.5
Time since PAH diagnosis						
≤6 months	18 (47.4)	167 (24.6)*	26 (41.3)	151 (23.9)†	38 (35.8)	128 (22.7)
>6 months	20 (52.6)	513 (75.4)*	37 (58.7)	482 (76.1)†	68 (64.2)	437 (77.3)
PAH classification						
IPAH, HPAH, HIV, drug/toxin	21 (55.3)	419 (61.6)*	42 (66.7)	390 (61.6)†	77 (72.6)	340 (60.2)
CTD	15 (39.5)	204 (30.0)*	20 (31.7)	188 (29.7)†	26 (24.5)	173 (30.6)
CHD	2 (5.3)	57 (8.4)*	1 (1.6)	55 (8.7)†	3 (2.8)	52 (9.2)
WHO functional class						
I/II	14 (36.8)	368 (54.0)	20 (31.7)	354 (55.7)	34 (32.1)	329 (58.2)
III/IV	24 (63.2)	314 (46.0)	43 (68.3)	281 (44.3)	72 (67.9)	236 (41.8)
6MWD, m	286.5 ± 98.2	365.1 ± 97.1	297.5 ± 94.5	370.0 ± 95.7	312.7 ± 93.7	375.7 ± 94.7
Use of PAH medication						
None	14 (36.8)	243 (35.6)	26 (41.3)	220 (34.6)	43 (40.6)	191 (33.8)
PDE-5i	23 (60.5)	400 (58.7)	36 (57.1)	377 (59.4)	54 (50.9)	345 (61.1)
Oral / inhaled prostanoid	1 (2.6)	16 (2.3)	1 (1.6)	15 (2.4)	3 (2.8)	12 (2.1)
PDE-5i + prostanoid	0	23 (3.4)	0	23 (3.6)	6 (5.7)	17 (3.0)

Values are n (%) or mean ± SD. Baseline characteristics of the cohorts of patients with and without a morbidity event before months 3, 6, and 12 in the SERAPHIN trial. *n = 680. †n = 633.

CHD = congenital heart disease; CTD = connective tissue disease; HIV = human immunodeficiency virus; HPAH = hereditary pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PDE-5i = phosphodiesterase type-5 inhibitor; WHO = World Health Organization; other abbreviations as in Table 1.

because only a small number of these events occurred in the SERAPHIN and GRIPHON trials.

Sensitivity analyses were performed by extending the Cox model to include the baseline characteristics that differed most between patients with and without a prior morbidity event to take potential differences between the groups into account. The associated hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for all 3 landmark time points for both studies.

RESULTS

PATIENT CHARACTERISTICS. In the SERAPHIN study, at the month 3 landmark time point, 720 patients were available for survival follow-up. At the month 6 and month 12 landmark time points, 698 patients and 671 patients were available, respectively (Figure 1A). In the GRIPHON study, the number of patients available for survival follow-up at the month 3, 6, and 12 landmark time points was 1,127, 1,089, and 964, respectively (Figure 1B).

The baseline characteristics of the patients, grouped according to whether or not they had experienced a morbidity event by each landmark time point, are provided in Table 2 (SERAPHIN) and Table 3 (GRIPHON). The patients who experienced a morbidity event tended to be more impaired, with higher WHO FC status and shorter 6MWD, compared with those who did not. The proportion of patients receiving PAH treatment at baseline did not vary greatly between those who did and those who did not experience morbidity events. The proportion of incident patients (enrolled ≤6 months after diagnosis) was greater among those who experienced a morbidity event before the 3-month landmark time point compared with those that did not. This difference dissipated at the later time points.

ASSOCIATION BETWEEN MORBIDITY EVENTS AND MORTALITY IN THE SERAPHIN TRIAL. At all 3 landmark time points, patients with a prior morbidity event had a higher risk of subsequent death. There were 720 patients at risk at the month 3 landmark, and 113 (15.7%) had died by the end of the study. Of the patients who had experienced a morbidity event before the month 3 landmark, 15 (39.5%) died; of those who had not experienced a morbidity event, 98 (14.4%) died (Figure 1A). There was an increased risk of death up to the end of the study for patients who experienced a morbidity event before the month 3 landmark, compared with those who did not (HR: 3.39; 95% CI: 1.94 to 5.92; median follow-up 27 months) (Central Illustration, Figure 2A). An increased risk of death up to the end of the study was also found for patients who experienced a morbidity

TABLE 3 Baseline Characteristics: GRIPHON

	Month 3 Landmark		Month 6 Landmark		Month 12 Landmark	
	Prior Morbidity Event (n = 62)	No Prior Morbidity Event (n = 1,065)	Prior Morbidity Event (n = 106)	No Prior Morbidity Event (n = 983)	Prior Morbidity Event (n = 147)	No Prior Morbidity Event (n = 817)
Female	47 (75.8)	852 (80.0)	87 (82.1)	790 (80.4)	123 (83.7)	662 (81.0)
Age, yrs	49.5 ± 15.4	48.0 ± 15.3	48.4 ± 15.9	48.0 ± 15.2	46.6 ± 15.9	48.1 ± 15.0
Time since PAH diagnosis						
≤6 months	28 (45.2)	362 (34.0)	43 (40.6)	330 (33.6)	59 (40.1)	269 (32.9)
>6 months	34 (54.8)	703 (66.0)	63 (59.4)	653 (66.4)	88 (59.9)	548 (67.1)
PAH classification						
IPAH, HPAH, HIV, drug/toxin	37 (59.7)	659 (61.9)	66 (62.3)	606 (61.6)	94 (63.9)	498 (61.0)
CTD	23 (37.1)	299 (28.1)	36 (34.0)	276 (28.1)	42 (28.6)	232 (28.4)
CHD	2 (3.2)	107 (10.0)	4 (3.8)	101 (10.3)	11 (7.5)	87 (10.6)
WHO functional class						
I/II	12 (19.4)	514 (48.3)	23 (21.7)	493 (50.2)	42 (28.6)	431 (52.8)
III/IV	50 (80.6)	551 (51.7)	83 (78.3)	490 (49.8)	105 (71.4)	386 (47.2)
6MWD, ms	287.6 ± 87.6	358.7 ± 76.5	310.9 ± 88.8	362.1 ± 74.0	333.1 ± 80.2	364.6 ± 72.8
Use of PAH medication						
None	17 (27.4)	208 (19.5)	19 (17.9)	195 (19.8)	28 (19.0)	164 (20.1)
ERA	7 (11.3)	158 (14.8)	17 (16.0)	143 (14.5)	19 (12.9)	122 (14.9)
PDE-5i	21 (33.9)	345 (32.4)	40 (37.7)	315 (32.0)	46 (31.3)	270 (33.0)
ERA plus PDE-5i	17 (27.4)	354 (33.2)	30 (28.3)	330 (33.6)	54 (36.7)	261 (31.9)

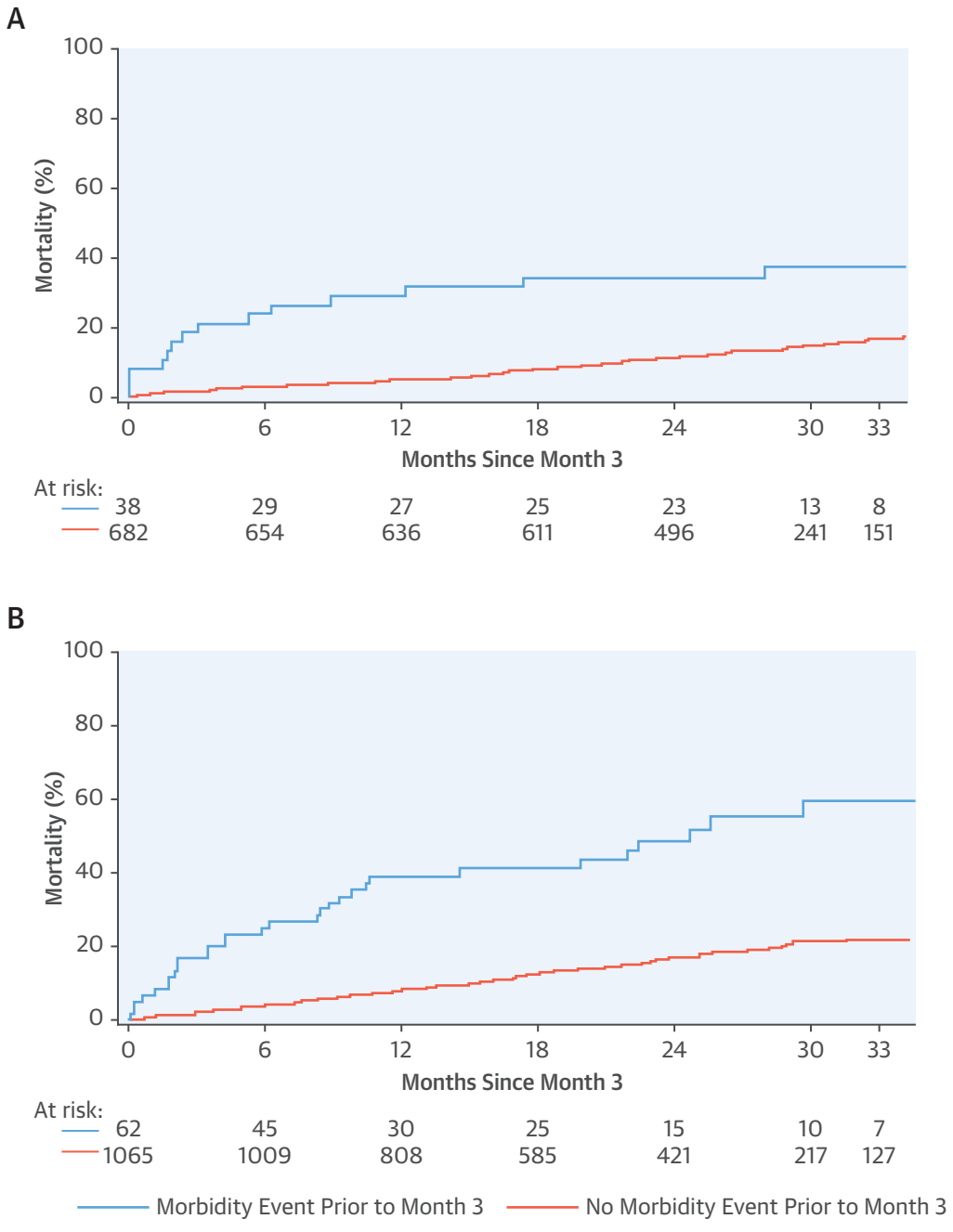
Values are n (%) or mean ± SD. Baseline characteristics of the cohorts of patients with and without a morbidity event before months 3, 6, and 12 in the GRIPHON trial.
ERA = endothelin receptor antagonist; other abbreviations as in Tables 1 and 2.

event before month 6 (HR: 1.84; 95% CI: 1.02 to 3.29; median follow-up 24 months) or month 12 (HR: 1.98; 95% CI: 1.17 to 3.35; median follow-up 19 months) compared with those who did not (**Figure 2A,** Online Figures 2A and 3A). The results of the sensitivity analyses that adjusted for baseline differences in WHO FC and 6MWD were consistent with the main analyses (**Table 4**).

ASSOCIATION BETWEEN MORBIDITY EVENTS AND MORTALITY IN THE GRIPHON TRIAL. Similar to the preceding results, in the GRIPHON trial at all 3 landmark time points, patients who had experienced a prior morbidity event had a higher subsequent risk of death. There were 1,127 patients at risk at the month 3 landmark time point, and 190 (16.9%) had died by the end of the study. Of the patients who had experienced a morbidity event before the month 3 landmark, 30 (48.4%) died; of those who had not experienced a morbidity event, 160 (15.0%) died (**Figure 1B**). There was an increased risk of death up to the end of the study for patients who experienced a morbidity event before month 3, compared with those who did not (HR: 4.48; 95% CI: 2.98 to 6.73; median follow-up 20 months) (**Central Illustration, Figure 2B**). An increased risk of death was also seen for patients who experienced a morbidity event before month 6 (HR: 4.10; 95% CI: 2.86 to 5.87; median follow-up 18 months); and month 12 (HR: 3.52; 95% CI: 2.34 to 5.31; median follow-up 14 months) compared with those who did not (**Figure 2B,** Online Figures 2B and 3B). The results of the sensitivity analyses that adjusted for baseline differences in WHO FC and 6MWD were consistent with the main analyses (**Table 4**).

In the GRIPHON trial, the number of events of hospitalization for worsening of PAH and PAH-related disease progression was sufficient to allow the association between these individual primary endpoint morbidity events and mortality to be evaluated. For the analyses with a month 3 landmark time point, we observed an increased risk of death up to the end of the study among patients who experienced a primary endpoint event of hospitalization for worsening of PAH compared with those who did not (HR: 6.55; 95% CI: 4.02 to 10.67) and an increased risk of death up to the end of the study among patients who experienced a primary endpoint event of disease progression compared with those who did not (HR: 2.38; 95% CI: 1.25 to 4.54). The increased risk of mortality among patients who experienced these individual events was also evident in analyses with a month 6 landmark (hospitalization due to PAH HR: 3.77; 95% CI: 2.35 to 6.04, and disease progression HR: 3.26; 95% CI: 2.02 to 5.25), and with a month 12 landmark (hospitalization due to PAH HR: 3.25; 95% CI: 1.94 to 5.44, and disease progression HR: 2.56; 95% CI: 1.49 to 4.40) (**Figure 3**).

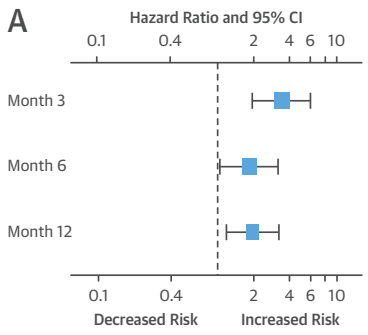
CENTRAL ILLUSTRATION **Association Between Morbidity Before Month 3 and Mortality in SERAPHIN and GRIPHON**



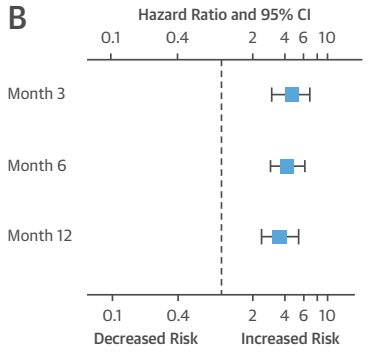
McLaughlin, V.V. et al. J Am Coll Cardiol. 2018;71(7):752–63.

Kaplan-Meier estimates for all-cause mortality up to the end of the study for patients with a morbidity event before month 3 versus patients without a morbidity event before month 3 in **(A)** SERAPHIN (HR: 3.39; 95% CI: 1.94 to 5.92) and **(B)** GRIPHON (HR: 4.48; 95% CI: 2.98 to 6.73) studies. CI = confidence interval; HR = hazard ratio.

FIGURE 2 Association Between Morbidity and Mortality in SERAPHIN and GRIPHON



	HR	95% CI	Prior Morbidity Event		No Prior Morbidity Event	
			Patients	Events	Patients	Events
Month 3	3.39	1.94-5.92	38	15	682	98
Month 6	1.84	1.02-3.29	63	14	635	81
Month 12	1.98	1.17-3.35	106	20	565	57



	HR	95% CI	Prior Morbidity Event		No Prior Morbidity Event	
			Patients	Events	Patients	Events
Month 3	4.48	2.98-6.73	62	30	1065	160
Month 6	4.10	2.86-5.87	106	42	983	120
Month 12	3.52	2.34-5.31	147	37	817	72

Hazard ratios for all-cause mortality up to the end of the study for patients with a morbidity event before months 3, 6 or 12 versus patients without a prior morbidity event in **(A)** SERAPHIN and **(B)** GRIPHON studies. CI = confidence interval; HR = hazard ratio.

DISCUSSION

Over the past 2 decades, PAH trials have evolved from short-term studies evaluating changes in exercise capacity to long-term studies investigating composite endpoints that capture morbidity and mortality events. Where assessing effects on mortality in a randomized controlled trial setting is not feasible, these composite endpoints offer a reasonable alternative for evaluating treatments for PAH patients. Importantly, the morbidity components of these composite endpoints have been extensively discussed and carefully defined (15-17). The robustness of these composite endpoints is further ensured by the adjudication of events by an independent committee of experienced physicians. Although much effort has been made to ensure the robustness and clinical relevance of these endpoints, formal association between the morbidity events captured by these endpoints and mortality were lacking. Our analyses indicate that morbidity, as captured in the primary endpoint events of the SERAPHIN and GRIPHON studies, is prognostic for mortality. These findings are strengthened by consistent results in 2 independent studies and at 3 different landmark time points within each of the studies. The analyses of the GRIPHON data also highlight the relevance of hospitalization for worsening of PAH as a risk factor for subsequent mortality.

Landmark analyses assess the association of an event before a landmark time point with events that occur subsequent to that time point, in this instance the association between morbidity and subsequent mortality. The nature of the analyses involves a compromise between the occurrence of the former and the latter events at each landmark time point. At earlier landmark time points, few morbidity events have occurred; however, a large number of patients are at risk of mortality and are therefore included in the analyses. Analyses at later landmark time points capture a greater number of morbidity events, but include fewer patients overall. We performed

analyses using landmark time points of month 3, month 6, and month 12. At each landmark time point, there may be different contributing factors that influence the risk of morbidity or mortality and the interpretation of the results. For the analyses with a month 3 landmark time point, ≥97% of the randomized patients from each trial were available for survival follow-up. Because very few patients were excluded, the month 3 analysis populations are more representative of the overall study populations compared with the populations available for analysis at later landmark time points. However, the month 3 landmark analyses may be impacted by the heterogeneity of the population, encompassing the inclusion of both incident and prevalent patients, and more pronounced differences in baseline characteristics between the cohorts with and without a prior morbidity event. By contrast, the month 12 landmark analyses included only prevalent patients and the differences in baseline characteristics between the cohorts were less pronounced compared with earlier time points. These nuances should be considered when interpreting the results at different time points and are likely contributing factors to the numerically smaller hazard ratios observed using later landmark time points compared with the earlier time points.

Overall, the consistent findings observed across 2 independent studies and at 3 time points per study, even after adjusting for differences in WHO FC and 6MWD at baseline, provide strong evidence for the prognostic relevance of the morbidity events captured in these studies. These findings are in line with observations made within the REVEAL registry, which indicate that clinical worsening, defined as the occurrence of either worsening WHO FC, a reduction in 6MWD, all-cause hospitalization or the initiation of a parenteral prostacyclin analogue, is associated with worse outcome (8). In the SERAPHIN and GRIPHON studies, the 1-year mortality rates for patients who

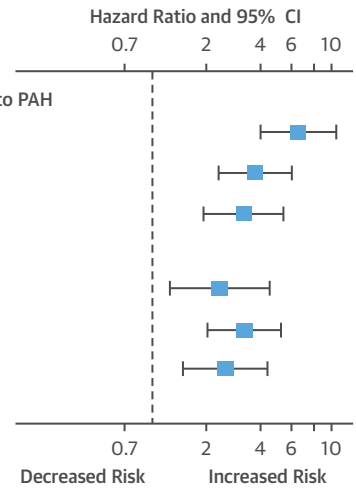
TABLE 4 Sensitivity Analyses of the Association Between Morbidity and Mortality in SERAPHIN and GRIPHON

	Morbidity Event vs. No Prior Morbidity Event		
	Month 3	Month 6	Month 12
SERAPHIN			
Main analysis	3.39 (1.94–5.92)	1.84 (1.02–3.29)	1.98 (1.17–3.35)
Sensitivity analysis	2.29 (1.30–4.05)	1.24 (0.68–2.26)	1.52 (0.89–2.61)
GRIPHON			
Main analysis	4.48 (2.98–6.73)	4.10 (2.86–5.87)	3.52 (2.34–5.31)
Sensitivity analysis	3.05 (2.01–4.61)	3.03 (2.09–4.40)	2.87 (1.89–4.37)

Values are hazard ratio (95% confidence interval). Hazard ratios for all-cause mortality up to the end of the study for patients with a morbidity event before months 3, 6, or 12 versus patients without a prior morbidity event after adjustment for treatment group (main analysis) or treatment group, 6MWD and WHO FC (sensitivity analysis) in a Cox regression model in the SERAPHIN and GRIPHON studies.

Abbreviations as in Table 1.

FIGURE 3 Association Between Individual Morbidity Components and Mortality in GRIPHON



	HR	95% CI	Prior Morbidity Event		No Prior Morbidity Event	
			Patients	Events	Patients	Events
Hospitalization Due to PAH						
Month 3	6.55	4.02-10.67	30	19	1097	171
Month 6	3.77	2.35-6.04	49	20	1040	142
Month 12	3.25	1.94-5.44	65	18	899	91
Disease Progression						
Month 3	2.38	1.25-4.54	28	10	1099	180
Month 6	3.26	2.02-5.25	52	20	1037	142
Month 12	2.56	1.49-4.40	68	16	896	93

Hazard ratios for all-cause mortality up to the end of the study for patients with an event of hospitalization due to PAH worsening or PAH-related disease progression before months 3, 6, and 12 versus patients without a prior event. PAH = pulmonary arterial hypertension; other abbreviations as in Figure 2.

experienced a morbidity event before month 3 were approximately 30% and 40% and are considerably higher than the estimated 1-year mortality rate (>10%) for patients classified as high risk according to the European Society of Cardiology/European Respiratory Society guidelines (2,3). These data further support the prognostic value of PAH-related morbidity events, and suggest that such events should be considered in the risk assessment of patients with PAH.

Current guidelines recommend monotherapy or dual oral combination therapy in newly diagnosed patients with characteristics indicative of low or intermediate risk of 1-year mortality, and suggest escalation of therapy in patients with an inadequate clinical response to this initial therapy (2,3). In the setting of 2 randomized controlled trials that enrolled many patients who were receiving a stable dose of 1 or more PAH medications (SERAPHIN trial 64%; GRIPHON trial 80%), our analyses show that morbidity events that occur early are associated with an increased risk of death. These results highlight that preventing morbidity events is of the utmost importance for patients with PAH, and suggest that an intensive approach to treatment may be warranted. Our results are complemented by the accumulating evidence supporting the use of combination therapy in patients with PAH (10–12,18).

In addition to the clinical and therapeutic implications outlined above, our findings may have an impact on the future design of clinical trials in PAH. Large and long-term clinical trials are required to provide sufficient statistical power to detect a survival benefit, and such a trial is unlikely to be feasible in PAH. Furthermore, assessment of mortality may be affected by patients receiving additional therapies or crossing over to an investigational therapy in the event of clinical deterioration. The association between morbidity events and mortality reported in these analyses, although not a validation of morbidity as a surrogate endpoint for determining a survival benefit, indicate that morbidity events, as defined in the SERAPHIN and GRIPHON trials, are clinically meaningful and indicative of an increased risk of mortality. These analyses may have a bearing on the duration of future clinical trials, and the relative requirement of long-term, event-driven trials compared with shorter, time to clinical worsening studies. Naturally, consideration must also be given to the need for long-term assessment of safety and persistent efficacy. The evaluations presented here, and the strength of the association between morbidity events and subsequent mortality, may influence statistical assumptions made in future clinical trials in PAH.

STUDY LIMITATIONS. A limitation of these evaluations is the post hoc nature of the analyses. Whereas the morbidity events were pre-specified as part of the primary endpoints and were independently adjudicated, the landmark time points were not pre-specified. The consistency of the results in 2 independent studies, and irrespective of the landmark time point used, to an extent mitigates the post hoc selection of the landmark time points. In addition, because the studies' primary endpoints capture only PAH-related morbidity, our analyses did not evaluate the association between non-PAH-related morbidity and mortality in this population.

CONCLUSIONS

Morbidity events, as defined in the SERAPHIN and GRIPHON studies, were prognostic for mortality in patients with PAH. These results highlight the risk associated with disease progression in PAH and emphasize that treatment regimens and management strategies that prevent deterioration are essential. In addition, our findings support the robustness and the clinical relevance of the SERAPHIN and GRIPHON primary endpoints.

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ADDRESS FOR CORRESPONDENCE: Dr. Vallerie V. McLaughlin, Department of Internal Medicine, University of Michigan Health System, 1500 East Medical Center Drive, SPC 5853, Ann Arbor, Michigan. E-mail: vmclaugh@med.umich.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PAH-related morbidity, as defined by specific criteria, is prognostic for survival. Preventing disease progression is of the utmost importance for patients with PAH, and an intensive approach to treatment may be warranted.

TRANSLATIONAL OUTLOOK: The strength of the association between defined PAH-related morbidity events and subsequent mortality may influence statistical assumptions made in future clinical trials in PAH.

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KEY WORDS disease progression, GRIPHON, landmark analysis, SERAPHIN, survival

APPENDIX For supplemental figures, please see the online version of this paper.