


# Congruency between clinician-assessed risk and calculated risk of 1-year mortality in patients with pulmonary arterial hypertension: A retrospective chart review

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## Abstract

The objective of this analysis was to compare clinician-based and formally calculated risk assessments by REVEAL Lite 2 and COMPERA 2.0 and to characterize parenteral prostacyclin utilization within 90 days of baseline in high-risk patients. A multisite, double-blind, retrospective chart review of patients with pulmonary arterial hypertension (PAH) was conducted with an index period of January 2014–March 2017. Patients were categorized into the “any PAH medication” or “prostacyclin-enriched” cohort based on latest PAH medication initiated within the index period. Clinicians classified the patient’s 1-year mortality risk as “low,” “intermediate,” or “high” based on their clinical assessment. REVEAL Lite 2 and COMPERA 2.0 scores were independently calculated. Risk assessment congruency was evaluated. Parenteral prostacyclin use was evaluated within 90 days of baseline. Thirty-two clinicians participated and abstracted data for 299 patients with PAH. At baseline, mean patient age was 52 years, 6-min walk distance was 226 m, and most patients were WHO functional class II or III. Half of the patients (53%) were classified by clinician assessment as intermediate risk, while most were classified as high risk by REVEAL Lite 2 (59%) and intermediate-high risk by COMPERA 2.0 (52%). Parenteral prostacyclins were underutilized in high-risk patients, and not initiated in a timely fashion. Clinician-assessed risk category was incongruent with tool-based risk assessments in 40%–54% of patients with PAH, suggesting an underestimation of the patient’s risk category by clinician gestalt. Additionally, there was a lack of timely prostacyclin initiation for patients with PAH stratified as high-risk by either tool.

## KEYWORDS

COMPERA, prostacyclin, REVEAL Lite 2, risk assessment, treprostinil

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive, incurable disease that leads to right heart failure and often death.<sup>1</sup> After diagnosis of PAH, the median overall transplant-free survival is 6.2 years.<sup>2</sup> To aid in guiding treatment decisions that can affect long-term outcomes, individuals with PAH are stratified by disease characteristics that predict risk of 1-year mortality.<sup>3–5</sup>

Multiparametric tools, such as REVEAL Lite 2 risk calculator, have been developed to aid with risk stratification and include subjective and objective measurements.<sup>6</sup> Another risk tool, COMPERA 2.0, assigns an integer score to cut-off values for three disease variables, and then stratifies patients into one of four risk groups.<sup>7</sup> These tools allow for a risk-based, goal-oriented treatment approach, where achieving or maintaining a low-risk status is recommended.<sup>4</sup>

The uptake of PAH risk assessment tools has been modest in clinical practice, with studies indicating that only about half of healthcare providers report using these tools routinely.<sup>8,9</sup> Without implementing a risk assessment tool, clinicians could misjudge the patient's actual risk profile, which can lead to suboptimal management of PAH.<sup>10</sup>

Prostacyclin-class therapy has been a key treatment for PAH due to the hallmark downregulation of the prostacyclin pathway in PAH.<sup>11</sup> Parenteral prostacyclin therapy may modify the disease pathophysiology and improve right heart structure and function, and is recommended as the treatment of choice for patients at high risk of mortality or with rapidly progressing PAH.<sup>3,4,12</sup> However, previous research has highlighted that parenteral prostacyclin therapy is underutilized, even in patients with more severe disease.<sup>13,14</sup>

Here, we conducted a multicenter, double-blind, retrospective chart review of patients with PAH treated in the United States. The objectives of this analysis were (1) to compare clinician-based risk assessment to calculated REVEAL Lite 2 and COMPERA 2.0 risk assessments and (2) to characterize parenteral prostacyclin utilization within 90 days of baseline visit among patients classified as high risk by REVEAL Lite 2 and COMPERA 2.0.

## METHODS

### Study design

A multisite, double-blind, retrospective chart review of patients with PAH treated in the United States was conducted in 2019–2020 by surveying PAH-treating clinicians who treated at least 15 patients with PAH during the index period of January 2014–March 2017. The New England Independent Review Board approved the research, and a waiver of documentation of informed consent was obtained.

Thirty-two clinicians were recruited for study participation. Once qualified to participate, clinicians and the assigned staff from each study site were provided with specific written instructions for the study, including patient selection criteria, rules and guidelines for randomly selecting and identifying patient charts, chart data abstraction, and data collection procedures. Each participating investigator completed a practice profile form to gather characteristics of clinicians.

Retrospective chart data were collected by investigators or their designee and abstracted directly from patient medical records via an electronic case report form, and a database was subsequently created. All data transferred to the sponsor/sponsor's representatives was deidentified and complied with the Health Insurance Portability and Privacy Act of 1996. Clinicians were instructed to assign and maintain a synthetic identifier for each patient record enrolled in the study that was to be used only for data validation and queries.

### Patient eligibility criteria

Patients were randomly selected if they met the 5th World Symposium on Pulmonary Hypertension diagnostic criteria of PAH (mean pulmonary arterial pressure  $\geq 25$  mmHg, pulmonary artery wedge pressure  $\leq 15$  mmHg, pulmonary vascular resistance  $> 3$  Wood units)<sup>15</sup>; began at least one FDA-approved PAH treatment during the index period (January 2014–March 2017); were  $\geq 18$  years of age at initial PAH diagnosis; had assessments at baseline and at least one follow-up visit for: N-terminal pro-B-type natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP), World Health Organization (WHO) functional class, and 6-min walk distance (6MWD); and were not enrolled in any PAH-related interventional clinical trial since the time of baseline assessments. Patients with sickle cell, sarcoidosis, CTEPH, and sleep apnea were excluded from this analysis. Baseline visit was defined as the most recent assessment before latest treatment initiation within the index period (January 2014–March 2017). Diagnosis was defined as the time of the patient's initial PAH diagnosis.

A two-cohort study design was used to support data collection: (1) "Any PAH medication" cohort: a randomly selected cohort consisting of a sample of approximately 200 patients with PAH who met inclusion and exclusion criteria and started any PAH medication as the latest therapy initiated during the index period (including prostacyclins); (2) "Prostacyclin-enriched" cohort: consisted of an oversample of approximately 100–125 patients with PAH who met inclusion criteria and were treated with a prostacyclin-class agent (by any route of administration) as the latest therapy initiated

during the index period and which continued for  $\geq 90$  days.

## Risk assessment methodology

At the time of chart abstraction, clinicians were asked to classify the patient's risk of death in 1 year as "low," "intermediate," or "high" at baseline based on their clinical assessment. Subsequently, the REVEAL Lite 2 and COMPERA 2.0 scores were independently calculated by healthcare providers for each patient using data from the baseline visit. REVEAL Lite 2 calculates a patient's risk score based on: WHO functional class, systolic blood pressure, heart rate, 6MWD, BNP or NT-proBNP, and renal insufficiency (by estimated glomerular filtration rate). Patients were assigned to low- ( $\leq 5$  points), intermediate- (6 to 7 points), or high-risk ( $\geq 8$  points) groups.<sup>6</sup> COMPERA 2.0 calculates a patient's risk score based on: WHO functional class, 6MWD, and BNP or NT-proBNP, giving a value of 1 to 4 for each variable based on prespecified cut points. Scores across the four variables were averaged, and patients were assigned to a risk category based on their average score: low risk  $< 1.5$ , intermediate-low risk = 1.5 to 2.49, intermediate-high risk = 2.5 to 3.49, or high risk  $\geq 3.5$ .<sup>7</sup>

For patients classified as high risk by REVEAL Lite 2 or high/intermediate-high risk for COMPERA 2.0, initiation of prostacyclin therapy within 90 days following baseline visit was then assessed in the two cohorts ("any PAH medication" vs. "prostacyclin-enriched") to understand the timing of prostacyclin treatment initiation. PAH-specific treatments are described at and after baseline. At least 1 day of prostacyclin therapy needed to fall within the first 90 days after baseline, and prostacyclin therapy must have continued for  $\geq 90$  days (per cohort definition above).

## Data analyses

For each patient, congruency of risk assessment was evaluated between clinician assessment and independent tool calculation. If the same risk category ("low," "intermediate," "high") was assigned by both the clinician and the tool, the risk categories were considered congruent. For COMPERA 2.0 analyses, scores were considered congruent if the clinician assigned a patient "intermediate" risk and the COMPERA 2.0 tool assigned either "intermediate-low" or "intermediate-high." Where applicable, "intermediate" risk assigned by REVEAL Lite 2 was considered equivalent to "intermediate-low" and "intermediate-high" risk strata assigned by COMPERA 2.0.

Summary statistics for continuous data are presented as median (interquartile range [IQR]) or mean (standard

deviation [SD]), as appropriate. Summary statistics for categorical or ordinal data are presented as frequency and percentage. Where exact dates were not available, the first day of the month was entered (e.g., an event recorded as occurring on an unknown day in September 2016 was entered as 9/1/2016). Analyses were completed with SAS version 9.4 or higher (Cary, NC; SAS Institute, Inc.; 2011).

## RESULTS

### Clinician characteristics

Thirty-two clinicians participated in the chart review. Most clinicians (88%) were male, and 78% were between 40 and 59 years of age (Supporting Information: Table S1). Seventeen clinicians (53%) reported a specialty of pulmonology, with the remaining clinicians reporting a specialty of cardiology. Thirteen clinicians (41%) were affiliated with a PAH comprehensive care center and 19 (59%) were affiliated with a PAH regional clinical program.

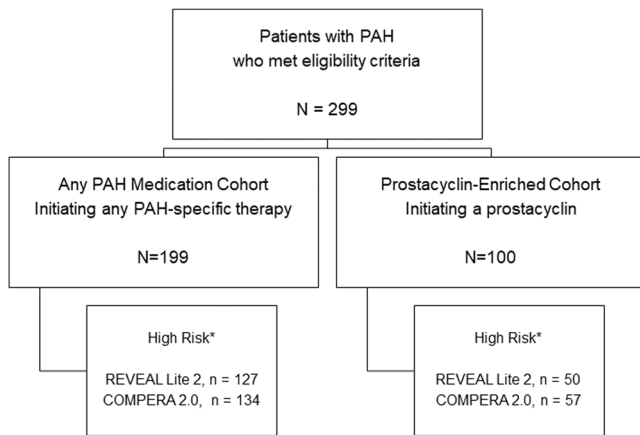
During the study period (2019–2020), 29 (91%) clinicians reported utilizing guidelines or protocols for the treatment of patients with PAH, with 66% following the 2019 American College of Chest Physicians (ACCP) guidelines and 59% following the 2015 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines.

### Patient characteristics

Of the 299 patients with PAH identified in the study, 199 were included in the "any PAH medication" cohort and 100 were included in the "prostacyclin-enriched" cohort (Figure 1). In the overall study population ( $N = 299$ ), 66% of patients were female, and most (64%) had idiopathic PAH (Table 1). At baseline, the mean (SD) age was 52 (12) years, 6MWD was 226 (113) m, and most patients were classified as WHO functional class II (32%) or III (58%). The median (IQR) time from diagnosis to baseline was 2.1 (0.4–8.8) months.

### Risk assessment: REVEAL Lite 2

The majority of patients were categorized by clinician assessment as intermediate risk, while the majority were classified as high risk using REVEAL Lite 2. Clinicians classified 21% (62/299), 53% (158/299), and 26% (79/299) of patients to be at low, intermediate, or high risk of death in 1 year, respectively, per their clinical judgment (Figure 2a). Using REVEAL Lite 2, 17% (52/299), 23%



\*Risk scores were calculated using REVEAL Lite 2 and COMPERA 2.0 risk assessments and are independent of each other. Thus, some patients may have been categorized as high risk based on REVEAL Lite 2 and/or COMPERA 2.0., depending on their specific patient factors.

**FIGURE 1** Study flow diagram for retrospective, double-blinded review of patient records. A total of 299 patients with PAH were included in the study. Of the 299 patients with PAH, approximately one-third were initiated on prostacyclin and two-thirds were initiated on any PAH-specific therapy as the latest treatment between January 2014 and March 2017. Risk scores were calculated using REVEAL Lite 2 and COMPERA 2.0 risk assessments and are independent of each other. Thus, some patients may have been categorized into different risk strata based on REVEAL Lite 2 and/or COMPERA 2.0, depending on their specific patient factors. PAH, pulmonary arterial hypertension.

(70/299), and 59% (177/299) of patients were classified as low, intermediate, and high risk.

Individual patient assessments were compared across methods to understand the variation between calculated scores and clinician gestalt. With REVEAL Lite 2, over half of the risk assessments at baseline were incongruent with clinician gestalt (54%; Figure 2b,c). Risk was underestimated most commonly in clinician-assessed intermediate-risk patients.

### Treatment of a high-risk patient population with prostacyclins using REVEAL Lite 2 to stratify patients

Baseline characteristics were generally similar between the two cohorts of patients who were assessed as intermediate or high risk by REVEAL Lite 2 (Supporting Information: Table S2). The mean (SD) 6MWD was 180 (73) m and 153 (80) m for the “any PAH medication” cohort and the “prostacyclin-enriched” cohort, respectively. Most patients in each cohort were classified as WHO functional class III (69% and 78%, respectively).

In the cohort initiating any PAH therapy at index, a higher proportion of patients were considered high risk

by REVEAL Lite 2 at baseline, compared with the cohort that initiated a prostacyclin therapy at index (64% vs. 50%; Figure 3a). Of the patients deemed high risk by REVEAL Lite 2 in the “prostacyclin-enriched cohort” who were not receiving parenteral prostacyclin therapy at baseline, 38% of patients initiated a parenteral prostacyclin within 90 days following baseline, as compared to 18% in the “any PAH medication” cohort (Figure 3b,c).

### Risk assessment: COMPERA 2.0

The majority of patients were classified by COMPERA 2.0 as high or intermediate-high risk. As noted above, clinicians classified 21% (62/299), 53% (158/299), and 26% (79/299) of patients to be at low, intermediate, or high risk of death in 1 year, respectively, per their clinical judgment (Figure 4a). Using COMPERA 2.0 risk assessment, 4% (11/299) of patients were classified as low risk, 32% (97/299) as intermediate-low, 52% (155/299) as intermediate-high, and 12% (36/299) as high risk (Figure 4a–c).

With COMPERA 2.0, risk assessments at baseline were incongruent with clinician gestalt for 40% of patients (Figure 4d). Risk was most commonly underestimated in clinician-assessed low-risk patients.

### Treatment of an intermediate-high and high-risk patient population with prostacyclins using COMPERA 2.0 to stratify patients

Baseline characteristics were generally similar between the two medication cohorts of patients who were assessed as intermediate-high or high-risk by COMPERA 2.0 (Supporting Information: Table S3). More patients in the cohort initiating any PAH therapy at index were considered high or intermediate-high risk by COMPERA 2.0 at baseline, compared with the cohort that specifically initiated a prostacyclin therapy at index (67% vs. 57%; Figure 5a). Of the patients deemed high risk by COMPERA 2.0 in the “prostacyclin-enriched cohort” who were not receiving a parenteral prostacyclin therapy at baseline, 37% initiated a parenteral prostacyclin within 90 days, as compared to 18% in the “any PAH medication” cohort (Figure 5b,c).

## DISCUSSION

Recent updates to diagnosis and management guidelines for PAH have incorporated risk assessment into the treatment of PAH.<sup>4</sup> Patients with PAH can have vast differences in their

**TABLE 1** Baseline and demographic characteristics.

	All patients (N = 299)	Any PAH medication cohort (N = 199)	Prostacyclin-enriched cohort (N = 100)
Time from diagnosis to baseline, months; median (Q1, Q3)	2.1 (0.4, 8.8)	2.2 (0.4, 8.0)	2.0 (0.5, 11.4)
Age at baseline, years; mean (SD)	51.6 (12.3)	51.4 (12.9)	51.9 (11.0)
Female, n (%)	198 (66.2)	132 (66.3)	66 (66.0)
Etiology, n (%)			
Idiopathic	192 (64.2)	124 (62.3)	68 (68.0)
Heritable/familial associated	21 (7.0)	19 (9.6)	2 (2.0)
Connective tissue disease	56 (18.7)	41 (20.6)	15 (15.0)
Congenital heart disease	7 (2.3)	0	7 (7.0)
Portal hypertension	11 (3.7)	5 (2.5)	6 (6.0)
Drugs/toxin-induced	4 (1.3)	3 (1.5)	1 (1.0)
HIV	7 (2.3)	6 (3.0)	1 (1.0)
Schistosomiasis	1 (0.3)	1 (0.5)	0
Baseline NYHA/WHO functional class, n (%)			
I	8 (2.7)	6 (3.0)	2 (2.0)
II	97 (32.4)	71 (35.7)	26 (26.0)
III	172 (57.5)	107 (62.2)	65 (65.0)
IV	22 (7.4)	15 (7.5)	7 (7.0)
Baseline 6MWD, in meters, mean (SD)	225.9 (112.7)	235.5 (110.1)	206.8 (116.0)
Baseline BNP, n (%)	179 (59.9)	114 (57.3)	65 (65.0)
Median, ng/L (IQR)	299 (110–492)	330 (125–475)	226 (72–565)
Baseline NT-proBNP, n (%)	159 (53.1)	89 (44.7)	70 (70.0)
Median, ng/L (IQR)	837 (261–1450)	933 (360–1342)	559 (90–1611)
Ongoing therapy at baseline, n (%)			
No therapy at baseline	180 (60.2)	121 (60.8)	59 (59.0)
PDE-5 inhibitor, soluble guanylate cyclase stimulator	101 (33.8)	65 (32.7)	36 (36.0)
Endothelin receptor antagonist	89 (29.8)	58 (29.1)	31 (31.0)
Non-parenteral prostacyclin	7 (2.3)	3 (1.5)	4 (4.0)
Parenteral prostacyclin	11 (3.7)	5 (2.5)	6 (6.0)

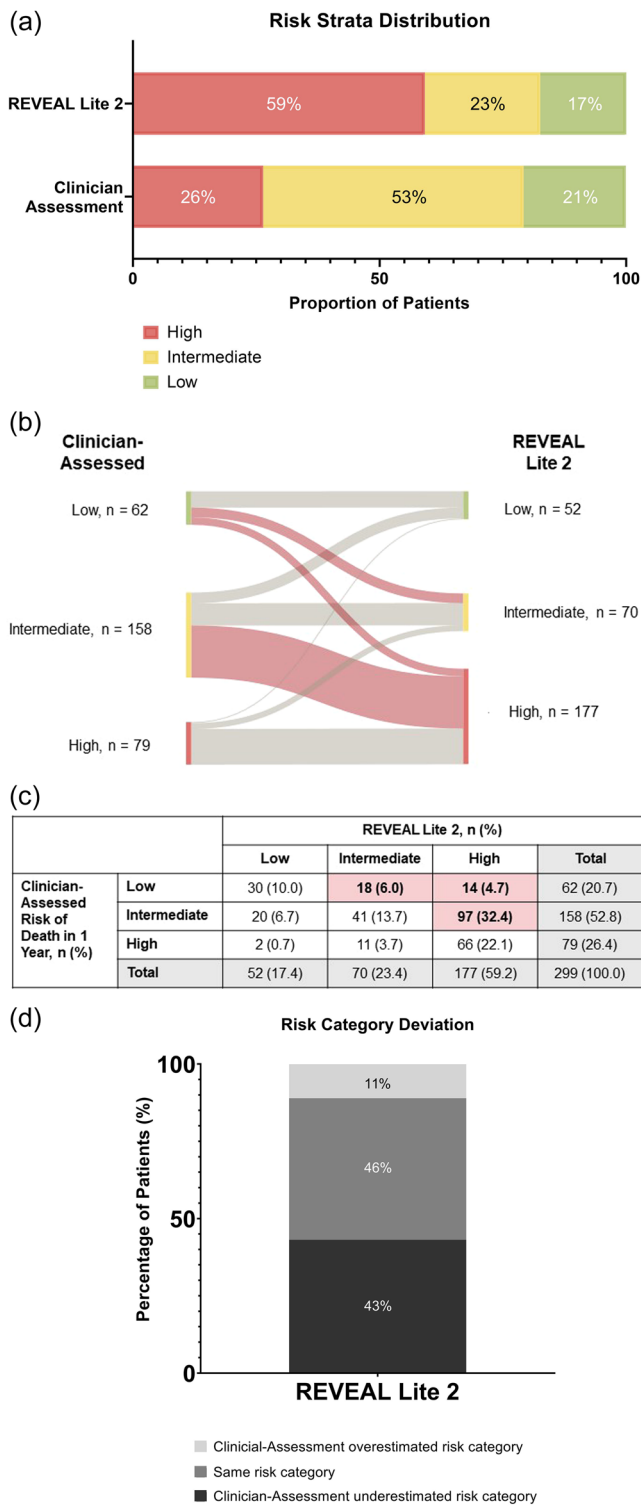
Note: Baseline visit was defined as the most recent assessment before latest treatment initiation within the index period (January 2014–March 2017).

The medication cohorts were defined as: “any PAH medication” = a randomly selected cohort consisting of a sample of ~200 patients with PAH meeting inclusion criteria; “prostacyclin-enriched” = an oversample (augment) sample of ~100–125 patients with PAH meeting inclusion/exclusion criteria treated with prostacyclin-class agent as the latest therapy initiated during the index period for  $\geq 90$  days, approximately half of which received a parenteral prostacyclin-class agent.

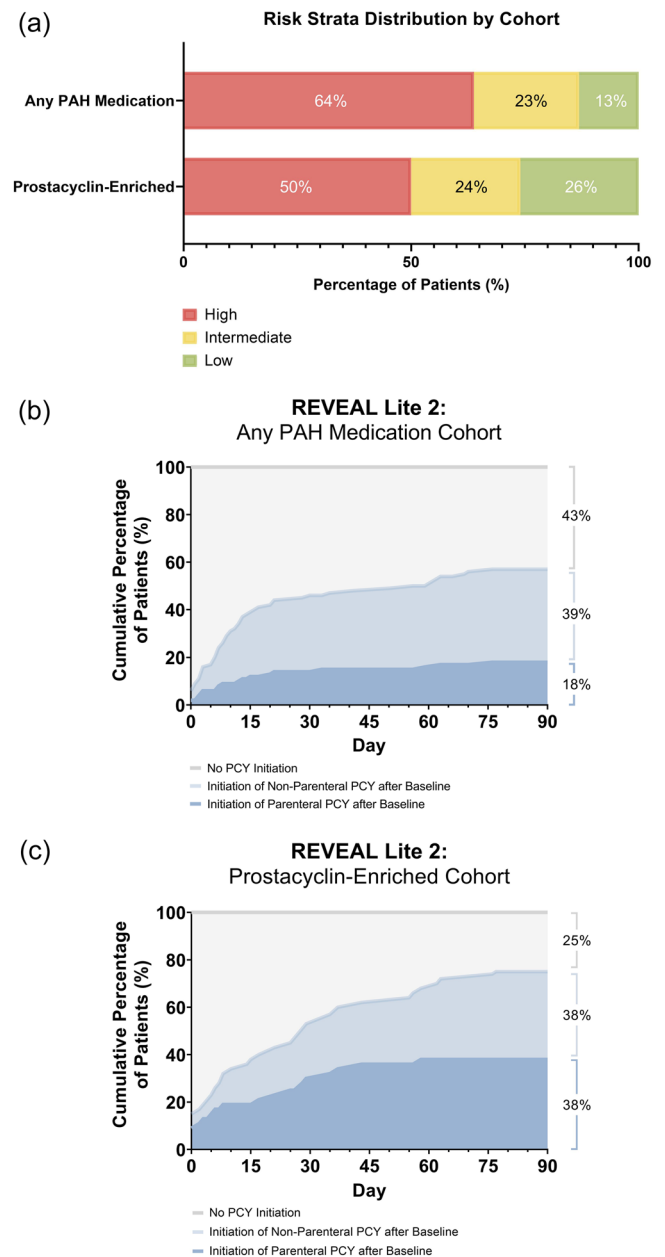
Abbreviations: 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase; SD, standard deviation; WHO, World Health Organization.

outcomes, depending on their assigned risk strata.<sup>6,16</sup> For example, using REVEAL Lite 2, patients who were deemed intermediate risk were estimated to be 2.3 times as likely to die within 1 year as patients deemed low risk; likewise,

patients who were high risk were estimated to be 6.4 times as likely to die within 1 year.<sup>6</sup> Previous guidelines recommended treatment based mainly on functional class, because validated risk scores were not available to guide therapy.<sup>3</sup>



**FIGURE 2** Risk strata distribution using REVEAL Lite 2 versus clinician assessment in total study population ( $N = 299$ ). (a) The majority of patients were categorized as intermediate risk by clinician assessment. The majority of patients were categorized as high risk by REVEAL Lite 2. (b, c) Red shaded lines and boxes show patients whose risk level was underestimated by clinicians, relative to that calculated by REVEAL Lite 2. Risk was underestimated most commonly in clinician-assessed intermediate patients. (d) Most risk assessments between clinician gestalt and REVEAL Lite 2 were incongruent at baseline (54.1%). Numbers may not add to 100% due to rounding.



**FIGURE 3** Risk strata distribution using REVEAL Lite 2 by medication cohort. (a) A higher proportion of patients with PAH who were initiated on PAH-specific therapy were considered high risk, as compared to those initiated on prostacyclin (64% vs. 50%). (b, c) Of the patients deemed high risk by REVEAL Lite 2 who were in the “prostacyclin-enriched” cohort not on parenteral prostacyclin therapy at baseline, 38% of patients initiated a parenteral prostacyclin within 90 days, as compared to 18% in the “any PAH medication” cohort. Numbers may not add to 100% due to rounding. PAH, pulmonary arterial hypertension; PCY, prostacyclin.

Depending on the patient's risk category, different treatment paradigms are recommended. In general, earlier initial treatment in PAH is associated with improved long-term outcomes for patients.<sup>17–19</sup> Some research has shown that initial triple combination therapy is

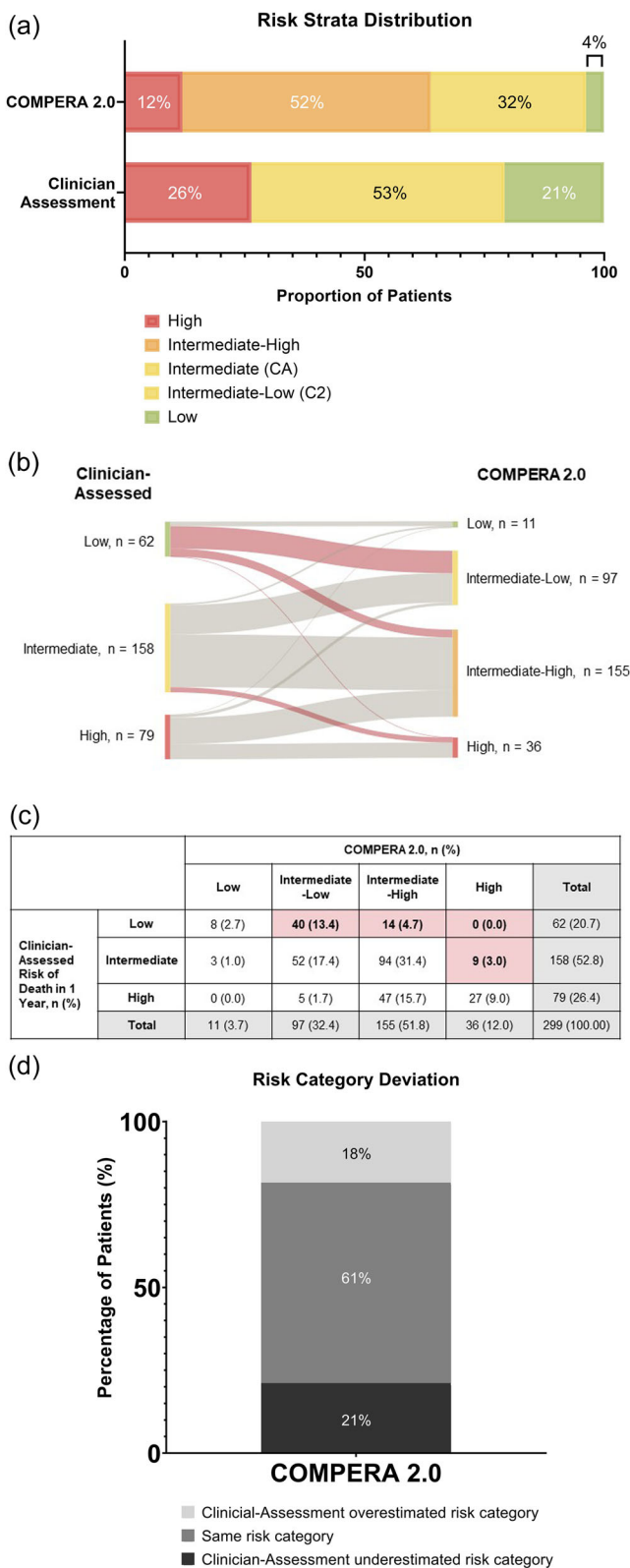
associated with a higher overall survival rate compared to initial dual therapy or monotherapy, despite greater disease severity at baseline in the patients treated with

triple therapy.<sup>20</sup> It is critical to continue implementing serial risk assessments in patients with PAH after the initial diagnosis to identify changes in disease trajectory that may warrant a change in treatment.<sup>21</sup>

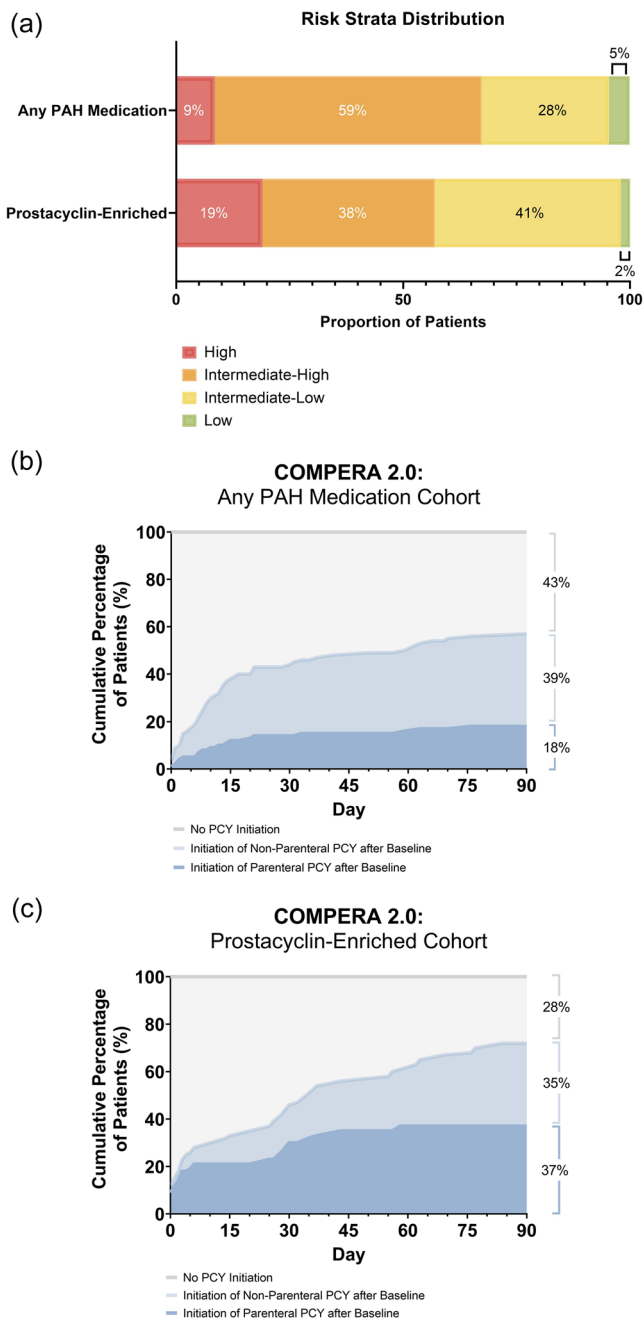
In this study, the clinician-assessed risk category was incongruent with risk assessment using a multiparametric tool in 40%–54% of patients with PAH, whether the assessment was performed with the REVEAL Lite 2 or COMPERA 2.0 tool. Most often, this incongruence was due to an underestimation of the patients' risk category by clinician gestalt relative to the tool assessment. This could potentially lead to an undertreatment, and as a consequence disease progression.<sup>21,22</sup>

The incongruence between clinicians' gestalt and risk assessment tools has been demonstrated in other studies. These studies show a similar trend of approximately half of the patients having an incongruent assessment of risk, with their clinician-assessed risk often underestimated relative to their calculated risk.<sup>8,23</sup> The current study adds to the literature by using the newest risk assessment methods and looking at timely prostacyclin initiation in the high-risk patient population.

Examining cohorts by medication use at baseline allowed us to consider differential treatment selections in a group of patients representative of the overall PAH population ("any PAH medication" cohort) and elucidate further details in those specifically started on a prostacyclin ("prostacyclin-enriched" cohort), where parenteral prostacyclin therapy is recommended. In the high-risk patient population in this study, prostacyclin therapy was underutilized in both cohorts given that current guidelines from the European Society of Cardiology and European Respiratory Society (ESC/ERS) recommend parenteral prostacyclin treatment for intermediate-high and high-risk patients.<sup>4</sup> Additionally, there was a lack of timely prostacyclin initiation (within 90 days of baseline) for high-risk patients. A Delphi panel recently recommended that clinicians should consider treatment escalation in patients at intermediate-low risk who are on treated triple therapy with a non-parenteral prostacyclin and have either abnormal or worsening right heart



**FIGURE 4** Risk strata using COMPERA 2.0 versus clinician assessment in total study population (N = 299). (a) The majority of patients were categorized as intermediate risk by clinician assessment. The majority of patients were categorized as intermediate-high or high risk by COMPERA 2.0. (b, c) Red shaded lines and boxes show patients whose risk level was underestimated by clinicians, relative to that calculated by COMPERA 2.0. Risk was underestimated most commonly in clinician-assessed low patients. (d) Risk assessments between clinician gestalt and COMPERA 2.0 were incongruent at baseline (40%). Numbers may not add to 100% due to rounding.



**FIGURE 5** Risk strata distribution using COMPERA 2.0 by medication cohort. (a) A higher proportion of patients with PAH initiated on any PAH therapy were considered high or intermediate-high risk, as compared to those initiated on prostacyclin (67% vs. 57%). (b, c) Of the patients categorized as high risk by COMPERA 2.0 in the “any PAH medication” cohort who were not on parenteral prostacyclin at baseline, (b) 18% initiated parenteral prostacyclin therapy within 90 days, and (c) 37% of patients in the “prostacyclin-enriched” cohort not on parenteral prostacyclin therapy at baseline initiated a parenteral prostacyclin within 90 days. Numbers may not add to 100% due to rounding. PAH, pulmonary arterial hypertension; PCY, prostacyclin.

imaging parameters.<sup>24</sup> For patients at intermediate-high risk, clinicians should consider treatment escalation to a parenteral prostacyclin if right heart imaging shows no improvement or shows worsening. Given retrospective nature of the study, we could not gather information on how clinicians made their treatment decisions. Therefore, it is unknown what factors may have led to the underutilization of prostacyclins in these groups of patients.

There was a higher proportion of patients in the “any PAH medication” cohort who were stratified as high risk by both REVEAL Lite 2 and COMPERA 2.0 than in the “prostacyclin-enriched” cohort. This might reflect a situation in which patients in the “any PAH medication” cohort, though stratified as higher risk initially, might have been initiated on non-prostacyclin treatment(s) as a first measure rather than a prostacyclin. One explanation is that the patients treated prostacyclins in the “prostacyclin-enriched” cohort may have previously been on other PAH medications and thus achieved a slightly lower risk status. However, as they still were not meeting their treatment goals, prostacyclin therapy was initiated.

In this study, most of the surveyed clinicians followed guidelines to treat patients with PAH, with the most common (66%) following the ACCP guidelines, which were published in 2019. According to the published literature, formal risk assessments in PAH are generally underutilized. Only about half of PAH clinicians report using risk assessment tools in regular practice and instead rely on their gestalt to assess clinical status.<sup>9,10</sup> Additional real-world evidence is needed to compare these risk instruments. Additionally, risk assessment tools may be underutilized due to real or perceived barriers to implementing them in clinical practice, such as lack of awareness and knowledge of the tools, time constraints and insufficient integration of technology or electronic medical record.<sup>9</sup> Though multiple risk calculators are available, some offer simplified versions that could make them easier to implement regularly in practice.<sup>6,25</sup>

Limitations of this study include the use of retrospective medical records, which could be affected by recall and/or selection bias with charts chosen and data abstracted. Of note, patients who met eligibility criteria in the timeframe specified were randomly selected by the surveyed clinician. Patient selection was not prescriptively described. Study results are projectable only to the patients with PAH who initiated treatment during the specified treatment index period, so extrapolation to other time periods is limited to understanding changes in disease management and treatment in these patient populations over time. As clinicians may not routinely capture all risk-stratification parameters



at each measurement period, responses might not be consistent with clinical trial behaviors. It is unknown whether the participating investigators used an objective risk assessment method when providing their clinician assessment. Bias may occur in the retrospective assessment of patient's clinical status, given potential knowledge of future treatment decisions. Further, treatment patterns represent only the practices of cardiologists and pulmonologists agreeing to participate in the study and could vary from non-responding clinicians. Most of these sites were affiliated with PAH care centers, so practices of community-based clinicians could also differ. Additionally, guideline-directed practice has evolved since the index period and treatment regimens may have been selected differently based on previously published guidelines.

In summary, clinician-assessed risk category was incongruent with a tool-based risk assessment in 40%–54% of patients with PAH, usually reflecting an underestimation of the patient's risk category by clinician gestalt. Underestimation of the patient's actual risk may result in undertreatment, worsening of signs and symptoms, and progression of PAH. Specifically, this study showed a lack of timely prostacyclin initiation for patients with PAH stratified as high-risk by two multiparametric tools.

#### AUTHOR CONTRIBUTIONS

Amresh Raina interpreted data, wrote and edited the original and revised versions of the manuscript; Margaret R. Sketch analyzed the data, wrote and edited the original and revised versions of the manuscript; Benjamin Wu analyzed the data, wrote and edited the original and revised versions of the manuscript; Meredith Broderick analyzed the data, wrote and edited the original and revised versions of the manuscript, and provided project administration; Oksana A. Shlobin interpreted data, wrote and edited the original and revised versions of the manuscript. All authors approved the final version of the manuscript for publication.

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#### CONFLICTS OF INTEREST STATEMENT

Amresh Raina reports no potential conflict of interest with the study. Oksana A. Shlobin has served as a consultant to

and on the speaker's bureau for United Therapeutics, Bayer, Merck, and Janssen; and has served as a consultant to Gossamer, Aerami, and Aerovate. Meredith Broderick, Benjamin Wu and Margaret R. Sketch are employees of United Therapeutics Corporation.

#### DATA AVAILABILITY STATEMENT

Data underlying the manuscript are available from United Therapeutics with the permission of Medical Data Analytics upon reasonable request.

#### ETHICS STATEMENT

The New England Independent Review Board approved the research, and a waiver of documentation of informed consent was obtained for this retrospective chart review.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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