Are Hemodynamics Surrogate End Points in Pulmonary Arterial Hypertension?

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Background—Although frequently assessed in trials and clinical practice, hemodynamic response to therapy has never been validated as a surrogate end point for clinical events in pulmonary arterial hypertension (PAH).

Methods and Results—We performed a patient-level pooled analysis of 4 randomized, placebo-controlled trials to determine whether treatment-induced changes in hemodynamic values at 12 weeks accounted for the relationship between treatment assignment and the probability of early clinical events (death, lung transplantation, atrial septostomy, PAH hospitalization, withdrawal for clinical worsening, or escalation in PAH therapy). We included 1119 subjects with PAH. The median (interquartile range) age was 48 years (37–59 years), and 23% were men. A total of 656 patients (59%) received active therapy (101 [15%] iloprost, 118 [18%] sitaxsentan, 204 [31%] sildenafil, and 233 [36%] subcutaneous treprostinil). Active treatment significantly lowered right atrial pressure, mean pulmonary artery pressure, and pulmonary vascular resistance and increased cardiac output and index (P<0.01 for all). Changes in hemodynamic values (except for right atrial pressure and mean pulmonary artery pressure) were significantly associated with the risk of a clinical event (P<0.02 for all). Although active treatment approximately halved the odds of a clinical event compared with placebo (P<0.001), changes in hemodynamics accounted for only 1.2% to 13.9% of the overall treatment effect.

Conclusions—Treatment-induced changes in hemodynamics at 12 weeks only partially explain the impact of therapy on the probability of early clinical events in PAH. These findings suggest that resting hemodynamics are not valid surrogate end points for short-term events in PAH clinical trials. (Circulation. 2014;130:768-775.)

Key Words: hemodynamics ■ hypertension, pulmonary ■ pulmonary heart disease ■ trials

Hemodynamic measures such as right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), and cardiac index (CI) are the cornerstones of diagnosis and risk assessment in pulmonary arterial hypertension (PAH). As such, hemodynamics often serve as primary or secondary end points in Phase 2 trials of investigational PAH therapies as a signal for efficacy. Although the US Food and Drug Administration (FDA) does not consider hemodynamics as adequate surrogate or primary end points, many Phase 3 trials of currently approved PAH treatments have included hemodynamics as secondary end points. Given the absence of other well-established surrogate end points in PAH, the validation of hemodynamic markers as surrogate end points in PAH would be critical to improving the efficiency of drug evaluation.

Clinical Perspective on p 775

Contrary to conventional wisdom, a recent study-level meta-analysis suggested that changes in hemodynamic measures with PAH therapy might not predict clinical events. The objective of the present study was to determine whether changes in RAP, mPAP, cardiac output (CO), CI, and pulmonary vascular resistance (PVR) are valid surrogate end points in PAH clinical trials using a mediator analytic approach with patient-level data, the “gold standard” approach to synthesizing data across trials. We pooled individual-level data from 4 randomized, placebo-controlled trials submitted to the FDA for drug approval. We hypothesized that changes in hemodynamics at 12 weeks (adjusted for measures at baseline) would account for a significant portion of the relationship between treatment assignment and the odds of a clinical event, validating hemodynamics as surrogate end points in PAH.

Methods

Study Population

We used deidentified individual patient data from placebo-controlled randomized trials of targeted PAH therapies submitted to the FDA through 2008. Twelve trials (ARIES [Ambrisentan in Pulmonary Arterial Hypertension, Randomized,
Hemodynamics as Surrogates in PAH Trials

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Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies]-1 and -2; Bosentan-351; BREATHE-1 [Bosentan Randomized Trial of Endothelin Antagonist Therapy]; AIR [Aerosolized Iloprost Randomized Study]; AIR II; PHIRST [Pulmonary Arterial Hypertension and Response to Tadalafil]; SUPER [Sildenafil Use in Pulmonary Arterial Hypertension]; STRIDE [Sitaxsentan to Relieve Impaired Exercise]-1, -2, and -4; and the subcutaneous treprost- nil trial] comparing 7 active therapies (ambrisentan, bosentan, iloprost, tadalafil, sildenafil, sitaxsentan, and subcutaneous treprostinil, respectively) to placebo were considered. Details of these trials are provided elsewhere, but all had similar inclusion criteria and data collection processes.10-15,20-24

We included patients from Phase 3 trials that collected baseline and 12-week hemodynamic values. We excluded patients with missing base-

line hemodynamics, ARIES 1 and 2, BREATHE-1, and STRIDE-2 and -4 were excluded because the trials did not assess hemodynamics at 12 weeks; Bosentan-351 and AIR II were excluded because they were small or were not Phase 3 trials; PHIRST was excluded because some subjects in that trial had been treated with background bosentan therapy. The final study population included patients from 4 trials (AIR, SUPER, STRIDE-1, and subcutaneous treprostinil) of 4 therapies (iloprost, sildenafil, sitaxsentan, and subcutaneous treprostinil, respectively).

Clinical Events

Clinical events included the first occurrence of any of the following before the end of the randomized portion of the trials: death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, withdrawal for clinical worsening, or escalation in PAH therapy. We did not include change in 6-minute walk distance (6MWD) as a clinical event in the primary analysis because it has not been established as a patient-centered outcome and is itself an imperfect surrogate for clinical outcomes in PAH.16-18 Sensitivity analyses that included a decrement in 6MWD in the composite end point were performed (described below).

Hemodynamics

Hemodynamic values at baseline and at 12 weeks as reported to the FDA were used to calculate the absolute change in RAP (ΔRAP), mPAP (ΔmPAP), CO (ΔCO), CI (ΔCI), and PVR (ΔPVR). In addi-
tion to traditional hemodynamic measures, we included pulmonary artery (PA) compliance, calculated as follows: (CO/heart rate)/(PA systolic pressure - PA diastolic pressure).27-29 Subjects missing baseline hemodynamic values were excluded from all analyses (n=20 for RAP, n=4 for mPAP, n=18 for CO, and n=60 for PVR; total number excluded, 102 [9%]).

Statistical Analysis

Continuous variables are expressed as median (interquartile range) and categorical variables as percentages. We used a mediator analy-
sis, which is the preferred approach to validating potential surrogate end points.30,31 Treatment assignment was designated as either active treatment or placebo. Regression analysis was used to evaluate 4 hypotheses. The rejection of all 4 null hypotheses was required to deem the change in a given hemodynamic measure a valid surrogate end point. The 4 alternative hypotheses included the following: (1) Treatment assignment has a significant effect on change in hemody-
namics (ΔRAP, ΔmPAP, ΔCO, ΔCI, ΔPVR, and ΔPA compliance) at 12 weeks; (2) change in hemodynamics (ΔRAP, ΔmPAP, ΔCO, ΔCI, ΔPVR, and ΔPA compliance) has a significant association with the odds of a clinical event; (3) treatment assignment has a significant effect on the odds of a clinical event; and (4) the effect of treatment assignment on the odds of a clinical event is attenuated when change in a given hemodynamic parameter (ΔRAP, ΔmPAP, ΔCO, ΔCI, ΔPVR, and ΔPA compliance) is added to the model.

 Logistic or linear regression was used for binary or continuous out-
comes, respectively. All models were adjusted for the given hemody-
namic measure at baseline and study.

After the tests for mediation, we determined the proportion of the treatment effect explained by ΔRAP, ΔmPAP, ΔCO, ΔCI, ΔPVR, and ΔPA compliance, respectively.23 Generalized linear modeling with a logit link was used to determine the effect estimate for treatment assignment and log odds of a clinical event, adjusted for baseline hemodynamic value and study. ΔRAP, ΔmPAP, ΔCO, ΔCI, ΔPVR, and ΔPA compliance were then individually added to the initial mod-
els, such that the change in the effect estimates between baseline and those containing the hemodynamic mediator provided the amount of variability in clinical events explained by a change in the mediator at 12 weeks. Estimates of percent change were obtained for each resam-
pled data set, and the standard deviation of the estimates across 1000 resampled data sets were used as the standard error.24

A number of sensitivity and subset analyses were performed. First, the clinical event definition was expanded to include a 15% decrement in 6MWD during the randomized portion of the trials (in addition to death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, withdrawal for clinical worsening, or escalation in PAH therapy). Those missing 12-week 6MWD values were counted as having had an event. Second, we tested whether achieving certain established thresholds of hemodynamic improvement (ie, CI >2 or >3 L/min/m², reduction in PVR >30% at 12 weeks), using absolute values of hemodynamics (rather than the change values), and nonparametric modeling (using local smoothers) revealed alternative hemodynamic cut points that performed better as surrogates.1,3,35 Third, we adjusted our primary analysis for New York Heart Association functional class. Fourth, we included subset analyses limiting our study population to those with idiopathic PAH or connective tissue disease– and congeni-
tal heart disease–associated PAH, respectively, as well as to the subset of patients who achieved a 12-week 6MWD of >380 m, which is sug-
gested as a treatment target in recent consensus guidelines.35,36 Finally, for the AIR study, we substituted hemodynamic values 60 minutes after iloprost inhalation (as opposed to those before inhalation for the main analysis) to calculate the change in hemodynamics.

Multiple imputation was used to derive missing 12-week hemody-
namic values (n=104 [9%] for RAP, n=100 [9%] for mPAP, n=100 for CO [9%], n=134 [12%] for PVR).19 Age, sex, race, height, weight, diagnosis (idiopathic, connective tissue disease, human immunodefi-
ciency virus infection/anorexigen use, or congenital heart disease), baseline 6MWD, baseline hemodynamic parameter, New York Heart Association functional class, warfarin use, and baseline sodium level were included as predictors in the imputation models for the missing 12-week hemodynamic values. All analyses were performed with SAS version 9.2 and R version 2.14.1. Statistical significance was defined as P<0.05.

This study was determined to be exempt by the Institutional Review Board of the University of Pennsylvania (No. 818239). All coauthors had access to study data, take responsibility for the analy-
sis, and contributed to manuscript preparation and the decision to submit for publication.

Results

The final study sample included 1119 patients from 4 trials (AIR, SUPER, STRIDE-1, and subcutaneous treprostinil) of 4 therapies (iloprost [n=202, 18%], sildenafil [n=269, 24%], sitaxsentan [n=178, 16%], and subcutaneous treprostinil [n=470, 42%], respectively). Characteristics of the study pop-
ulation and those assigned to active treatment (n=656, 59%) or placebo (n=463, 41%) are shown in Table 1. The median age was 48 years (range 37–59 years), and 23% were men. Six hundred thirty-seven patients (60%) had idiopathic PAH, 247 (23%) had connective tissue disease–associated PAH, and 482 (45%) were New York Heart Association functional class III or IV. Demographics, anthropometrics, diagnoses, baseline 6MWD, and baseline hemodynamics were similarly balanced by treatment allocation (as would be expected with randomization). A total of 110 patients (10%) had a clinical event between baseline and 12 weeks. Hospitalization for worsen-

ing PAH (n=70) and premature withdrawal (n=35) constituted
the majority of these events; 29 deaths occurred during the 12-week randomized portion of the trials.

The results for the 4 criteria necessary to establish changes in selected hemodynamic indices as mediators in the relationship between treatment allocation and clinical events are presented in Tables 2 to 4. Assignment to active treatment significantly reduced RAP, mPAP, and PVR and increased CO, CI, and PA compliance (criterion No. 1; Table 2). Second, the relationship between the change in a given hemodynamic value at 12 weeks and the odds of a clinical event was tested (criterion No. 2; Table 3). A decrease in PVR and increases in CO and CI were associated with significant reductions in the odds of a clinical event. Effect estimates may appear small because they refer to the odds of a clinical event per 1 unit increase in the hemodynamic measure (eg, odds ratio [OR] 1.07 for every 1 Wood unit increase in PVR; 95% confidence
Table 2. Criterion No. 1: Treatment Assignment Has a Significant Effect on Change in Hemodynamics at 12 Weeks

<table>
<thead>
<tr>
<th>Hemodynamic Measure</th>
<th>Mean Difference Between Active Treatment and Placebo</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆RAP, mm Hg</td>
<td>−1.2</td>
<td>−1.8–−0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆mPAP, mm Hg</td>
<td>−2.4</td>
<td>−3.4–−1.3</td>
<td>0.003</td>
</tr>
<tr>
<td>∆CO, L/min/m²</td>
<td>0.4</td>
<td>0.2–0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆CI, L/min/m²</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆PVR, Wood units</td>
<td>−2.1</td>
<td>−2.7–−1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>∆PA compliance, mL/mm Hg</td>
<td>0.2</td>
<td>0.1–0.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All models include adjustment for baseline hemodynamic value and study. CI indicates confidence interval; ∆CI, change in cardiac index; ∆CO, change in cardiac output; ∆mPAP, change in mean pulmonary artery pressure; ∆PA compliance, change in pulmonary artery compliance; ∆PVR, change in pulmonary vascular resistance; and ∆RAP, change in right atrial pressure.

We next quantified the proportion of the treatment effect explained by the hemodynamic change values (Figure 1). These mediators accounted for little (∆CO, ∆CI, ∆PVR) to none (∆RAP, ∆mPAP, ∆PA compliance) of the treatment effect. At most, ∆CI and ∆PVR accounted for 11.7% and 13.9% of the impact of treatment on clinical outcomes, well below the proposed cutoff of 50% to 75% necessary to declare a surrogate valid.32

Sensitivity and Subset Analyses
The results were unchanged when a 15% decrement in 6MWD was included in the definition of a clinical event (Table 5). The ORs shown for criterion No. 4 were not substantially attenuated with inclusion of the hemodynamic measures compared with the models for criterion No. 3. Although the proportions of the treatment effect were generally greater than in the main analysis (eg, ∆PVR accounted for 26.9% of the treatment–clinical event relationship), they were still well below 50%, which suggests the hemodynamic change values were not acting as mediators. Similarly, analyses that used predefined thresholds to indicate hemodynamic improvement, absolute values of hemodynamics (rather than change values), cut points derived from nonparametric modeling, and adjustment for New York Heart Association functional class did not improve the performance of hemodynamics as surrogates (data not shown). Subset analysis that included only idiopathic patients (n=637) yielded results similar to our primary analysis (Table I in the online-only Data Supplement). In the small subgroups of patients with connective tissue disease or congenital heart disease and those patients who achieved a 6MWD >380 m at 12 weeks (n=469), findings were also unchanged, although the estimates were imprecise because of the very low number of events (n=21, 11, and 9 events, respectively; data not shown). We repeated our analysis substituting hemodynamic values 60 minutes after iloprost inhalation (in patients from the AIR study) to calculate the change values, and the results were nearly identical (Table II in the online-only Data Supplement).

Discussion
On the basis of this large pooled analysis of patient-level data, we are unable to conclude that treatment-induced changes in resting hemodynamics are valid surrogate end points for short-term outcomes in PAH. Although (1) active treatment was significantly associated with modest improvement in hemodynamics at 12 weeks, (2) changes in some hemodynamics were significantly associated with the odds of clinical events, and (3) treatment assignment considerably reduced the odds of a clinical event, the relationship between treatment and clinical events was not mediated or “explained” by treatment-induced changes in hemodynamics. This held true in multiple secondary analyses that included the incorporation of 6MWD decrement in the clinical event definition and with the restriction of the study sample to patients with idiopathic PAH.

The use of hemodynamic measures as surrogate end points in PAH clinical trials is appealing, given that these measures may in theory be standardized, are widely available, and are integral to our understanding and definition of PAH.38,39 Observational studies have consistently shown associations between hemodynamics (especially those that pertain to
right-sided heart function, such as CO) and event-free survival (as seen in the present study); however, such observational data are not sufficient to validate potential surrogates. Changes in hemodynamics with PAH treatment predict outcome, but the specific measures of import have been inconsistent across studies (eg, mPAP and CI versus a reduction in PVR). A useful surrogate end point should be reliable, valid, and account for most of the impact of a therapy on the ultimate clinical end point in multiple studies and settings.

The present study demonstrates that treatment-induced changes in hemodynamics do not account for the treatment-associated reduction in events at 12 weeks, which calls into question traditional assumptions about the mechanisms that underpin the effects of targeted PAH therapy on clinical outcomes. Treatment-associated changes in hemodynamics have been reported to be rather modest in short-term Phase 3 trials in PAH. In a randomized clinical trial of epoprostenol, the difference in the mean change for PVR between treatment and placebo groups was -4.9 Wood units (95% confidence interval, -7.6 to -2.3 Wood units), for example.

A recent study-level meta-analysis by Savarese and colleagues yielded similar results. Assignment to active treatment was associated with hemodynamic improvements and significantly reduced the odds of the composite outcome (OR, 0.3; 95% confidence interval, 0.3–0.5). However, there was no association between hemodynamic changes and the composite outcome at the study level. This null finding could be explained by the analytic methods used, because meta-analyses at the study level are less robust and may suffer from aggregation bias (known as the ecological fallacy). We used patient-level data and the currently accepted approach to establishing surrogacy and found that short-term improvements in hemodynamics actually contributed very little (at most 13.9% for ΔPVR in our primary analysis) to the impact of treatment on early clinical events. It has been proposed that a valid surrogate end point should explain between 50% and 75% of the exposure-outcome relationship of interest.

There are several possible explanations for these findings. Effective PAH therapies may act via heretofore unmeasured (or insufficiently measured) physiological pathways to affect outcome. For example, effects on the systemic circulation or other organ systems rather than changes in the pulmonary vasculature could contribute substantially to therapeutic benefit. Advanced or novel RV imaging techniques, such as speckle-tracking Doppler and positron emission tomography, have been linked to clinical deterioration and RV metabolic changes in PAH, respectively, although more work is needed to establish clear correlations between these measures, PAH treatment response, and outcomes. Although brain natriuretic peptide is an easily obtained and reliable measure of RV strain, a recent study of changes in plasma brain natriuretic peptide after treatment failed to discriminate 2-year survival in patients with PAH. Although we incorporated a measure of PA compliance in our study, there may be more sophisticated and comprehensive measures of the cardiopulmonary interaction that will prove to be valid surrogates in PAH.

Although short-term hemodynamic response may be a poor surrogate for short-term clinical events, these results may not apply to trials of longer duration. It is possible that changes...
Table 5. Criteria to Establish the Change in a Hemodynamic Measure (ΔHD) as a Mediator in the Relationship Between Treatment Assignment and Clinical Events Including a 15% Decrement in 6MWD at 12 Weeks

<table>
<thead>
<tr>
<th>Hemodynamic Measure</th>
<th>ΔRAP (mmHg)</th>
<th>ΔmPAP (mmHg)</th>
<th>ΔCO (L/min)</th>
<th>ΔCI (L/min/m²)</th>
<th>ΔPVR (Wood units)</th>
<th>ΔPA Compliance (mL/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment</td>
<td>−1.2</td>
<td>−2.4</td>
<td>0.37</td>
<td>0.22</td>
<td>−2.1</td>
<td>0.15</td>
</tr>
<tr>
<td>assignment has a</td>
<td>(−1.8 − −0.63)</td>
<td>(−3.4 − −1.31)</td>
<td>(0.24–0.50)</td>
<td>(0.14–0.29)</td>
<td>(−2.7 − −1.5)</td>
<td>(0.09–0.21)</td>
</tr>
<tr>
<td>significant effect</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
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<tr>
<td>on ΔHD (mean difference between active treatment and placebo)</td>
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</tr>
<tr>
<td>2. ΔHD has a</td>
<td>OR per 1-mm-Hg increase 1.06</td>
<td>OR per 1-mm-Hg increase 1.02</td>
<td>OR per 1-L/min increase 0.65</td>
<td>OR per 1-L/min/m² increase 0.46</td>
<td>OR per 1-Wood unit increase 1.10</td>
<td>OR per 1-mL/mmHg increase 0.63</td>
</tr>
<tr>
<td>significant association</td>
<td>(1.02–1.09)</td>
<td>(1.00–1.04)</td>
<td>(0.53–0.78)</td>
<td>(0.32–0.65)</td>
<td>(1.06–1.15)</td>
<td>(0.40–0.98)</td>
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<tr>
<td>with the odds of a</td>
<td>OR=0.002</td>
<td>OR=0.036</td>
<td>OR=0.001</td>
<td>OR=0.001</td>
<td>OR=0.001</td>
<td>OR=0.003</td>
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<tr>
<td>clinical event</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
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<tr>
<td>3. Treatment</td>
<td>0.51</td>
<td>0.55</td>
<td>0.56</td>
<td>0.56</td>
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<tr>
<td>assignment has a</td>
<td>(0.38–0.69)</td>
<td>(0.41–0.73)</td>
<td>(0.42–0.75)</td>
<td>(0.42–0.76)</td>
<td>(0.40–0.73)</td>
<td>(0.41–0.73)</td>
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<tr>
<td>significant effect</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
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<td>clinical event (OR for active treatment vs placebo)</td>
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<td>4. The effect of</td>
<td>0.54</td>
<td>0.56</td>
<td>0.63</td>
<td>0.64</td>
<td>0.64</td>
<td>0.57</td>
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<tr>
<td>treatment assignment</td>
<td>(0.40–0.73)</td>
<td>(0.42–0.76)</td>
<td>(0.47–0.85)</td>
<td>(0.47–0.87)</td>
<td>(0.47–0.87)</td>
<td>(0.42–0.77)</td>
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<tr>
<td>on the odds of a</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P=0.003</td>
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<td>clinical event is</td>
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<td>the model (OR for</td>
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<tr>
<td>% Variability</td>
<td>7.6</td>
<td>5.4</td>
<td>20.6</td>
<td>22.2</td>
<td>26.9</td>
<td>7.4</td>
</tr>
<tr>
<td>explained by ΔHD</td>
<td>(1.9–19.0)</td>
<td>(−1.6–15.4)</td>
<td>(9.5–44.8)</td>
<td>(10.7–49.2)</td>
<td>(12.9–60.5)</td>
<td>(0.6–19.9)</td>
</tr>
</tbody>
</table>

All models include adjustment for baseline hemodynamic value and study. Values in parentheses are 95% confidence intervals.

ΔI indicates change in cardiac index; ΔCO, change in cardiac output; ΔHD, change in hemodynamic measure at 12 wk compared with baseline; ΔmPAP, change in mean pulmonary artery pressure; ΔPA compliance, change in pulmonary artery compliance; ΔPVR, change in pulmonary vascular resistance; ΔRAP, change in right atrial pressure; and OR, odds ratio.

in hemodynamics after longer-term therapy are adequate surrogates for long-term outcomes. We are not able to answer this question, because essentially all clinical trials that included hemodynamic measures had a placebo-controlled period of only a few months (and long-term, open-labeled extension studies are not sufficient for the required analyses). Larger time-to-event trials incorporating composite clinical outcomes have only recently been conducted in PAH (www.ClinicalTrials.gov No. NCT01106014 and No. NCT01178073). Although treatment-induced changes in hemodynamics were not adequate surrogates in patients without treatment at baseline, the validity in patients with background treatment or combination therapy or in patients evaluated or reassessed sequentially is unknown.

The present study has some limitations. The patient-level data were limited by design of the individual trials. As the FDA and other regulatory bodies accept changes in short-term intermediate end points (6MWD) for registration, these Phase 3 trials were, not surprisingly, of short duration, which limited our conclusions regarding surrogacy for long-term outcomes. The exclusion of those subjects with missing baseline values could result in selection bias; however, those excluded (<10%) were similar to those in the final study sample, which makes this less likely. The imputation of 12-week hemodynamic values (at most 12% for PVR) may have been an additional source of bias. Four Phase 3 trials (of 12 in the data set) included treatment-naïve patients and had repeat hemodynamics available, although >1000 patients were included, as were all major therapeutic classes (ie, prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors), increasing generalizability. The endothelin receptor antagonist sitaxsentan was shown to be efficacious in STRIDE-1 and other trials but was withdrawn from the market for hepatic toxicity. Sitaxsentan was the only endothelin receptor antagonist with follow-up hemodynamics in a Phase 3 trial. Although 2 of the trials included, AIR and the subcutaneous treprostinil trial, met their respective primary end points for efficacy, effect sizes were smaller in these trials than in Phase 3 trials for other targeted PAH therapies. An additional subset analysis that included only the SUPER and STRIDE-1 trials did not alter the present results, although precision was limited because of the smaller sample size and lower event rate (data not shown). The results could differ with other treatments, in patients receiving background therapy, or for trials performed in other geographic regions or eras. Last, it is unknown whether the validity of hemodynamic measures would be enhanced by using highly standardized measurement techniques or by capturing serial or dynamic (eg, exercise or composite) values.

Treatment-induced changes in pulmonary hemodynamics measured at rest are not valid surrogates for short-term clinical outcomes in PAH trials. Although active treatment was
associated with significant hemodynamic improvement, this response to therapy mediated very little of the treatment effect on key clinical end points at 12 weeks. The impact of longer-term therapy on hemodynamics and the validity of these changes over time remain unknown. Future work should focus on validating commonly accepted surrogates in PAH before their use in clinical trials and on defining more robust and dynamic measures of disease burden in PAH.

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References


Hemodynamic measures are the cornerstones of diagnosis and risk assessment in pulmonary arterial hypertension (PAH) and as such are frequently assessed in clinical practice. Hemodynamics often serve as primary or secondary end points in Phase 2 trials of investigational PAH therapies as a signal for efficacy. Our study, a large (n=1,119) patient-level analysis of 4 randomized clinical trials in PAH, demonstrates that although active therapy was associated with favorable hemodynamic changes and a reduction in clinical events, including death, lung transplantation, atrial septostomy, hospitalization for worsening PAH, withdrawal for clinical worsening, or escalation in PAH therapy at 12 weeks, changes in hemodynamics did not account for the impact of therapy on the probability of short-term outcomes. These findings suggest that resting hemodynamics are not valid surrogate end points for short-term events in PAH clinical trials and challenge our understanding of the physiologic pathways impacted by PAH therapies.
Are Hemodynamics Surrogate End Points in Pulmonary Arterial Hypertension?
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James R. Klinger, Scott D. Halpern and Steven M. Kawut

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Supplemental Material

Are Hemodynamics Surrogate Endpoints in Pulmonary Arterial Hypertension?
Supplemental Table 1. Criteria to establish the change in a hemodynamic measure (ΔHD) as a mediator in the relationship between treatment assignment and clinical events at 12 weeks in the subgroup of patients with idiopathic pulmonary arterial hypertension.

<table>
<thead>
<tr>
<th>Hemodynamic measure</th>
<th>ΔRAP</th>
<th>ΔmPAP</th>
<th>ΔCO</th>
<th>ΔCI</th>
<th>ΔPVR</th>
<th>ΔPA Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment assignment has a significant effect on ΔHD</td>
<td>Mean difference (95% CI) between treatment and placebo -1.9 mm Hg (-2.8, -1.1) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo -2.5 mm Hg (-4.0, -1.1) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo 0.40 L/min (0.21, 0.58) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo 0.22 L/min/m² (0.12, 0.32) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo -2.3 Wood units (-3.1, -1.4) p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2. ΔHD has a significant effect on the odds of a clinical event</td>
<td>OR (95% CI) per 1 mm Hg increase 1.08 (1.02, 1.16) p = 0.011</td>
<td>OR (95% CI) per 1 mm Hg increase 1.01 (0.97, 1.06) p = 0.494</td>
<td>OR (95% CI) per 1 L/min increase 0.66 (0.45, 0.98) p = 0.033</td>
<td>OR (95% CI) per 1 L/min/m² unit increase 0.46 (0.23, 0.95) p = 0.031</td>
<td>OR (95% CI) per 1 Wood unit increase 1.04 (0.98, 1.10) p = 0.186</td>
<td></td>
</tr>
<tr>
<td>3. Treatment assignment has a significant effect on the odds of a clinical event</td>
<td>OR (95% CI) for treatment vs. placebo 0.40 (0.22, 0.72) p = 0.002</td>
<td>OR (95% CI) for treatment vs. placebo 0.41 (0.23, 0.74) p = 0.003</td>
<td>OR (95% CI) for treatment vs. placebo 0.43 (0.24, 0.76) p = 0.004</td>
<td>OR (95% CI) for treatment vs. placebo 0.43 (0.24, 0.76) p = 0.004</td>
<td>OR (95% CI) for treatment vs. placebo 0.45 (0.24, 0.77) p = 0.004</td>
<td></td>
</tr>
<tr>
<td>4. The effect of treatment assignment on the odds of a clinical event is attenuated with the addition of ΔHD to the model (compare with #3 above)</td>
<td>OR (95% CI) for treatment vs. placebo 0.45 (0.25, 0.81) p = 0.008</td>
<td>OR (95% CI) for treatment vs. placebo 0.42 (0.24, 0.75) p = 0.004</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.26, 0.87) p = 0.016</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.26, 0.88) p = 0.016</td>
<td>OR (95% CI) for treatment vs. placebo 0.45 (0.25, 0.81) p = 0.008</td>
<td></td>
</tr>
<tr>
<td>% variability explained by ΔHD (95% CI)</td>
<td>12.2 (8.0, 38.1)</td>
<td>1.8 (-9.3, 16.2)</td>
<td>13.9 (1.4, 42.9)</td>
<td>14.1 (1.5, 42.2)</td>
<td>7.1 (-10.3, 45.0)</td>
<td>4.9 (-14.5, 24.7)</td>
</tr>
</tbody>
</table>

All models include adjustment for baseline hemodynamic value and study. ΔRAP=change in right atrial pressure; ΔmPAP=change in mean pulmonary artery pressure; ΔCO=change in cardiac output; ΔCI=change in cardiac index; ΔPVR=change in pulmonary vascular resistance; ΔPA compliance=change in pulmonary artery compliance; ΔHD=change in hemodynamic measure at 12 weeks as compared to baseline; OR=odds ratio; CI=confidence interval.
Supplemental Table 2. Criteria to establish the change in a hemodynamic measure (ΔHD) as a mediator in the relationship between treatment assignment and clinical events at 12 weeks; in AIR study patients hemodynamics 60 minutes post-iloprost inhalation were used to calculate the change values.

<table>
<thead>
<tr>
<th>Hemodynamic measure</th>
<th>ΔRAP</th>
<th>ΔmPAP</th>
<th>ΔCO</th>
<th>ΔCI</th>
<th>ΔPVR</th>
<th>ΔPA Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment assignment has a significant effect on ΔHD</td>
<td>Mean difference (95% CI) between treatment and placebo -1.2 mm Hg (-1.8, -0.61) p = 0.020</td>
<td>Mean difference (95% CI) between treatment and placebo -2.3 mm Hg (-3.3, -1.2) p = 0.019</td>
<td>Mean difference (95% CI) between treatment and placebo 0.37 L/min (0.24, 0.50) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo 0.22 L/min/m² (0.15, 0.29) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo 2.1 Wood units (-2.7, -1.5) p &lt; 0.001</td>
<td>Mean difference (95% CI) between treatment and placebo 0.14 mL/mm Hg (0.08, 0.21) p &lt; 0.001</td>
</tr>
<tr>
<td>2. ΔHD has a significant effect on the odds of a clinical event</td>
<td>OR (95% CI) per 1 mm Hg increase 1.04 (0.99, 1.09) p = 0.107</td>
<td>OR (95% CI) per 1 mm Hg increase 1.01 (0.98, 1.04) p = 0.381</td>
<td>OR (95% CI) per 1 L/min increase 0.69 (0.52, 0.92) p = 0.010</td>
<td>OR (95% CI) per 1 L/min/m² unit increase 0.53 (0.32, 0.87) p = 0.012</td>
<td>OR (95% CI) per 1 Wood unit increase 1.08 (1.03, 1.13) p = 0.002</td>
<td>OR (95% CI) per 1 mL/mmHg increase 0.68 (0.22, 2.13) p = 0.450</td>
</tr>
<tr>
<td>3. Treatment assignment has a significant effect on the odds of a clinical event</td>
<td>OR (95% CI) for treatment vs. placebo 0.43 (0.28, 0.66) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.31, 0.72) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.32, 0.74) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.49 (0.30, 0.72) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.47 (0.31, 0.73) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.29, 0.68) p = 0.003</td>
</tr>
<tr>
<td>4. The effect of treatment assignment on the odds of a clinical event is attenuated with the addition of ΔHD to the model (compare with #3 above)</td>
<td>OR (95% CI) for treatment vs. placebo 0.44 (0.29, 0.68) p = 0.003</td>
<td>OR (95% CI) for treatment vs. placebo 0.48 (0.32, 0.73) p &lt; 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.53 (0.34, 0.81) p = 0.003</td>
<td>OR (95% CI) for treatment vs. placebo 0.53 (0.33, 0.82) p = 0.005</td>
<td>OR (95% CI) for treatment vs. placebo 0.49 (0.32, 0.76) p = 0.001</td>
<td>OR (95% CI) for treatment vs. placebo 0.44 (0.29, 0.68) p &lt; 0.001</td>
</tr>
<tr>
<td>% variability explained by ΔHD (95% CI)</td>
<td>3.8 (-2.1, 12.5)</td>
<td>1.8 (-3.6, 11.5)</td>
<td>11.9 (2.8, 38.0)</td>
<td>12.2 (2.5, 39.6)</td>
<td>15.9 (4.0, 51.6)</td>
<td>3.4 (-5.3, 15.8)</td>
</tr>
</tbody>
</table>

All models include adjustment for baseline hemodynamic value and study. ΔRAP=change in right atrial pressure; ΔmPAP=change in mean pulmonary artery pressure; ΔCO=change in cardiac output; ΔCI=change in cardiac index; ΔPVR=change in pulmonary vascular resistance; ΔPA compliance=change in pulmonary artery compliance; ΔHD=change in hemodynamic measure at 12 weeks as compared to baseline; OR=odds ratio; CI=confidence interval.