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The heterogeneity of clinical practice patterns among an international cohort of pulmonary arterial hypertension experts

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Abstract: The extent to which pulmonary arterial hypertension (PAH) experts share common practice patterns that are in alignment with published expert consensus recommendations is unknown. Our objective was to characterize the clinical management strategies used by an international cohort of self-identified PAH experts. A 32-item questionnaire composed mainly of rank order or Likert scale questions was distributed via the Internet (August 5, 2013, through January 20, 2014) to four international pulmonary vascular disease organizations. The survey respondents (N = 105) were field experts reporting 11.6 ± 8.7 years of PAH experience. Likert scale responses (1 = disagree, 7 = agree) were 3.0–5.0, indicating a disparity in opinions, for 78% of questions. Respondent (dis)agreement scores were 4.4 ± 2.2 for use of expert recommendations to determine catheterization timing in PAH. For PAH patients without cardiogenic shock or known vasoreactivity status, the most and least preferred first-line therapies (1 = most preferred, 5 = least preferred) were phosphodiesterase type 5 inhibitors (PDE-Vi) and subcutaneous prostacyclin analogues, respectively (1.4 ± 0.8 vs. 4.0 ± 1.1; P < 0.05). Compared with US-practicing clinicians (N = 46), non-US-practicing clinicians (N = 57) favored collaboration between cardiology and pulmonary medicine for clinical decision making (1 = disagree, 7 = agree; 3.1 ± 2.2 vs. 4.8 ± 2.2; P < 0.0001) and PDE-Vi (6.5% vs. 22.4%) as first-line therapy for PAH patients with cardiogenic shock but were less likely to perform vasoreactivity testing in patients with lung disease–induced pulmonary hypertension (4.3 ± 2.1 vs. 2.2 ± 1.6; P < 0.0001). In conclusion, practice patterns among PAH experts diverge from consensus recommendations and differ by practice location, suggesting that opportunity may exist to improve care quality for this highly morbid cardiopulmonary disease.

Keywords: clinical care, survey, pulmonary arterial hypertension, right ventricle.


INTRODUCTION

Adherence to standardized care is an established contributor to improved outcome in various cardiovascular and respiratory diseases, including coronary artery disease, genetic cardiomyopathies, and asthma, among others.1-3 The development of evidence-based expert consensus guidelines, which now exist across virtually all clinical scenarios in cardiopulmonary medicine,4 define disease-specific metrics for diagnosis, treatment, and long-term patient management. Consensus guideline recommendations, in turn, have evolved as a premium strategy by which to improve quality of care and clinical outcomes for patients with cardiopulmonary disease.5

Pulmonary arterial hypertension (PAH) is a severe cardiopulmonary disease associated with substantial morbidity and premature longevity.6,7 A range of pulmonary circulation–specific pharmacotherapeutic and surgical strategies has emerged recently to improve functional capacity, quality of life, and survival in PAH.8,9 Despite these advances, there is substantial underdiagnosis and inappropriate treatment of PAH in clinical practice.10,11 To address these issues, an international effort was undertaken in 2009 to establish the first expert consensus documents in the contemporary era for the diagnosis, treatment, and management of PAH patients.12,13 Since then, however, there have been numerous
reports of ongoing heterogeneity in diagnostic and treatment strategies for patients with PAH. Practice patterns in PAH are reported to differ by institution, by era of practitioners, and even by geographic region. 

Taken together, these findings suggest that penetration of expert consensus recommendations into clinical practice in PAH may as yet be unrealized. However, there are few empirical data with which to address this concern. To fill this gap in our present understanding of treatment patterns in PAH and to identify areas in which a significant lack of consensus remains among experts regarding care, a survey containing questions relevant to assessment, diagnosis, and treatment of PAH was distributed to an international cohort of PAH and pulmonary vascular disease specialists.

METHODS
This survey study was approved by the investigational review board for patient safety and privacy at Brigham and Women’s Hospital and complies with the Declaration of Helsinki. Written consent was implied by completion of the questionnaire.

Survey content
The complete survey is available at http://pvri.info/content/pulmonary-hypertension-clinician-survey. In general, surveys consisted of (1) a cover letter outlining the purpose of the survey and soliciting participation from self-identified PAH experts, (2) a general information respondent form, and (3) 28 multiple choice, rank order, or 7-point Likert scale questions (1 = disagree, 7 = agree; Table 1). The topics relevant to PAH clinical practice under investigation were practice patterns related to hemodynamic and pulmonary vasoreactivity testing, selection and implementation of PAH-specific drug therapies, and clinical management of PAH patients. In some cases, questions involving clinical practice preferences for pulmonary vascular diseases other than PAH were included, particularly with respect to patients with pulmonary hypertension due to lung disease (i.e., World Health Organization [WHO] group 3 pulmonary hypertension). The rationale for including questions addressing practice profile differences in these patients was based on overlap in pathophenotype and diagnostic approach reported by some for WHO group 3 and PAH patients and on ongoing debate within the larger pulmonary vascular disease community regarding optimal treatment of WHO group 3 pulmonary hypertension. An expert in the field of survey science performed survey validation, and the survey respondents were from 25 countries and 6 continents. Comparisons between multiple groups were made using one-way analysis of variance (ANOVA).

Statistical analysis
All statistical analyses were performed using Origin (ver. 9.1; Northampton, MA). Categorical variables are reported as frequencies; unless otherwise indicated, continuous data are expressed as mean ± SD (range). The unpaired Student t test was used to compare two independent groups.

RESULTS
Study population
A total of 105 anonymous individual surveys were completed and submitted during the study period (80 men; mean age, 47.3 years; age range, 29–68 years; Table 2). Survey respondents were from 25 countries and 6 continents (Fig. 1A) and were trained principally in pulmonary medicine (N = 63) and cardiology (N = 29), although a total of 6 clinical specialties and nursing were represented (Fig. 1B).

Participants reported 11.6 ± 8.7 years of PAH clinical practice, with 43.1% of all clinical effort devoted to PAH patients. Clinicians’ PAH patient panels were generated by local and nonlocal referrals for 91.4% and 80.0% of respondents, respectively, and a majority (57.4%) reported employment at an institution with an active heart/lung transplant program. All survey respondents reported participation in PAH research, which involved basic science (48.5%), preclinical studies (30.4%), and/or clinical trials (80.9%). Involvement in ≥2 areas of research was reported by 38 (36.1%) survey participants, and 20 (19.0%) respondents reported participation in all research areas. Among 4 commonly available clinical practice resources, study participants rank ordered expert consensus recommendations as the most influential on clinical practice (1.6 ± 0.9 on a scale of 1 [most useful] to 5 [least useful]), followed by international scientific sessions (1.7 ± 0.9), personal clinical experience (3.5 ± 1.3), and information provided...
by pharmaceutical companies (4.5 ± 0.6; \( P < 0.05 \) for comparison across groups).

**Invasive cardiopulmonary hemodynamic assessment and pulmonary vasoreactivity testing**

Despite the importance of invasive cardiopulmonary hemodynamic assessment and vasoreactivity testing on diagnosis and prognosis in PAH, the application of right heart catheterization (RHC), left heart catheterization (LHC), and/or confrontational pulmonary vasodilator testing in clinical practice is controversial. Thus, the survey consisted of a series of questions relevant to RHC (Table 3) and LHC (Table 4) in PAH. Participants reported 4.4 ± 2.2 (1–7) on a 7-point Likert scale (1 = disagree, 7 = agree) in response to a statement assessing (dis)agreement with expert consensus recommendations as a key resource for determining the timing of RHC for diagnosis/prognosis of PAH. Similar trends were reported for the role of invasive cardiopulmonary hemodynamic assessment in PAH patient management beyond diagnosis: (dis)agreement scores for RHC as a routine method to assess treatment efficacy or to evaluate further clinical deterioration were 4.1 ± 2.0 (1–7) and 4.4 ± 2.1 (1–7), respectively. Increased parity was reported for the role of repeat vasoreactivity testing as a component of routine clinical care in PAH (2.9 ± 2.0 [1–7]), and agreement was reported in favor of echocardiography for the routine monitoring of right ventricular function in clinically stable patients (6.1 ± 1.4 [1–7]).

(Dis)agreement scores for pulmonary vasoreactivity testing in patients with suspected WHO group 3 pulmonary hypertension (i.e., lung disease–induced pulmonary hypertension), for which evidence-based guidelines do not exist, were 3.1 ± 2.1 (1–7). However, it is worthwhile to note that differences with respect to this issue were observed
according to the mode of healthcare reported for PAH patients by survey respondents. Compared with survey participants for whom health insurance of patients was reported to be mainly through a national health plan ($N = 62$), those survey participants for whom health insurance of patients was reported to be mainly through private health insurance ($N = 17$) tended to be more agreeable with vaso-reactivity testing for WHO group 3 patients ($2.8 \pm 2.0$ vs. $4.4 \pm 2.1$; $P < 0.01$; Fig. 2).

**PAH treatment**

A key determination of the 2009 expert consensus guidelines in PAH was establishing the role of treatment with calcium channel antagonists as the primary phar-

Table 3. Responses to questions involving the relevance of cardiac catheterization and pulmonary vasoreactivity testing to the diagnosis/management of pulmonary arterial hypertension

<table>
<thead>
<tr>
<th>Survey question</th>
<th>Response ($N = 105$), mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A key guideline for determining the timing of invasive hemodynamic assessment for patients with pulmonary arterial hypertension (PAH) in your practice is the expert consensus guideline statement on the topic published in 2009$^{12}$</td>
<td>$4.4 \pm 2.2$ (1–7)</td>
</tr>
<tr>
<td>It is reasonable to perform pulmonary vasoreactivity testing as part of the clinical evaluation for patients with suspected chronic lung disease–induced pulmonary hypertension (i.e., World Health Organization [WHO] group 3 pulmonary hypertension)</td>
<td>$3.1 \pm 2.1$ (1–7)</td>
</tr>
<tr>
<td>A substantial decrease in pulmonary hypertension severity on pulmonary vasoreactivity testing influences your choice of first-line pulmonary vasodilator therapy in patients requiring treatment of symptomatic PAH</td>
<td>$5.6 \pm 1.7$ (1–7)</td>
</tr>
<tr>
<td>Right heart catheterization is a routine strategy by which to monitor (i.e., follow-up) the treatment responsiveness of PAH patients to pulmonary vasodilator therapy</td>
<td>$4.1 \pm 2.0$ (1–7)</td>
</tr>
<tr>
<td>Among patients initiated on pulmonary circulation–specific therapy following invasive hemodynamic assessment, a repeat right heart catheterization is performed in your practice in patients with clinical deterioration only</td>
<td>$4.3 \pm 2.1$ (1–7)</td>
</tr>
</tbody>
</table>

Note: Answers are reported on the basis of a 7-point Likert scale (1 = disagree, 7 = agree).
macotherapy for patients demonstrating pulmonary vasoreactivity in response to acute pulmonary vasodilator challenge in the absence of cardiogenic shock. In response to a survey question addressing (dis)agreement with this recommendation (1 = disagree, 7 = agree), results were 4.7 ± 2.3 (1–7). In turn, among PAH patients with unknown vasoreactivity status without cardiogenic shock, (dis)agreement with calcium channel antagonist therapy as first-line treatment was (1 = disagree, 7 = agree) 1.6 ± 1.5 (1–7). Furthermore, rank order analysis of first-line agents under these clinical conditions presented in order of most to least preferred was phosphodiesterase type 5 inhibitor (PDE-Vi), nonselective endothelin receptor antagonist (ERA), selective endothelin type A receptor antagonist (ETARA), inhaled prostacyclin analogue (PGI2), parenteral PGI2, and subcutaneous PGI2 (1.4 ± 0.8 vs. 2.3 ± 1.0 vs. 2.5 ± 1.1 vs. 3.4 ± 1.2 vs. 3.6 ± 1.3 vs. 4.0 ± 1.1; N = 105; P < 0.05 by ANOVA; Fig. 3A). Interestingly, preference for PDE-Vi as first-line therapy in WHO group 3 pulmonary hypertension was less well established, with respondents reporting a (dis)agreement score of 4.0 ± 2.1 (1–7). With respect to strategies involving initiation of dual pulmonary vasodilator therapy, a tendency toward agreement with maximizing the drug dose of a single pulmonary hypertension–specific therapy prior to initiation of an additional pulmonary hypertension–specific therapy was observed (4.9 ± 1.6 [1–7]).

In concert with expert consensus recommendations, parenteral PGI2 was identified by a majority (69.5%) of survey respondents as the preferred first-line treatment of PAH patients with cardiogenic shock, although PDE-Vi and ERA were selected by 16.5% and 10.5% of respondents, respectively (Fig. 3B). Greater disparity was observed for the preferred inotropic agent to support cardiac output in patients with right ventricular dysfunction due to PAH (Fig. 4).

Five common barriers to the implementation of preferred therapy in PAH across the study cohort were ranked by survey participants (N = 105; 1 = most common, 5 = least common; Table 5). Overall, patients’ social circumstances preventing drug compliance was reported as the strongest factor to limit optimal treatment selection, while access to drug therapy was least likely to influence drug selection (2.3 ± 0.1 vs. 3.6 ± 0.1; P < 0.001).

**Ambulatory care strategies**

Periodically measuring biochemical evidence of heart failure and functional capacity is reported as an acceptable strategy by which to monitor the clinical trajectory of PAH in the ambulatory setting, although the extent to which this is applied in clinical practice is unknown. Responses indicating (dis)agreement with the routine measurement of 6-minute walk distance or plasma brain natriuretic peptide concentration were 4.5 ± 2.3 (1–7). An international cohort of pulmonary vascular disease experts (N = 105) completed an Internet-based survey soliciting a response of (dis)agreement to the following statement: “It is reasonable to perform pulmonary vasoreactivity testing as part of the clinical evaluation for patients with suspected chronic lung disease–induced pulmonary hypertension (i.e., World Health Organization [WHO] group 3 pulmonary hypertension).” Results are presented by primary health insurance coverage (national healthcare system vs. private healthcare insurance) of PAH patients in the practice of each respondent, as reported in the survey by respondents. Data are expressed as mean ± SD.
triuretic peptide concentration were 5.0 ± 1.7 and 4.7 ± 1.6, respectively. Along these lines, an evolving trend in the management of patients with complex pulmonary vascular disease is through a multidisciplinary effort between pulmonary medicine and cardiology, among other disciplines.31 Whereas (dis)agreement scores were 4.2 ± 2.2 that key decisions for the management of PAH patients are achieved through a consensus decision between a pulmonary medicine and a cardiology expert, we observed a significant difference with respect to this issue by geographic location. Compared with US-practicing clinicians (N = 46), a greater tendency to report joint pulmonary-cardiology collaborations in PAH management was observed among non-US-practicing clinicians (N = 59; 3.1 ± 2.2 vs. 4.8 ± 2.2; P < 0.0001; Fig. 5).

Regional differences in care and treatment patterns

Owing to our observation that use of joint pulmonary-cardiology collaborations in PAH differs between US and non-US experts, we next explored the effect of these regional differences on diagnostic and treatment strategies in PAH and other pulmonary vascular diseases. We observed no significant difference between US-practicing (N = 46) and non-US-practicing (N = 59) clinicians with respect to (dis)agreement scores (1 = disagree, 7 = agree) for use of 6-minute walk distance (4.7 ± 1.7 vs. 5.2 ± 1.8; P = 0.11), plasma B-type natriuretic peptide (4.8 ± 1.8 vs. 4.6 ± 1.3; P = 0.38), and echocardiography (6.0 ± 1.5 vs. 6.1 ± 1.2; P = 0.64) to monitor the clinical progress of PAH patients in the ambu-
latory setting. Compared with non-US-practicing clinicians, US-practicing clinicians reported a similar tendency to utilize invasive cardiopulmonary hemodynamic assessment as a routine test performed during follow-up of PAH patients prescribed vasodilator therapy (1 = disagree, 7 = agree; 4.1 ± 2.0 vs. 4.2 ± 2.0; P = 0.91); however, a significant difference was observed between groups with respect to performing vasoreactivity testing in the diagnostic evaluation of patients with WHO group 3 pulmonary hypertension (2.2 ± 1.6 vs. 4.3 ± 2.1; P < 0.0001; Fig. 6A).

Rank order analysis of 6 potential first-line agents for the treatment of PAH patients without cardiogenic shock in the absence of known pulmonary vasoreactivity status revealed that PDE-Vi therapy is favored similarly by non-US-practicing and US-practicing clinicians (1 = most preferred, 5 = least preferred; 1.4 ± 0.9 vs. 1.5 ± 0.7; P = 0.71). However, whereas US-practicing physicians were more likely than non-US-practicing clinicians to favor first-line therapy in this clinical situation with subcutaneous PGI2 (3.7 ± 1.3 vs. 4.3 ± 0.9; P < 0.01) and parenteral PGI2 (3.2 ± 1.3 vs. 3.8 ± 1.2; P < 0.02), the opposite trend was observed for ERA use (2.7 ± 0.9 vs. 2.0 ± 1.0; P < 0.002). The percentage of respondents identifying each of 6 therapies as preferred for the first-line treatment of symptomatic PAH patients with cardiogenic shock according to practice location is provided in Figure 6B, which illustrates differences between non-US-practicing and US-practicing clinicians for the selection of PGI2 (56.9% vs. 86.9%), PDE-Vi (22.4% vs. 6.5%), and inhaled PGI2 (15.5% vs. 2.1%).

DISCUSSION
This is the largest empirical report to date to characterize the opinions and clinical practice patterns of PAH experts, which was defined in this study as substantial PAH experience, academic focus, and international distribution of practice locations reported by the survey respondents. Our findings demonstrate important disparity among study participants in each of the measured facets of relevance to PAH clinically, including strategies for diagnosis, pharmacotherapy selection, and ambulatory patient management. Although participants identified expert consensus recommendations as the most valued resource for clinical decision making in PAH, results from this survey indicate that practice patterns diverge from these recommendations in several areas, particularly with respect to indications for RHC/pulmonary vasoreactivity testing as well as evidence-based algorithms for PAH therapy initiation.

Several recent publications have demonstrated that a mismatch between expert consensus recommendations and applied clinical care patterns exists for patients with pulmonary vascular disease and have shown that this trend is consistent across various patient populations, including community-based, referred, and military veteran cohorts.11,15,32 Failure to adhere to consensus recommen-

### Table 5. Potential barriers to prescribing preferred therapy in pulmonary arterial hypertension (PAH)

<table>
<thead>
<tr>
<th>Potential treatment barrier</th>
<th>Rank order response (N = 105), mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social circumstances prevent drug therapy compliance</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>Comorbid psychological/psychiatric disease prevents drug therapy compliance</td>
<td>2.8 ± 0.1</td>
</tr>
<tr>
<td>Patients’ financial circumstances prevent access to drug therapy</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td>Patient refuses drug therapy</td>
<td>3.4 ± 0.1</td>
</tr>
<tr>
<td>Drug therapy is not provided by the pharmacy accessed by the patient or the healthcare provider</td>
<td>3.7 ± 0.1</td>
</tr>
</tbody>
</table>

Note: Answers are reported on the basis of a rank order scale (1 = most common barrier to PAH treatment, 5 = least common barrier to PAH treatment).

Respondents’ Opinion on the Use of Joint Pulmonary-Cardiology Collaboration for the Management of PAH Patients.

Figure 5. Regional differences and the use of a multidisciplinary approach to the management of pulmonary arterial hypertension (PAH) patients. An international cohort of pulmonary vascular disease experts (N = 105) completed an Internet-based survey soliciting a response of (dis)agreement to the following statement: “Key management decisions for PAH patients are achieved through a consensus decision between a pulmonary medicine and cardiology expert in pulmonary hypertension.” Results are presented according to geographic location of practice. Data are expressed as mean ± SD.
dations in pulmonary vascular disease, in turn, is associated with suboptimal rates of diagnosis and treatment. In one study by Deáņo and colleagues, pulmonary hypertension misdiagnosis rates were as high as 52%, which was associated with similar rates of inappropriate therapy. Similar findings are reported for evaluation completeness for PAH, in which appropriate screening for root cause of pulmonary vascular dysfunction, such as connective tissue disease or human immunodeficiency virus, may be as low as 29% in nonreferral populations. Our findings are in concert with these earlier observations by suggesting that variability in care patterns are observed in practice globally even among expert PAH clinicians.

Disparity was observed for drug class preference in PAH relative to consensus recommendations: whereas parenteral PGI$_2$ therapy initiation is supported by a class 1 recommendation in current and recent guidelines for patients with PAH, cardiogenic shock, and unknown vasoreactivity status, several alternative therapies were identified in our survey as preferred first-line treatment under these clinical conditions. Disparity in opinion was also reported for the use of calcium channel antagonist therapy in PAH patients with preserved vasoreactivity despite reproducible clinical trial data and a class 1 recommendation in support of this drug class as an effective treatment for this
PAH clinical profile. However, these findings may be accounted for by published expert recommendations indicating that PDE-Vi, in addition to calcium channel antagonist therapy, is an acceptable treatment option under these clinical conditions.37,38 No consensus was observed among experts for the use of PDE-Vi therapy in WHO group 3 pulmonary hypertension, which is in concert with varying opinions reported on this issue in the literature.32,38

There are several limitations to this study beyond factors intrinsic to survey research that merit discussion when interpreting our findings. First, our approach was to solicit survey responses from self-identified PAH experts belonging to medical organizations with an established commitment to pulmonary vascular disease. The precise survey response rate expressed as a fraction of participants relative to the overall universe of PAH experts, thus, cannot be calculated, nor were objective criteria for defining PAH expert used a priori to determine inclusion eligibility in this study. Taken together, the degree to which our study cohort was truly representative of the PAH expert community cannot be quantified beyond PAH-specific experience, PAH research involvement, and time commitment in clinical practice devoted to PAH patients (as provided in Table 2). Nevertheless, since survey completion alone may be indicative of participation bias among the study cohort, interpretation of our data also requires consideration of this potentially confounding effect.

Second, the survey was distributed internationally in English. Thus, it is not possible to characterize the potential confounding effect of language barriers to study participation and/or answer accuracy. Along these lines, the possibility remains that statement formatting resulted in ambiguous questions and/or answer selections, which would undoubtedly introduce a response bias to our results. Additionally, physicians practicing in the United States represented the largest geographical group of survey respondents, although the effect of this on the results of analyses involving the entire cohort was not addressed specifically.

Third, this survey was not intended to identify a rationale by which to account for respondents’ survey question answers. Therefore, it is conceivable that inaccessibility to resources (or clinical experiences) necessary to interpret question(s) accurately contributed to answer selection, rather than clinical acumen alone.

Conclusions
Despite the availability of a contemporary expert consensus statements, there is disparity in opinion regarding the clinical approach to PAH among experts in the field. Specifically, divergence from evidence-based recommendations was reported in this survey study for diagnostic strategies and application of drug therapy for patients, which was observed across different hypothetical clinical scenarios. These data illustrate the need for standardized and validated clinical guidelines in the field of pulmonary vascular disease, which is anticipated to improve outcome in patients afflicted with PAH and other diseases of similar pathophysiology.

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Conflict of Interest: BAM receives funding from Gilead Sciences to research pulmonary arterial hypertension. GB receives consulting funding from Bayer, Novartis, Pfizer, and Ikaria.

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