

Patients' perceptions on clinical trials outcomes in pulmonary arterial hypertension therapy

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ABSTRACT

The value placed by patients and their caregivers on the components of composite outcomes in pulmonary arterial hypertension (PAH) remains unknown. We surveyed the importance of these outcomes from a patients' and caregivers' perspective, with participants (n=335, including 257 patients with PAH) rating individual components defining clinical worsening in PAH trials as of critical, major, mild-to-moderate or minor importance. Most outcomes were considered of major or mild-to-moderate importance to patients. Death was the only outcome considered of critical importance. Perceptions of clinical outcomes varied between patients and caregivers. Integrating patients' perception in the elaboration of clinical trials is essential.

INTRODUCTION

Clinical worsening (CW), a composite endpoint, has been increasingly used in pulmonary arterial hypertension (PAH) clinical trials to evaluate the effects of novel treatments. While attempts were made to assess the relevance of the individual occurrence of CW in PAH,^{1,2} clinically meaningful outcomes are not necessarily 'patient-important'. With an increasing emphasis on patient centeredness in clinical research, involving patients in the research process is mandatory to ensure that trials assess outcomes and interventions relevant to patients' priorities.³ However, PAH impacts individuals' lives on different aspects,⁴ and the importance of outcome components for PAH patients is not known. Therefore, the real impact of PAH therapy on patients' global health perception is uncertain.

The aim of our study was to evaluate the importance, from the patient and caregiver perspectives, of the various component outcomes previously used to define CW in PAH clinical trials.

METHODS

A secured web-based survey (REDCap, V.11.1.2) was completed anonymously by patients with PAH and caregivers from two patient associations (Fondation HTAPQ and PHA Canada) and medical caregivers from 15 PAH centres in Canada. Each participant provided an informed consent. The study was approved by the IUCPQ-UL ethics board (CER 21940) and was reported according to the ethically approved process. Twenty-three specific CW components used in PAH clinical trials were identified as part of a systematic review (PROSPERO-CRD42020178949).⁵ Participants

categorised the prevention of each component as of (1) critical (would almost prefer to die rather than experiencing it); (2) major (major impact on the patient's general well-being); (3) mild-to-moderate (would live without a significant impact on their well-being) or (4) minor (no impact the patient's well-being) importance. The importance of each outcome was determined based on the categorisation most commonly selected by patients and their caregivers as well as across PAH patients' subgroups (sex, age, PAH type and PAH severity). To quantify concordance among patients with PAH and caregivers, we calculated the Gwet second-order agreement coefficient (AC2). The categorisation of individual outcomes by patients versus caregivers were compared using the Fisher's exact test.

RESULTS

Of the 335 participants, 257 were patients with PAH and 78 were caregivers. Most patients were 50–79-year-old Caucasian women with high school or higher-level diploma living in larger cities (table 1). Most patients had idiopathic/hereditary PAH (39%) with slight-to-moderate functional limitations (49%) despite diverse therapies.

Individual patients most commonly rated outcomes as being of major and mild-to-moderate importance (figure 1). Only preventing death was considered critical by a majority of patients, whereas hospitalisation, addition of an oral therapy, change in the epoprostenol dose and 5%–15% decrease in 6 min walk test were mostly considered of mild-to-moderate importance (figure 2). However, the overall concordance between patients was poor (AC2: 0.06; 95% CI 0.03 to 0.09). Of interest, the prevention of hospitalisation, start of a prostacyclin analogue and persistent functional decline were generally perceived as more valuable for caregivers compared with patients, although the overall agreement among caregivers was also poor (AC2: 0.14; 95% CI 0.08 to 0.19). Exploratory subgroup analyses also suggested that the value given to many components varied according to patients' characteristics.

DISCUSSION

This study showed that the importance of the outcomes defining CW in PAH trials was heterogeneous across patients and their caregivers. While a critical and major importance was attributed to preventing death and transplantation, respectively, around one-third of the outcome components were perceived as only of mild-to-moderate importance

Table 1 Characteristics of the participants

Characteristics	Patients (n=257)	Others* (n=78)	Total (n=335)
Role—n (%)			
Patients	257 (100.0)	0 (0.0)	257 (76.7)
Caregivers	0 (0.0)	25 (32.1)	25 (7.5)
Friend/family members	0 (0.0)	23 (29.5)	23 (6.9)
Medical caregivers	0 (0.0)	30 (38.5)	30 (9.0)
Sex—n (%)			
Men	41 (16.0)	25 (32.1)	66 (19.7)
Women	197 (76.7)	49 (62.8)	246 (73.4)
No answer	19 (7.4)	4 (5.1)	23 (6.9)
Age—n (%)			
18–49 years old	59 (23.0)	30 (38.5)	89 (26.6)
50–64 years old	78 (30.4)	27 (34.6)	105 (31.3)
≥65 years old	101 (39.3)	17 (21.8)	118 (35.2)
No answer	19 (7.4)	4 (5.1)	23 (6.9)
Ethnicity—n (%)			
African Heritage	2 (0.8)	0 (0.0)	2 (0.6)
Asian	5 (1.9)	5 (6.4)	10 (3.0)
Latin American	3 (1.2)	1 (1.3)	4 (1.2)
Middle Eastern	1 (0.4)	2 (2.6)	3 (0.9)
North American Indigenous	1 (0.4)	2 (2.6)	3 (0.9)
White (Caucasian)	213 (82.9)	63 (80.8)	276 (82.4)
Other†	11 (4.3)	0 (0.0)	11 (3.3)
Prefer not to say	2 (0.8)	1 (1.3)	3 (0.9)
No answer	19 (7.4)	4 (5.1)	23 (6.9)
Province—n (%)			
Alberta	21 (8.2)	6 (7.7)	27 (8.1)
Ontario	84 (32.7)	29 (37.2)	113 (33.7)
British Columbia	32 (12.5)	9 (11.5)	41 (12.2)
Quebec	69 (26.8)	15 (19.2)	84 (25.1)
Prince Edward Island	2 (0.8)	1 (1.3)	3 (0.9)
Saskatchewan	1 (0.4)	1 (1.3)	2 (0.6)
Manitoba	5 (1.9)	1 (1.3)	6 (1.8)
Northwest Territories	0 (0.0)	0 (0.0)	0 (0.0)
New Brunswick	4 (1.6)	2 (2.6)	6 (1.8)
Newfoundland and Labrador	3 (1.2)	3 (3.8)	6 (1.8)
Nova Scotia	3 (1.2)	3 (3.8)	6 (1.8)
Yukon	0 (0.0)	1 (1.3)	1 (0.3)
Nunavut	0 (0.0)	0 (0.0)	0 (0.0)
Outside Canada‡	10 (3.9)	2 (2.6)	12 (3.6)
Prefer not to say	4 (1.6)	1 (1.3)	5 (1.5)
No answer	19 (7.4)	4 (5.1)	23 (6.9)
Community size in which the participants live—n (%)			
>500 000 persons	70 (27.2)	30 (38.5)	100 (29.9)
100 000–500 000 persons	50 (19.5)	12 (15.4)	62 (18.5)
30 000–99 999 persons	46 (17.9)	16 (20.5)	62 (18.5)
1000–29 999 persons	45 (17.5)	11 (14.1)	56 (16.7)
<1000 persons	19 (7.4)	5 (6.4)	24 (7.2)
Do not know	8 (3.1)	0 (0.0)	8 (2.4)

Continued

Table 1 Continued

Characteristics	Patients (n=257)	Others* (n=78)	Total (n=335)
No answer	19 (7.4)	4 (5.1)	23 (6.9)
Schooling—n (%)			
Less than high school diploma or its equivalent	18 (7.0)	2 (2.6)	20 (6.0)
High school diploma or a high school equivalency certificate	53 (20.6)	5 (6.4)	58 (17.3)
Postsecondary certificate or diploma	94 (36.6)	20 (25.6)	114 (34.0)
University degree	71 (27.6)	46 (59.0)	117 (34.9)
Prefer not to say	2 (0.8)	1 (1.3)	3 (0.9)
No answer	19 (7.4)	4 (5.1)	23 (6.9)

*Medical and non-medical caregivers.
†Bosnia and Herzegovina, Český, East Indian, French Canadian, Metis, North Africa, Turkey, South Asian.
‡Australia, Česká republika, Congo DRC, India, Italy, Saudi Arabia, Tunisia, United Kingdom, USA.

to patients. Of interest, caregivers attributed more importance to preventing some of these outcomes, which also varied according to patients' characteristics. Taken together, the various components defining CW in PAH trials are heterogeneously valuable to individual patients.

By definition, endpoints are 'well-defined and reliable measures that assess important aspects of patient health status in order to enhance the informativeness of clinical trials regarding benefits and risks of treatments'.⁶ In PAH, the composite outcome of CW has been increasingly used to capture the treatment effects on several aspects of the disease considered as clinically meaningful.⁷ However, noticeable changes in the occurrence of adverse events may be clinically relevant without necessarily being 'patient important'. Consistently, one-third of the components were considered of mild-to-moderate importance to patients, suggesting that many outcomes are not truly valuable

to patients.

On the other side, patients assigned significant importance to the lack of clinical improvement, the need for long-term oxygen therapy and any decrease in health-related quality of life, supporting the fact that PAH affects many aspects of patients' lives and contributes to physical, financial, social and emotional burden.⁴ Moving towards greater inclusion of patient-reported outcomes in PAH clinical trials is challenged by the fact that many PAH studies showed improvements in quality of life that failed to meet the minimal important difference.⁸ Of interest, some components judged as of mild-to-moderate importance to patients were commonly considered of major importance by caregivers, such as hospitalisations. This discordance is not unique to PAH, as caregivers have traditionally made implicit judgments overstating the importance of outcomes' or symptoms for patients.⁹ Moreover, patients assign varying importance

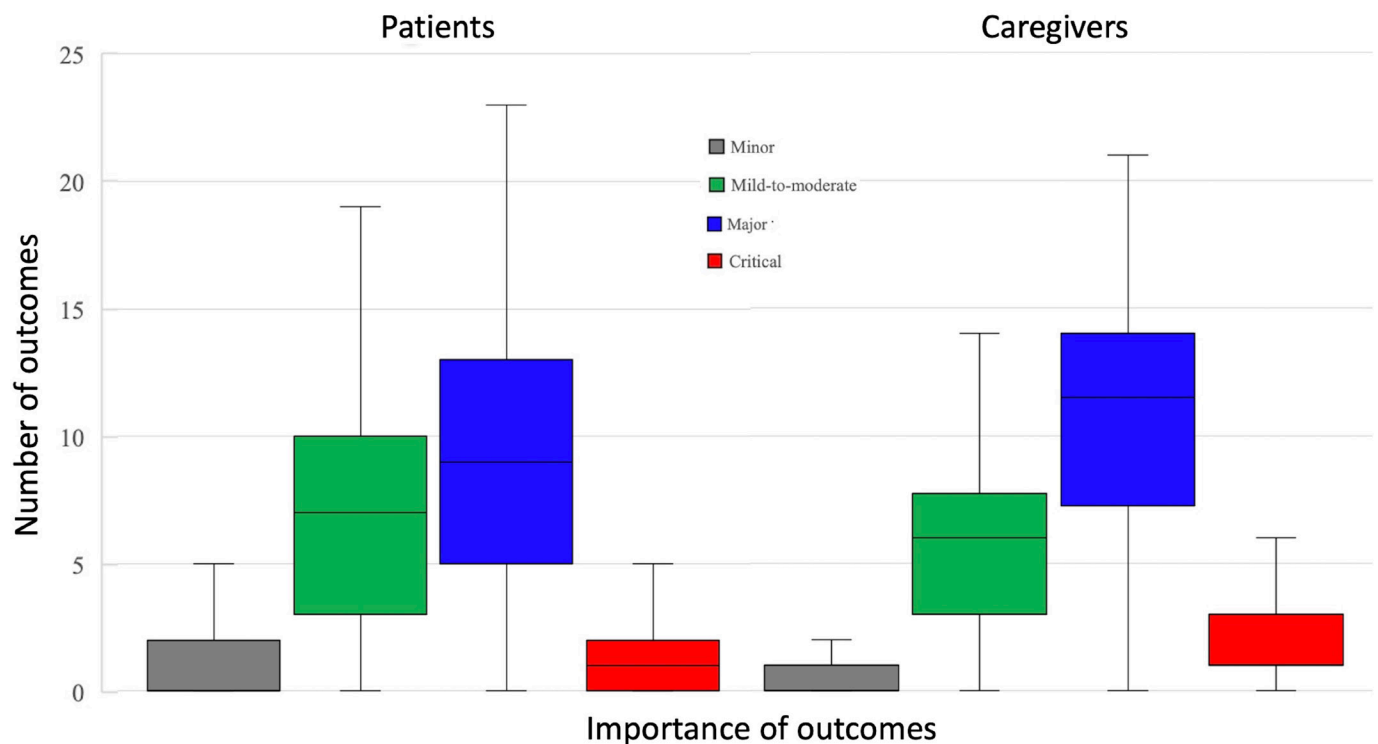


Figure 1 Number of outcomes perceived as being minor, mild-to-moderate, major and critical by patients with PAH and their caregivers. Box plots represent the median number of outcomes perceived as minor, mild-to-moderate, major and critical by individual patients and caregivers, IQR (box) as well as minimum and maximum values. PAH, pulmonary arterial hypertension.

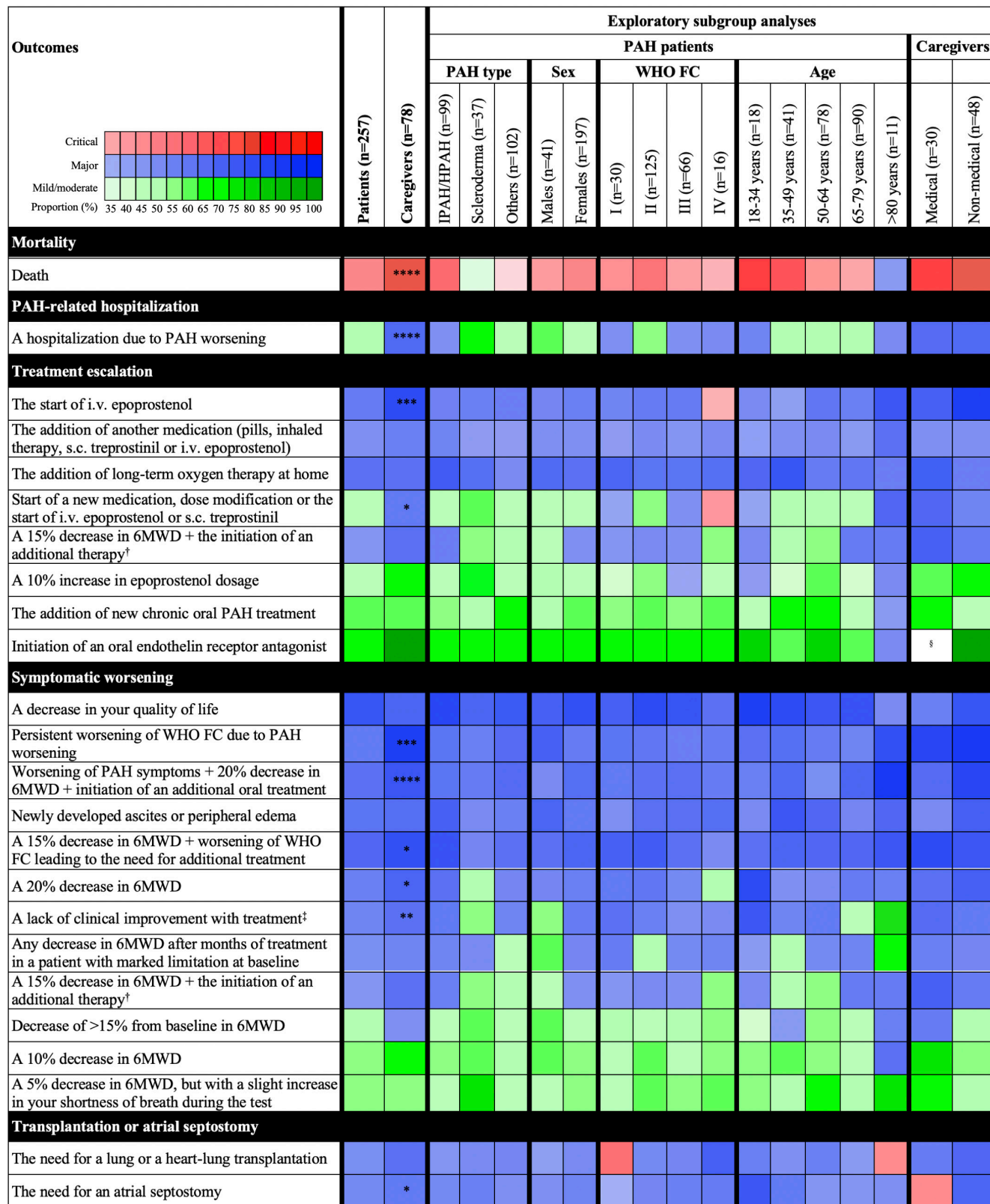


Figure 2 Heatmap depicting the importance of clinical outcomes perceived by the patients and their caregivers and PAH patients' subgroup analyses based on PAH type, sex, PAH severity and age. For patients with PAH, their caregivers and each subgroup, the importance of each outcome is categorised as critical (red), major (blue), mild-to-moderate (green) based on the response most commonly selected within each subgroup. The intensity of the heatmap representing the proportion of participants within each subgroup with that specific response. The categorisation of individual outcomes by patients vs caregivers were compared using the Fisher's exact test, whereas other subgroup comparisons were exploratory (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001). †Considered as part of both treatment escalation and symptomatic worsening categories. ‡Considered a symptomatic progression for the sake of the presentation. §No categorisation was possible with the available data. 6MWD, 6 min walking distance; 6MWT, 6 min walk test; PAH, pulmonary arterial hypertension; WHO FC, WHO functional class.

to different health outcomes and their expectations may change overtime or as the disease progresses.¹⁰ This concept, pictured in our exploratory subgroup analyses, suggests that outcome components might not equally reflect the impact of the disease on various subgroups or represent meaningful differences for a person over time.

Importantly, valuable changes are also likely influenced by contextual factors such as geographical localisation, culture, side-effect profile and disease severity. Since most of the participants were Canadian Caucasians and >50% of patients with PAH had mild-to moderate functional limitations, the external validity of these findings requires further validation. Study results may have also been influenced by the study design, potential selection bias as well as variable interpretation of CW components and their importance categorisation, resulting in some uncertainties around which outcomes are truly 'patient-important'.

CONCLUSION

The importance to patients of outcomes previously used to define CW in PAH clinical trials was highly heterogeneous, likely varying between patients with PAH and their caregivers and according to patients' characteristics. To ensure that researchers identify interventions and outcomes of greatest value to those affected by PAH, it is essential to involve a diversity of patients throughout the research process as participants and as key stakeholders.

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