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RESEARCH ARTICLE

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Treatment and management of chronic thromboembolic pulmonary hypertension (CTEPH): A global cross-sectional scientific survey (CLARITY)

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Abstract

Advances in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) over the past decade changed the disease landscape, yet global insight on clinical practices remains limited. The CTEPH global cross-sectional scientific survey (CLARITY) aimed to gather information on the current diagnosis, treatment, and management of CTEPH and to identify unmet medical needs. This paper focuses on the treatment and management of CTEPH patients. The survey was circulated to hospital-based medical specialists through Scientific Societies and other medical organizations from September 2021 to May 2022. The majority of the 212 respondents involved in the treatment of CTEPH were from centers performing up to 50 pulmonary

endarterectomy (PEA) and/or balloon pulmonary angioplasty (BPA) procedures per year. Variation was observed in the reported proportion of patients deemed eligible for PEA/BPA, as well as those that underwent the procedures, including multimodal treatment and subsequent follow-up practices. Prescription of pulmonary arterial hypertension-specific therapy was reported for a variable proportion of patients in the preoperative setting and in most nonoperable patients. Reported use of vitamin K antagonists and direct oral anticoagulants was similar (86% vs. 82%) but driven by different factors. This study presents heterogeneity in treatment approaches for CTEPH, which may be attributed to center-specific experience and region-specific barriers to care, highlighting the need for new clinical and cohort studies, comprehensive clinical guidelines, and continued education.

KEYWORDS

balloon pulmonary angioplasty, chronic thromboembolic pulmonary hypertension, clinical practice, medical therapy, pulmonary endarterectomy

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare form of pulmonary hypertension (PH)[1] characterized by the presence of proximal or distal obstructive fibrotic clots and secondary microvasculopathy, leading to increased pulmonary vascular resistance and progressive right heart failure.[2] Advances in surgical, interventional, and medical treatments over the past decade have influenced how CTEPH cases are evaluated and treated, considerably improving the outcomes of patients[3-6] who have a poor prognosis if left untreated.[7]

Pulmonary endarterectomy (PEA), established as the treatment of choice for eligible patients, is a surgical procedure with proven long-term outcomes, able to achieve hemodynamic normalization, increased functional capacity, and improved quality of life.[1,2,8,9] However, persistent/recurrent PH is observed in up to 25% of patients,[10] necessitating additional interventional treatment, medical therapy, and long-term follow-up.[1]

International registry data has shown that approximately 40% of CTEPH patients do not undergo PEA due to distal disease, unfavorable risk/benefit profile, or patient refusal.[11] In some countries, this proportion may be as high as 75%, depending on patient demographics, patient preference, and the availability or expertise of treatment centers.[5,11] For selected inoperable patients and patients with persistent/recurrent PH after PEA, balloon pulmonary angioplasty (BPA) has been shown to improve hemodynamics, right heart function, and exercise capacity.[1,2,9,12,13]

Patients may also benefit from medical therapy, which targets the underlying microvascular disease.[1,2,9] Three drugs are approved for the treatment of inoperable CTEPH and persistent/recurrent PH after PEA: riociguat (an oral guanylate cyclase stimulator), continuous S.C. treprostinil (a prostacyclin analog) in Europe, and selexipag (an oral IP prostacyclin receptor agonist) in Japan. Furthermore, off-label use of other pulmonary arterial hypertension (PAH)-specific therapies (such as PDE5i, ERAs, and prostacyclin analogs [e.g., epoprostenol and iloprost]) has been observed.[14-20]

To target the mixed anatomical lesions (proximal, distal, and microvasculopathy), a multimodal treatment approach, including PEA, BPA, and medical therapy, is commonly used. In addition, lifelong anticoagulation is recommended in all patients to prevent recurrent pulmonary embolism (PE) and secondary in situ thrombus formation.[1]

Several knowledge gaps remain in the evolving therapeutic algorithm for CTEPH.[1,2,21] First, there is no consensus on therapeutic targets (e.g., functional class, hemodynamic results, etc.) for PEA, BPA, or medical therapy. Second, the role of PAH-specific therapy in the preoperative[22-26] and interventional setting requires further evaluation.[27,28] Moreover, only a few randomized controlled trials on PAH-specific monotherapy[29-32] and combination therapy[20,30-32] provide data on the impact of medical therapy on patient outcomes. Thus, the optimal sequence of treatments by patient subpopulation remains undefined. Similarly, best practice regimens for anticoagulation have not been established due to a lack of comparative evidence on vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).

Recent clinical practice guidelines, consensus statements, and position statements have acknowledged the

evolving landscape of CTEPH management, including broader experience with BPA and medical therapy.[1,2,9,33] Although the impact of the latest recommendations has yet to be established, some insights on real-world treatment patterns come from recent international registry data, revealing regional differences in treatment approaches. For example, the international CTEPH registry has shown that the majority of patients in Europe and America were deemed suitable for PEA, while patients from Japan were mainly treated by BPA.[11] Variation in clinical practices and barriers to care amongst medical specialists and across other regions of the world is not well documented.

The **C**TEPH g**l**ob**a**l c**r**oss-sect**i**onal scien**t**ific surve**y** (CLARITY) was developed to gather insights from the physician's perspective into the current diagnosis, treatment, and management of CTEPH and to identify unmet medical needs.

METHODS

Survey development

The survey used for this research was developed with the support of a Scientific Committee of 11 international CTEPH experts from the regions of Europe, North America, Latin America, and Asia-Pacific, using a modified Delphi Technique,[34] for which the process has previously been described in detail.[35] The online survey consisted of 110 closed- and open-ended questions and was available in 12 languages (English, French, German, Italian, Spanish, Portuguese, Polish, Russian, Turkish, simplified Chinese, Japanese, and Korean). The survey was tailored to each individual respondent's clinical practice and previous responses through the use of conditions and display logic functions. A copy of the survey has been published as Supporting Information Material.[35]

Survey distribution

Hospital-based medical specialists involved in the clinical management of patients with acute PE and/or CTEPH were invited to complete the survey through 21 international, regional, and national Scientific Societies and other medical organizations recommended by the Scientific Committee (see Acknowledgments) between September 10, 2021 and May 1, 2022. Distribution of the survey was at the discretion of each individual organization and included email newsletters, website announcements, and social media posts targeted to their membership. No formal sample size was predetermined, and no compensation was offered for completion of the survey.

Data analysis

Categorical responses from the closed-ended questions were reported as proportions. Qualitative data from the open-ended questions were analyzed, recoded into categorical variables, and reported as proportions. Subanalyses were performed to explore the impact of experience in PEA/BPA on clinical practices and regional variation in the findings.

RESULTS

A total of 416 responses were collected, of which a total of 63 responses were excluded because the respondents indicated no involvement in PE diagnosis and/or follow-up, CTEPH diagnosis, or CTEPH operability assessment, treatment, and/or follow-up (27%, $n = 17$) or were general practitioners (73%, $n = 46$). Among these exclusions, all had initiated the survey, but their lack of involvement along the CTEPH patient journey meant they were no longer required to complete it. The respondent characteristics of the included 353 responders have been described elsewhere.[35] This paper presents the findings on contemporary clinical practices and challenges in the treatment and management of CTEPH patients.

Characteristics of respondents involved in CTEPH treatment

Out of 353 respondents, a total of 212 were involved in the treatment of CTEPH, of whom the characteristics are presented in Table 1. Most respondents were from Asia-Pacific (39%, $n = 83$) or Europe (32%, $n = 67$), specialized in pulmonology (50%, $n = 107$) or cardiology (37%, $n = 78$), and had between 5 and 29 years of working experience (80%, $n = 168$). The majority of respondents were working in an expert PH/CTEPH center (71%, $n = 150$), and out of the other 62 respondents, 44% were affiliated with such a center ($n = 27$).

Anticoagulation

Prescription of VKAs (86%, $n = 182$) and DOACs (82%, $n = 173$) was widely reported. The most important factors

TABLE 1 Demographics and characteristics of respondents involved in the treatment of chronic thromboembolic pulmonary hypertension.

Parameter	Respondents $N = 212$ (%)
Geography	
Europe	67 (32)
Asia-Pacific	83 (39)
North America	29 (14)
South America	29 (14)
Middle East & Africa	4 (2)
Medical specialty	
Pulmonology	107 (50)
Cardiology	78 (37)
Cardiothoracic surgery	13 (6)
Internal medicine	7 (3)
Vascular medicine	3 (1)
Hematology	2 (1)
Radiology	1 (0)
Other	1 (0)
Years of working experience in specialization (years)	
<5	9 (4)
5–14	70 (33)
15–29	98 (46)
≥30	35 (17)
Level of involvement in acute PE and CTEPH	
PE diagnosis and/or follow-up, CTEPH diagnosis, and CTEPH operability assessment, treatment, and/or follow-up	187 (88)
CTEPH diagnosis and CTEPH operability assessment, treatment, and/or follow-up	20 (9)
CTEPH operability assessment, treatment, and/or follow-up only	5 (2)
Care setting and affiliation	
Working in a unit or department that is dedicated to acute PE management	26 (12)
Working in a PH/CTEPH expert center	112 (53)
Working in a unit or department dedicated to acute PE management and a PH/CTEPH expert center	38 (18)
None of the above	36 (17)
If not working in a PH/CTEPH expert center ($n = 62$)	
Affiliated with a PH/CTEPH expert center	27 (44)
Not affiliated with a PH/CTEPH expert center	24 (39)
Unknown/uncertain	11 (18)

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; PH, pulmonary hypertension.

driving the use of one class over the other appeared to be convenience, underlying thrombophilia (i.e., antiphospholipid syndrome), risk of bleeding, presence of atrial fibrillation or other conditions requiring anticoagulants, guideline recommendation, and age (Supporting Information S1: Table 1). Approximately a third of respondents (34%, $n = 139$) reported some barriers to the use of DOACs and/or VKAs, the most frequent being cost and product features, respectively, while lack of evidence was mentioned for both anticoagulants.

PEA

Out of the 103 respondents working in a center performing PEA, 83% ($n = 85$) indicated that their center performed up to 50 procedures per year, 9% ($n = 9$) performed between 51 and 100 procedures per year, and 9% ($n = 9$) performed more than 100 procedures per year. Most respondents indicated that their center (58%, $n = 59$) had been performing PEA for less than 10 years.

The proportion of patients with CTEPH who were reportedly deemed eligible for PEA varied widely and was relatively lower in the Asia-Pacific region. Similarly, the reported proportion of patients that underwent PEA in the previous year varied and was relatively lower in the Asia-Pacific and South America regions. See Figure 1 for further details.

A total of 77 respondents (75%) reported that some patients refused PEA last year, although 36% ($n = 28$) reported that this occurred in ≤5% of eligible patients. A total of 14 respondents (14%) indicated that PEA was not refused by any patient last year (Table 2a). Regional-level analysis showed that respondents from Asia-Pacific were more likely to report that >15% of eligible patients refused PEA last year compared to all other regions combined (37%, $n = 16$ vs. 7%, $n = 4$). The most frequently reported reason for PEA refusal was fear of adverse events (88%, $n = 91$) (Table 2b), which was more commonly reported by

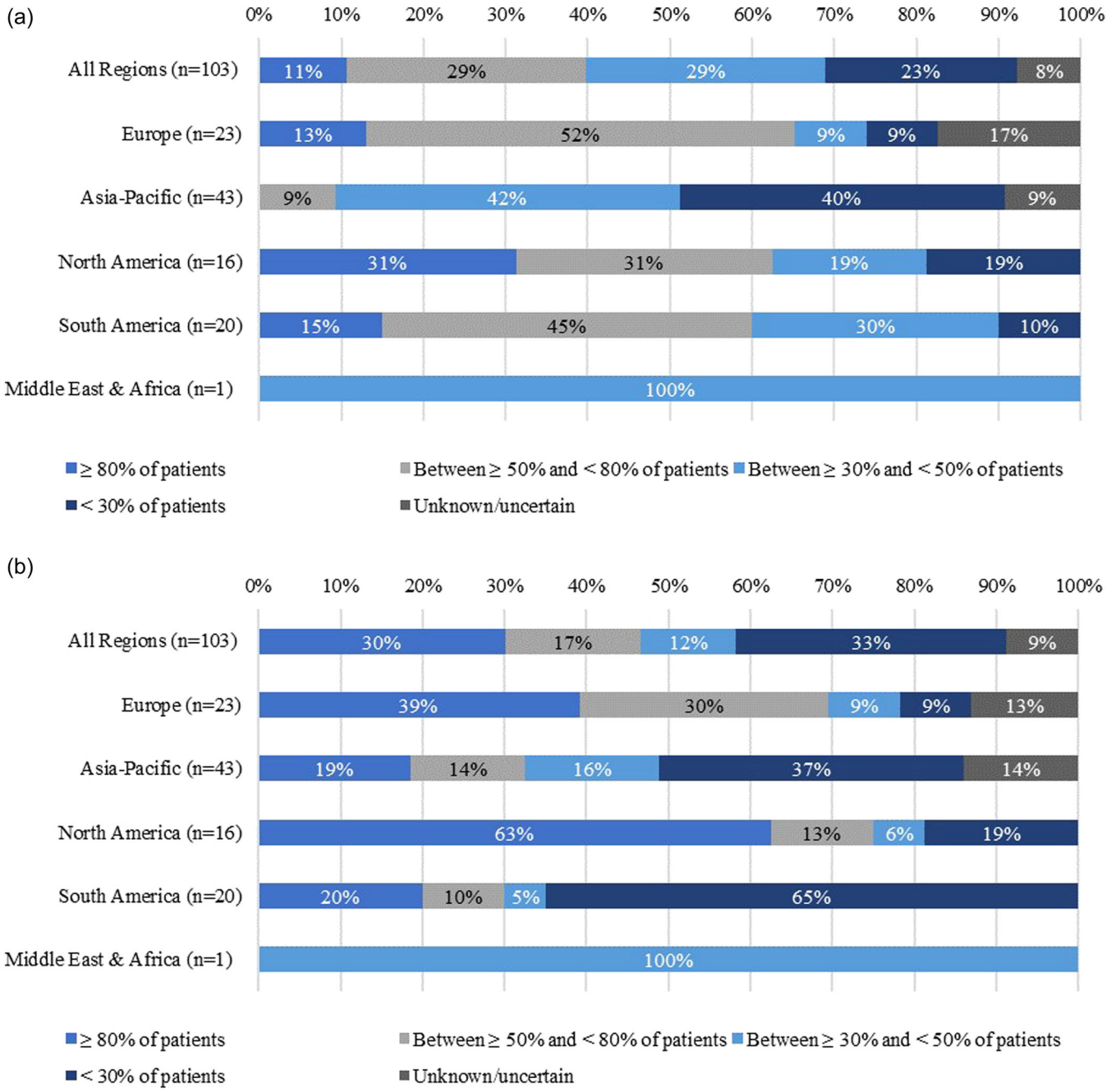

FIGURE 1 (a) Reported proportion of patients with chronic thromboembolic pulmonary hypertension deemed eligible for pulmonary endarterectomy (PEA) in the previous year. (b) Reported proportion of patients with chronic thromboembolic pulmonary hypertension that underwent PEA in the previous year.

respondents who were working in a center that performed up to 50 procedures per year (73%, $n = 75$).

Respondents commonly considered PEA success to encompass hemodynamic improvement (79%, $n = 81$), in particular, reduced PAP (48%, $n = 49$), as well as improvement in function/symptomatic relief (40%, $n = 41$) (other reported definitions not shown). Most respondents reported scheduling the first standard follow-up visit after PEA within 3 months postsurgery (54%, $n = 56$) or at 3 months postsurgery (32%, $n = 33$). During these visits, the most commonly reported performed tests or assessments to evaluate the outcomes of PEA were echocardiography (97%, $n = 100$), NYHA functional class (95%, $n = 98$), and 6-min walk test (93%, $n = 96$), while the use of right heart catheterization was reported by 62% of respondents ($n = 64$) (Supporting

TABLE 2a Approximate proportion of chronic thromboembolic pulmonary hypertension patients deemed technically suitable for pulmonary endarterectomy that refused surgery last year.

Reported reasons	Respondents $N = 103$ (%)
None of the patients	14 (14)
≤5% of patients	28 (27)
Between >5% and ≤10% of patients	16 (16)
Between >10% and ≤15% of patients	13 (13)
>15% of patients	20 (19)
Unknown/uncertain	12 (12)

TABLE 2b Reasons for pulmonary endarterectomy refusal.

Reported reasons	Respondents $N = 103$ (%)
Fear of adverse events	91 (88)
Patient preference for BPA	33 (32)
Lack of awareness on treatment (outcomes)	27 (26)
Patient out-of-pocket expenses for the surgery and/or hospital stay	22 (21)
Lack of confidence in the physician's ability to perform the procedure	11 (11)
Cultural/religious reasons	9 (9)
Other	1 (1)

Note: The total does not equal 100% due to multiple response options.
Abbreviation: BPA, balloon pulmonary angioplasty.

Information S1: Table 2). Lifetime follow-up was reported by 40% ($n = 41$) and 51% ($n = 53$) of respondents in the case of successful and unsuccessful PEA outcomes (as per the respondent's interpretation), respectively (Figure 2).

Respondents indicated using variable parameters to define persistent/recurrent PH after PEA, with mPAP >25 mmHg (54%, $n = 56$) and return, exacerbation, or no improvement of symptoms (45%, $n = 46$) being the most common (Supporting Information S1: Table 3). Amongst the 87 respondents (85%) who reported on the approximate proportion of patients presenting with persistent/recurrent PH following PEA, 28% ($n = 24$) reported presentation in ≤10% of patients, 47% ($n = 41$) reported presentation in between >10% and ≤25% of patients, and 25% ($n = 22$) reported presentation in >25% of patients. Only a minority of respondents (18%, $n = 19$) reported that >1% of patients with persistent/recurrent PH undergo a second PEA, while a larger proportion of respondents (70%, $n = 72$) reported that these patients undergo BPA.

Out of the 212 respondents involved in the treatment of CTEPH, the most frequently reported factors limiting the use of PEA were limited access to centers performing PEA (49%, $n = 104$), lack of expertise in performing PEA (41%, $n = 87$), and financial reasons (patient out-of-pocket expenses (20%, $n = 43$) or reimbursement status of PEA and/or hospital stay (17%, $n = 36$) (Table 3). Regional-level analysis showed that respondents from Europe most often reported that there were no limitations regarding the use of PEA (46%, $n = 31$) (data not shown).

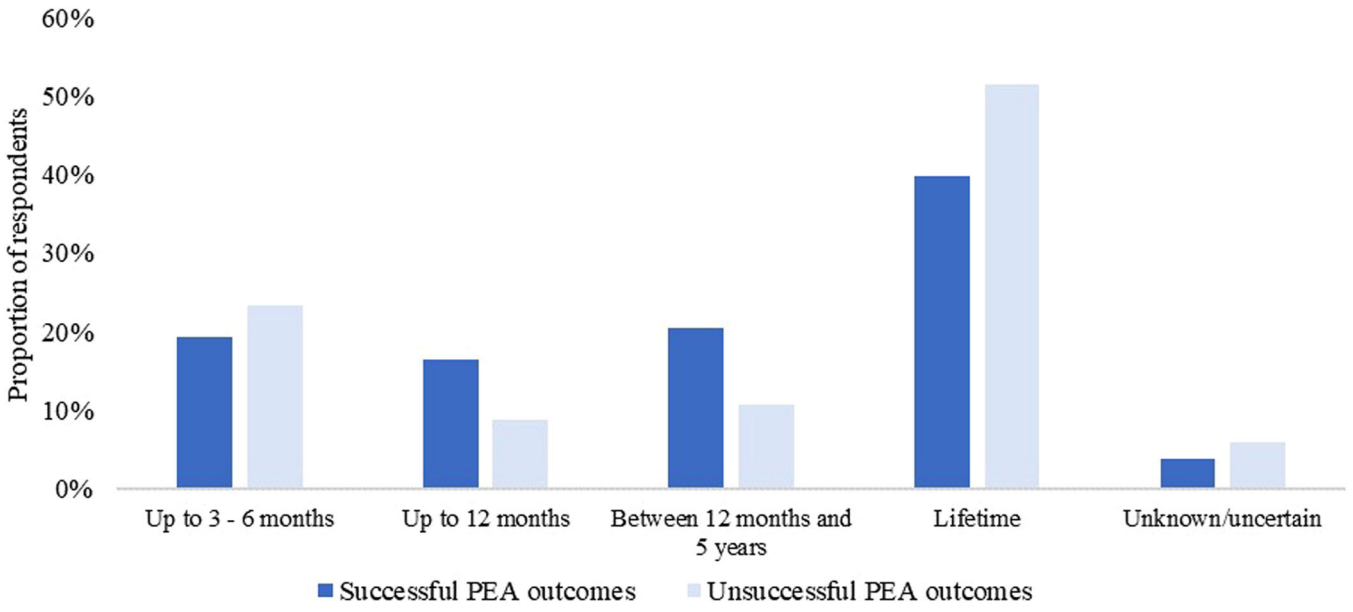

FIGURE 2 Duration of patient follow-up following successful and unsuccessful PEA outcomes. PEA, pulmonary endarterectomy.

BPA

Out of the 120 respondents working in a center performing BPA, 54% ($n = 65$) indicated that their center performed up to 50 procedures per year, 24% ($n = 29$) performed between 51 and 100 procedures per year, and 22% ($n = 26$) performed more than 100 procedures per year. The majority of respondents indicated that their center (69%, $n = 82$) had been performing BPA for less than 5 years.

TABLE 3 Factors limiting the use of pulmonary endarterectomy as a treatment modality for chronic thromboembolic pulmonary hypertension.

Reported barriers	Respondents $N = 212$ (%)
Limited access to centers that can perform PEA	104 (49)
Lack of expertise in performing PEA	87 (41)
Patient out-of-pocket expenses for PEA and/or hospital stay	43 (20)
Reimbursement status of PEA and/or hospital stay	36 (17)
Provider misinformation about the safety and efficacy of PEA	30 (14)
Other	7 (3)
Unknown/uncertain	5 (2)
No perceived limitations	48 (23)

Note: The total does not equal 100% due to multiple response options.
Abbreviation: PEA, pulmonary endarterectomy.

The proportion of patients with CTEPH who were reportedly deemed eligible for BPA varied widely and was higher in the Asia-Pacific region (Figure 3). Respondents working in a center performing up to 50 procedures per year more often reported that <50% of patients were deemed eligible for BPA (30%, $n = 36$) compared to those working in a center performing more than 50 procedures per year (13%, $n = 15$). No trend was observed between center-specific years of experience in BPA and the reported proportion of patients deemed eligible (data not shown). The vast majority of respondents would consider BPA in inoperable patients due to distal lesions (94%, $n = 113$), in patients with persistent/recurrent PH after PEA (88%, $n = 105$), in operable patients with an unfavorable risk/benefit ratio (84%, $n = 101$), and in patients with inoperable CTEPH or persistent/recurrent CTEPH and an inadequate response to medical therapy (82%, $n = 98$).

The most frequently reported treatment goals of BPA were improved quality of life (85%, $n = 102$), improved NYHA functional class (82%, $n = 98$), symptom relief (79%, $n = 95$), improved right ventricular function (71%, $n = 85$), and normalization of pulmonary vascular resistance (47%, $n = 56$) (Table 4). Out of 82 respondents that additionally reported on BPA completion, most considered BPA to be accomplished based on improvement in hemodynamics (91%, $n = 75$), in particular mPAP (59%,

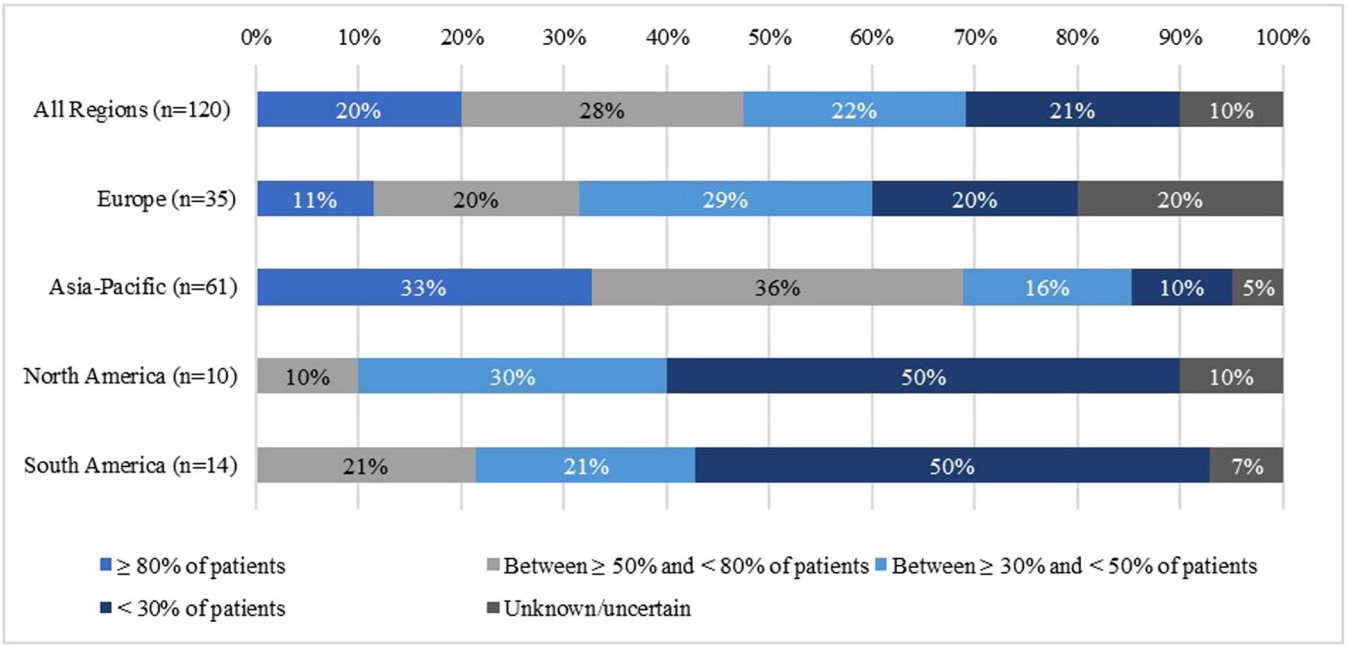

FIGURE 3 Reported proportion of patients with chronic thromboembolic pulmonary hypertension deemed eligible for balloon pulmonary angioplasty in the previous year.

TABLE 4 Treatment goals of balloon pulmonary angioplasty.

Reported treatment goals	Respondents $N = 120$ (%)
Improved quality of life	102 (85)
Improved NYHA functional class	98 (82)
Symptom relief	95 (79)
Improved RV function	85 (71)
Normalization of pulmonary vascular resistance	56 (47)
Oxygen saturation >95% without using any vasodilators or oxygen	43 (36)
Mean pulmonary artery pressure <25 mmHg	41 (34)
Mean pulmonary artery pressure <30 mm Hg	37 (31)
Improved perfusion imaging	33 (28)
Cessation or reduction in specific medication needs	32 (27)
Mean pulmonary artery pressure <20 mmHg	15 (13)
Other	1 (1)
Unknown/uncertain	3 (3)

Note: The total does not equal 100% due to multiple response options.
Abbreviations: NYHA, New York Heart Association; RV, right ventricular.

TABLE 5 Factors limiting the use of balloon pulmonary angioplasty as a treatment modality for chronic thromboembolic pulmonary hypertension.

Reported barriers	Respondents $N = 212$ (%)
Lack of expertise in performing BPA	93 (44)
Limited access to centers that can perform BPA	92 (43)
Limited long-term follow-up data on the benefit of BPA	38 (18)
Patient out-of-pocket expenses for BPA and/or hospital stay	31 (15)
Reimbursement status of BPA and/or hospital stay	29 (14)
Provider misinformation about the safety and efficacy of BPA	19 (9)
Other	11 (5)
Unknown/uncertain	7 (3)
No perceived limitations	55 (26)

Note: The total does not equal 100% due to multiple response options.
Abbreviation: BPA, balloon pulmonary angioplasty.

$n = 48$). There were variations in patient re-evaluation practices amongst respondents; 66% ($n = 79$) reported to re-evaluate after each BPA session, while 38% ($n = 45$) reported to do so only after the final BPA session. Most respondents reported scheduling the first standard follow-up visit after the last BPA session and within 3 months postintervention (49%, $n = 59$) or at 3 months postintervention (32%, $n = 38$). During these visits, the most commonly reported performed tests or assessments to evaluate the outcomes of BPA were NYHA functional class (91%, $n = 109$), echocardiography (90%, $n = 108$), 6-min walk test (85%, $n = 102$), and NTproBNP (83%, $n = 100$) (Supporting Information S1: Table 2). Most respondents reported lifetime follow-up after BPA (67%, $n = 80$). Others reported between 12 months and 2 years of follow-up (12%, $n = 14$), between 2 and 5 years of follow-up (11%, $n = 13$), or up to 12 months of follow-up (3%, $n = 4$).

Out of the 212 respondents involved in the treatment of CTEPH, the most frequently reported factors limiting the use of BPA were lack of expertise in performing BPA (44%, $n = 93$), limited access to centers performing BPA (43%, $n = 92$), limited long-term follow-up data on the benefit of BPA (18%, $n = 38$), and financial reasons (patient out-of-pocket expenses [15%, $n = 31$], reimbursement status of BPA, and/or hospital stay [14%, $n = 29$]) (Table 5). Regional-level analysis suggested that there were less perceived factors limiting the use of BPA amongst respondents from Europe, where 43% ($n = 29$) of these respondents did not report any limiting factors. In comparison, 22% ($n = 18$) of respondents from Asia-Pacific did not report any limiting factors, of which the majority were from Japan (78%, $n = 14$).

Medical therapy

The vast majority of respondents (99%, $n = 209$) reported prescribing PAH-specific therapy for patients with nonoperable CTEPH in all patients (44%, $n = 94$) or in ≥80% of these patients (33%, $n = 70$) (Figure 4). All drug classes were reported to be prescribed as first-line monotherapy, with sGC (85%, $n = 177$) and PDE-5i (25%, $n = 53$) most commonly prescribed. A first-line combination of sGC and ERAs was reportedly used by 56% ($n = 117$) of the respondents.

Adherence to PAH-specific therapy was reportedly promoted through patient education on disease importance (87%, $n = 184$), medication counseling (66%, $n = 140$), individualized dose adjustment (64%, $n = 136$), counseling on lifestyle management strategies (35%, $n = 75$), and patient support groups

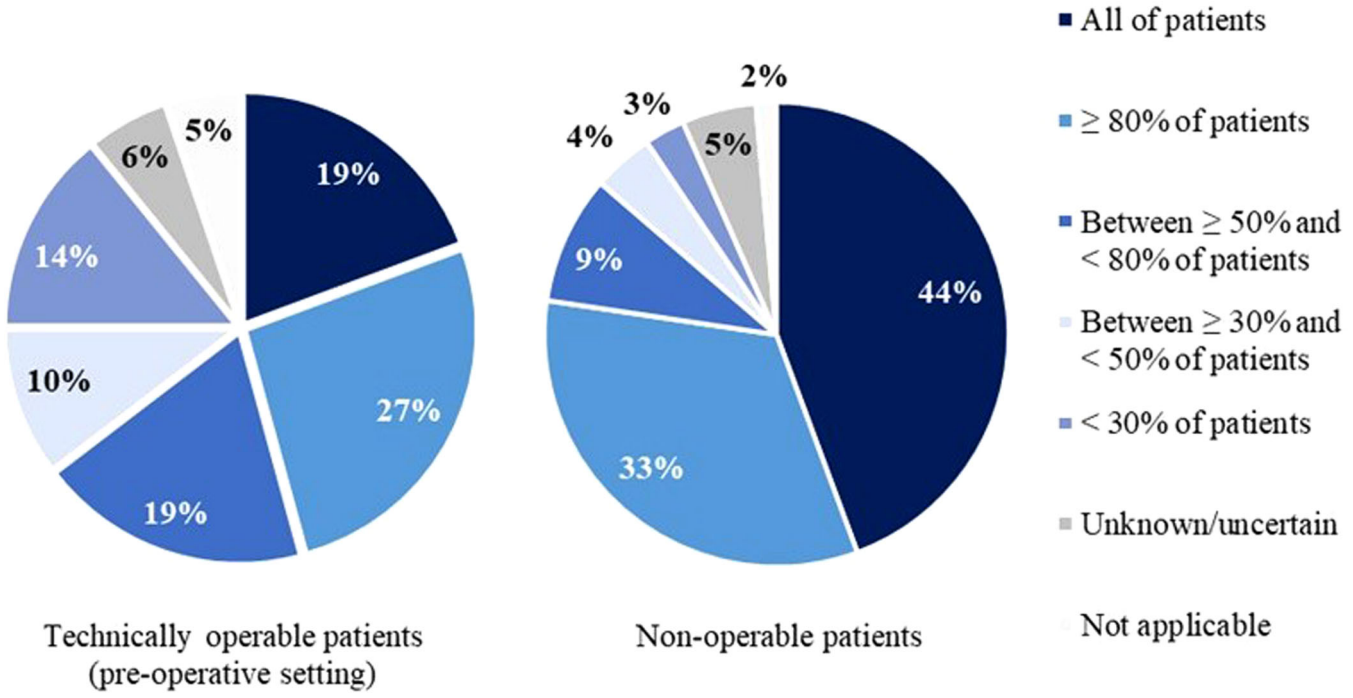

FIGURE 4 Proportion of patients with chronic thromboembolic pulmonary hypertension that receive pulmonary arterial hypertension (PAH)-specific therapy. A total of 212 respondents reported on the proportion of patients that receive PAH-specific therapy.

(30%, $n = 64$). Methods used to measure adherence to PAH-specific therapy included nursing interventions (47%, $n = 99$), pharmacist interventions (32%, $n = 68$), patient diaries (23%, $n = 49$), and specialty pharmacy tracking (20%, $n = 43$). Approximately one in five respondents reported that they did not have an established process to measure adherence. Medication use barriers were reported by 58% of respondents ($n = 124$) and were mostly reported for oral or inhaled prostanoids (64%, $n = 79$) and sGC (56%, $n = 69$), followed by ERAs (45%, $n = 56$) and PDE-5i (28%, $n = 35$).

Multimodal treatment

A variable proportion of respondents reported that their center had been using a multimodal treatment approach in operable and nonoperable patients (Figure 5). Out of the 212 respondents involved in the treatment of CTEPH, 95% ($n = 201$) reported prescribing PAH-specific therapy for a variable proportion of patients with technically operable CTEPH in the preoperative (PEA) setting (Figure 4). All drug classes were reported to be prescribed as first-line monotherapy, with sGC (72%, $n = 145$) and PDE-5i (38%, $n = 77$) most commonly prescribed. A first-line combination of sGC and ERAs was reportedly used by 50% ($n = 100$) of the respondents. In the postoperative setting, respondents reported continuing PAH-specific therapy dependent on immediate postoperative hemodynamic results (60%, $n = 127$), as a standard approach (28%, $n = 59$), or dependent on the quality of thromboembolic material removed during PEA (18%, $n = 39$). Some respondents (16%, $n = 33$) reported stopping PAH-specific therapy at the time of PEA until the first follow-up.

Amongst 116 respondents working in a center performing BPA and that had been using a multimodal treatment approach in nonoperable patients, treatment of patients with PAH-specific therapy before BPA and after, if appropriate, for most-to-all patients or severe patients only was reported by 72% ($n = 83$) and 17% ($n = 20$) of respondents, respectively. Only 4% ($n = 5$) of respondents reported that patients would not be treated with PAH-specific therapy before BPA and after only if appropriate.

Management of chronic thromboembolic pulmonary disease (CTEPD) without PH

Out of the 212 respondents who were involved in the treatment of CTEPH, 52% ($n = 111$) and 41% ($n = 87$) of respondents reported using BPA and PEA for the management of CTEPD without PH, respectively.

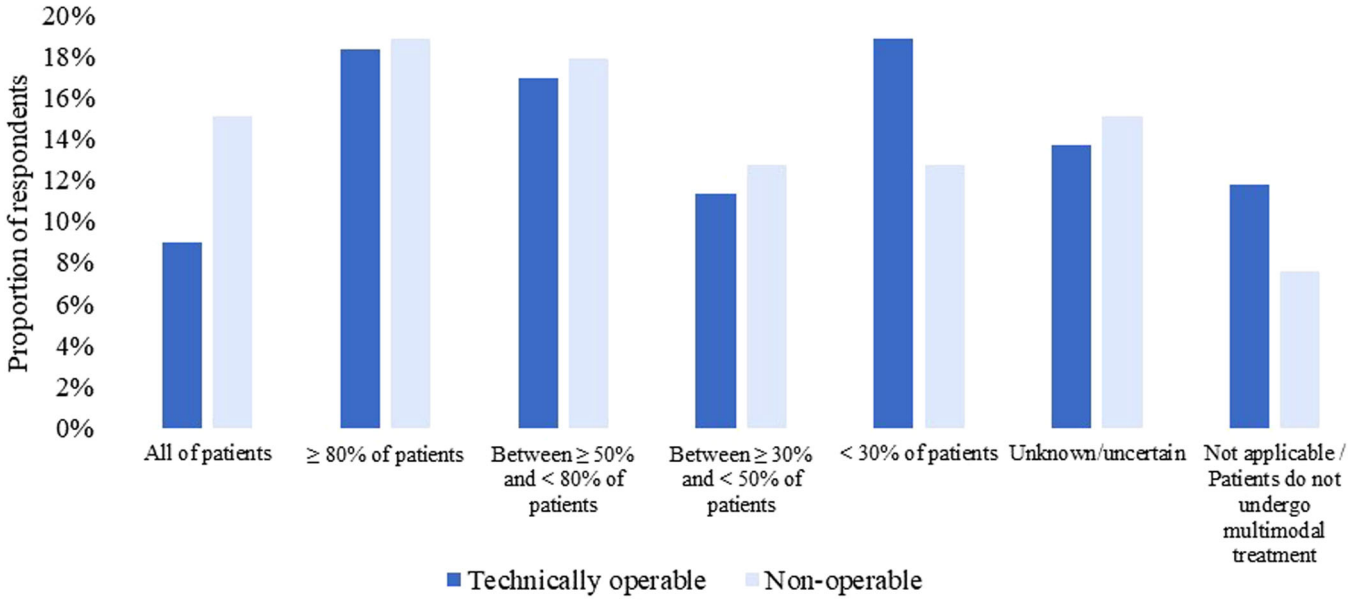

FIGURE 5 Proportion of technical operability and nonoperable patients with chronic thromboembolic pulmonary hypertension that undergo multimodal treatments.

DISCUSSION

Our results reflect that there are many emerging treatment centers with less than 10 and 5 years of experience in performing PEA and BPA, respectively. Regional differences were captured in the proportion of patients deemed eligible and who underwent PEA and BPA. Patient refusal of PEA and persistent/recurrent PH following PEA were typically reported for a small proportion of operable patients. The majority of respondents (82%) would consider BPA in patients with persistent/recurrent CTEPH and an inadequate response to medical therapy, highlighting that BPA is not considered as an alternative to PEA for operable patients unless there is an unfavorable risk/benefit (84%). Although riociguat is the only worldwide approved pharmacotherapy for CTEPH, respondents reported using variable medical therapy approaches, including the use of other PAH-specific therapies and the common use of combination therapy, despite limited evidence from RCTs. While the use of multimodal treatment, including medical therapy before and after PEA or BPA, was reported by many respondents, applicability across patient subpopulations and treatment sequencing varied. The observed variability in treatment patterns may be attributed to center-specific expertise and access barriers, in addition to the existing knowledge gaps.

This international cross-sectional scientific survey was deployed through recognized scientific and medical organizations and enabled the collection of contemporary data that is otherwise difficult to obtain. Although the international CTEPH registry provided early insights on the real-world adoption of new treatment approaches between February 2015 and September 2019 across participating treatment centers, not all treatment options were available in these centers, most centers were based in Europe, and most were referral centers for PEA and/or BPA, limiting the global picture.[11] Ongoing prospective registry data collection at the international [NCT02656238] and national levels, such as the Japanese multicenter registry of CTEPH [UMIN000033784 2020], will allow for an improved understanding of current treatment approaches worldwide. However, inherent limitations of such data sources, including their retrospective nature, limiting the extent of variables captured, and under-utilization of CTEPH-specific codes,[36] may result in a lack of specificity of individual databases and comparability across geographies.[37] Furthermore, local documentation on patients referred to treatment centers in neighboring countries for PEA or BPA assessment may be lacking, and the use of off-label PAH-specific therapies may not be captured.

Our findings reveal that over the past decade, differences in access to treatment across countries have remained. A previous international physician survey conducted in 2012 showed regional variation in the proportion of patients clinically evaluated and deemed eligible for PEA (Europe, 47% and 53%; the United States, 35% and 50%; Argentina, 37% and 52%; Japan, 18% and 38%). However, the proportion of patients receiving PAH-specific therapy previously varied from 64% in Europe to 80% in Japan,[38] whereas our research suggests

that the overall rate of medical therapy prescription, regardless of operability status, has increased.

Residual PH after PEA has been shown to negatively impact long-term prognosis.[39] In line with previously observed rates of persistent/recurrent PH,[9] our results suggest that persistent/recurrent PH after PEA is still common, with 21% of respondents observing this in >25% of patients. The majority of respondents (88%) would consider PAH-specific therapy for these patients, either as a standard approach or dependent on post-operative hemodynamic results. Aligned with the guideline recommendations,[40] 70% of respondents indicated that these patients would be candidates for BPA. Disease progression should be monitored in these patients considering that long-term follow-up data on BPA outcomes in patients previously treated by PEA is currently lacking.[41]

The observed heterogeneity in treatment approaches highlights the need to address access barriers to PEA and BPA, taking into consideration country-specific healthcare system factors, including the financing and organization of care. In addition, the optimal sequence of multimodal therapies, taking into account the disease distribution, patient status, and respective treatment goals, warrants further research. Lastly, our findings confirm under-utilization of right heart catheterization[42] and suggest suboptimal long-term follow-up, as prescribed by the latest guidelines,[1] presenting an opportunity for further education and adoption of best practices for patient follow-up.

While DOACS are increasingly prescribed in CTEPH as opposed to VKAs,[43,44] clinical guidelines do not offer preferred first-line regimen recommendations. Our research showed that respondents were similarly likely to prescribe DOACs or VKAs (82% vs. 86%, respectively), where the decision to prescribe DOACs versus VKAs was mainly driven by APLS status, chronic kidney disease, risk of bleeding, and convenience (see Supporting Information S1: Table 3).

It is important to acknowledge the limitations of this research. While our survey sought broad representation through distribution by 21 Scientific Societies and other medical organizations, the voluntary nature of the survey may have introduced self-selection bias among respondents. Furthermore, the organizations independently determined how to circulate the survey among their members, potentially influencing the survey's reach and sample size, resulting in variations in response rates among different physicians and geographic locations. These considerations are important when interpreting the generalizability of our findings. Furthermore, definitions were not provided in the survey, leaving interpretation open to the respondents. Potential differences in respondent understanding of expertise and successful treatment, amongst other concepts, were not captured. For example, working at an expert PH/CTEPH center was self-reported by the respondents and was not verified against established criteria,[1] meaning that the expertise of respondents could not be confirmed. In addition, it is important to consider that our survey captures practices and perceptions before May 1, 2022. Clinical decision-making may have changed amongst our respondent sample since the publication of the new ESC/ERS guidelines for the diagnosis and treatment of PH in August 2022.[1]

This international cross-sectional scientific survey identified heterogeneity in treatment approaches for patients with CTEPH, likely attributed to center-specific expertise and region-specific barriers to care. Our findings highlight the importance of additional clinical and cohort studies, comprehensive clinical guidelines, and continued education to optimize patient care from treatment decision-making to patient follow-up. To evaluate the impact of the latest clinical practice guidelines, further studies using real-world data from prospective registries and claims databases will be necessary. In addition, further research on several open clinical questions will enable improved treatment decision-making, leading to improved patient outcomes. International registries such as the BPA registry (NCT03245268) and the TEAM registry (NCT05629052) may provide insights on some of these research questions.

AUTHOR CONTRIBUTIONS

All authors made a substantial contribution to the concept or design of the work and analysis of the data. All drafted the article or revised it critically for important intellectual content. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Facilitation of the Delphi exercise, data analyses, medical writing, and editorial support for the development of this manuscript, under the direction of the authors, was provided by Catherina Meijer and Yan Zhi Tan of Monitor Deloitte (Zaventem, Belgium) and was funded by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland, a Janssen Pharmaceutical company of Johnson and Johnson.

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CONFLICT OF INTEREST STATEMENT

Nika Skoro-Sajer reports fees for lectures and/or consultations from Actelion, AOP Orphan Pharmaceuticals, Bayer, Cordis, GlaxoSmithKline, Janssen, Pfizer, Medtronic, and United Therapeutics. Karen Sheares reports educational support and honoraria for consultations from Actelion, Janssen. Gustavo Heresi reports fees for non-branded, non-promotional lectures from Bayer and fees for consultations from Bayer and Janssen. Grzegorz Kopeć reports fees for lectures and/or consultations from Acceleron, Actelion, AOP Health, Bayer, Ferrer, Janssen, and MSD. Mario Terra-Filho reports consultation fees from Bayer and Janssen. Amélie Beaudet and Virginie Gressin are employees of Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson. Kohtaro Abe reports having received a research grant from Actelion Pharmaceuticals Japan. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The authors have nothing to report.

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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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