ORIGINAL RESEARCH

Outcomes of Chronic Thromboembolic Pulmonary Hypertension After Balloon Pulmonary Angioplasty and Pulmonary Endarterectomy

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ABSTRACT

BACKGROUND The contemporary outcome of balloon pulmonary angioplasty (BPA) and pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) are unclear.

OBJECTIVES This study aimed to clarify the characteristics and outcomes of CTEPH patients treated with BPA and PEA in Japan.

METHODS Among 1,270 participants enrolled between 2018 and 2023 in the CTEPH AC (Chronic Thromboembolic Pulmonary Hypertension Anticoagulant) registry, a Japanese nationwide CTEPH registry, 369 treatment-naive patients (BPA strategy: n = 313; PEA strategy: n = 56) and 690 on-treatment patients (BPA strategy: n = 561; PEA strategy: n = 129) were classified according to the presence of prior reperfusion therapy. Morbidity and mortality events (all-cause death, rescue mechanical reperfusion therapy, and/or initiation of parenteral pulmonary vasodilators), pulmonary hemodynamics, exercise tolerance, and relevant laboratory test results were evaluated.

RESULTS The BPA strategy was chosen in older patients than the PEA strategy (mean age, BPA vs PEA: 66.5 ± 12.6 years vs 62.5 ± 11.8 years; P = 0.028). Median follow-up period was 615 (Q1-Q3: 311-997) days in treatment-naive patients and 1,136 (Q1-Q3: 684-1,300) days in on-treatment patients. BPA strategy had as acceptable morbidity and mortality as PEA strategy (5-year morbidity and mortality event rate, BPA vs PEA: 10.2% [95% CI: 5.2%-19.5%] vs 16.1% [95% CI: 4.3%-50.6%] in treatment-naive patients; 9.7% [95% CI: 6.7%-13.8%] vs 6.9% [95% CI: 2.7%-17.3%] in on-treatment patients), with greater improvement of renal function; glomerular filtration rate in propensity score-matched population (difference between change: 4.9 [95% CI: 0.5-9.3] mL/min/1.73 m^2; P = 0.030).

CONCLUSIONS BPA strategy was more frequently chosen in older patients compared with PEA strategy and showed acceptable outcomes for efficacy with greater advantage for improvement in renal function. (Multicenter registry of chronic thromboembolic pulmonary hypertension in Japan; UMIN000033784) (JACC Asia 2024;4:577–589) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening disease characterized by pulmonary hypertension and right-sided heart failure caused by pulmonary artery obstruction with organized thrombus.[1] Pulmonary endarterectomy (PEA) is the treatment option for patients with CTEPH who have surgically accessible lesions.[2,3] For inoperable patients, treatment strategies using pulmonary vasodilators and balloon pulmonary angioplasty (BPA) have been developed during the past decade.[4-9] Two randomized controlled trials in patients with inoperable CTEPH have demonstrated the potent effect of BPA on improving pulmonary hemodynamics compared with a riociguat, a pulmonary vasodilator.[10,11] These studies highlight the beneficial effects of BPA on hemodynamics and exercise tolerance. Recent studies from registries of several countries have not included sufficient data on outcomes of BPA strategy.[12-16] Japanese CTEPH experts have more than 10 years of experience using BPA and have been refining the multimodal approach including the BPA strategy.[4-6] The ongoing international CTEPH registry has shown that CTEPH patients in Japan opt for BPA more often than in other countries.[17]

The latest European Society of Cardiology/European Respiratory Society guideline added a Class IIb recommendation for BPA in patients with a large proportion of distal lesions and an unfavorable risk-benefit ratio for PEA. However, there are no clear characteristics for the risk-benefit ratio for BPA that have been established. The choice of reperfusion strategy in this borderline population remains dependent on the experience of the institutional experts. Data on the characteristics and treatment outcomes of Japanese patients may foster better understanding of the position of BPA and contribute to better treatment strategies for CTEPH patients. The objective of this study was to clarify the patients' characteristics and long-term outcome of CTEPH after mechanical reperfusion treatment, using the CTEPH AC registry.

METHODS

STUDY DESIGN. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki on investigations involving human subjects and was approved by the institutional review board of each participating center. After written informed consent was obtained, each participant was assigned a unique patient identification number to ensure confidentiality. The CTEPH AC (Chronic Thromboembolic Pulmonary Hypertension Anticoagulant) registry is a nationwide multicenter, prospective, observational registry of patients diagnosed with CTEPH, with 35 participating institutions across Japan. The registry was inaugurated in August 2018 and is currently ongoing. The cut-off date of this study for enrollment data was from August 2018 to July 2023. The investigators documented the latest available data up to 12 months before enrollment as baseline data. Mandatory entry of follow-up data was defined annually in November. Complementary data were entered when the predefined clinical worsening of CTEPH events occurred, or right-sided heart catheterization examination was performed. Patients with no follow-up data for more than 1 year were considered missing follow-up data. This study was registered in the UMIN Clinical Trials Registry, an open-access database (UMIN000033784).

STUDY POPULATION. The inclusion criteria were patients aged 20 years or older diagnosed with CTEPH. The diagnosis was made based on findings of

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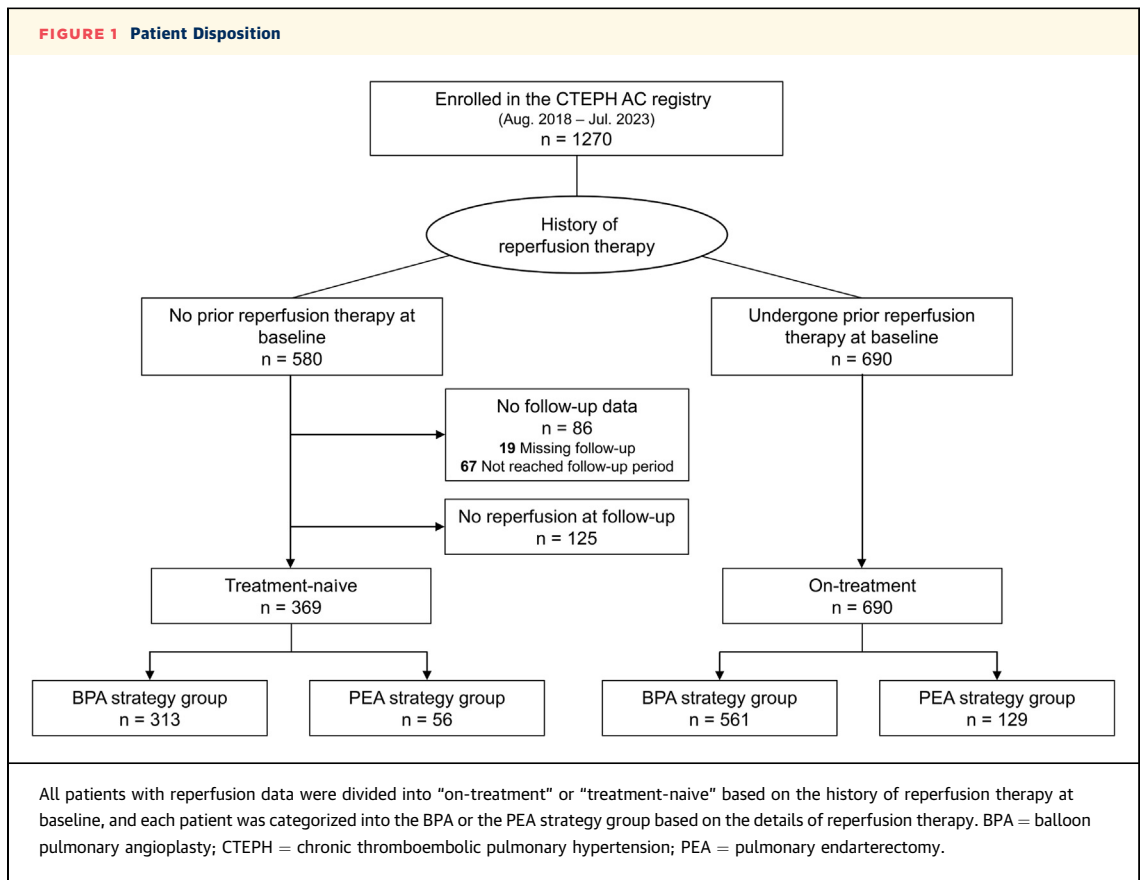
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

at least 2 imaging modalities (ventilation-perfusion scan, computed tomography pulmonary angiography, and/or catheter-based pulmonary angiography) and hemodynamic criteria (mean pulmonary artery pressure [mPAP] at rest ≥25 mm Hg and pulmonary artery wedged pressure ≤15 mm Hg).[2] Patients who were treated with BPA, PEA, and/or pulmonary vasodilators were eligible. The registry was designed to serve as a nationwide database of CTEPH in Japan by collecting information on a wide range of cases and real-world clinical practice of CTEPH, and both treatment-naive and on-treatment patients were included. The patients were divided into 2 groups based on the history of mechanical reperfusion therapy including BPA and PEA at baseline. "Treatment-naive" patients were those without prior reperfusion therapy at baseline. "On-treatment" patients were those who had undergone prior reperfusion therapy at baseline. Treatment-naive patients were further categorized according to the details of reperfusion therapy during follow-up into the "BPA strategy group" (BPA performed without PEA) or the "PEA strategy group" (PEA performed regardless of concomitant BPA). On-treatment patients were further categorized according to the details of prior reperfusion therapy at baseline into the "BPA strategy group" or the "PEA strategy group." Patients without follow-up data ("no follow-up") included those who were missing follow-up data and who did not reach the observation period of the annual regular follow-up in November. Patients without mechanical reperfusion therapy ("no reperfusion") were those who did not receive any reperfusion therapy at the last follow-up. The full analysis set was defined as all enrolled patients. Patients with "no follow-up" and "no reperfusion" were excluded from the primary analysis.

REPERFUSION STRATEGY IN JAPAN. Selection of mechanical reperfusion therapy in Japan is in accordance with international standards. It depends on the lesion location, comorbidities including older age, lesion type (eg, total occlusion), which are related to suitability for BPA, experience of the institution, and patient preference. The Japanese institution tends to select BPA strategy because of its long history and experience with BPA. In addition, outcomes of BPA for patients with surgically accessible lesions in the Japanese expert institution were demonstrated to be acceptable.[18] By the time this registry was launched in 2018, the strategy was well established and reported in detail as a review article.[19] The latest European Society of Cardiology clinical statement on BPA in CTEPH reflects this strategy.[20]

OUTCOME MEASURES. The prespecified efficacy endpoints in the registry were morbidity and mortality events comprising all-cause death, rescue mechanical reperfusion therapy (BPA or PEA) or initiation of parenteral pulmonary vasodilators, and/or deterioration (≥15%) in 6-minute walk distance (6MWD) with worsening of World Health Organization (WHO) functional class. Symptomatic venous thromboembolism was also collected as a clinical endpoint. Other clinical outcome measures including WHO functional class, 6MWD, brain natriuretic peptide (BNP) level, relevant laboratory test results, and catheter-based pulmonary hemodynamics were collected. The primary outcome was the incidence of morbidity and mortality events, and the secondary outcomes were changes at follow-up from baseline in WHO functional class, 6MWD, mPAP, pulmonary vascular resistance (PVR), cardiac index, and BNP. The incidence of symptomatic venous thromboembolism and changes in relevant laboratory test results were also assessed as exploratory outcomes. These outcomes were evaluated by the strategy groups.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or percentage, unless noted otherwise. Continuous data with non-normal distribution are presented as median (Q1-Q3). Categorical variables are presented as number (percentage). Differences between groups were analyzed using unpaired t-test for parametric variables, Wilcoxon rank sum test for nonparametric variables, and chi-square test for categorical variables. Morbidity and mortality events were aggregated to determine the time from baseline to the first occurrence of these events. Kaplan-Meier estimates were used to estimate the time-to-event function. Noninformative censoring was defined by a process in which each institution made an effort to collect participant information. The administration sent a request to each institution to enter data for patients with missing follow-up data before database lock. Changes in the clinical outcome measures at follow-up from baseline were analyzed using paired t test for parametric variables, Wilcoxon signed-rank test for nonparametric variables, and McNamar test for categorical variables. For treatment-naive patients, propensity score matching was implemented using the greedy nearest neighbor 1-to-3 ratio matching within a caliper of 0.25 SD. For the propensity score-matched population, we compared the changes in clinical outcome measures between groups using the difference-in-differences method. A P value <0.05 was considered significant.

FIGURE 1 Patient Disposition

All patients with reperfusion data were divided into "on-treatment" or "treatment-naive" based on the history of reperfusion therapy at baseline, and each patient was categorized into the BPA or the PEA strategy group based on the details of reperfusion therapy. BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PEA = pulmonary endarterectomy.

Imputation of missing data was not performed. SAS version 9.4 (SAS Institute Inc) was used for analysis.

RESULTS

STUDY POPULATION. Between August 2018 and July 2023, a total of 1,270 patients from 35 centers were enrolled in the CTEPH AC registry. Of the 580 patients not receiving reperfusion therapy at baseline, 369 patients (29.1%) were classified as treatment-naive after excluding 86 (6.8%) with no follow-up data (n = 67: follow-up period not reached; n = 19: follow-up data missing) and 125 (9.8%) without mechanical reperfusion therapy at last follow-up. A total of 313 (84.8%) were categorized into the BPA strategy group and 56 (15.2%) into the PEA strategy group. A total of 690 (54.3%) were classified as on-treatment, 561 (81.3%) were categorized into the BPA strategy group, and 129 (18.7%) into the PEA strategy group (Figure 1). Supplemental Table 1 shows details of patient disposition by institution. The baseline characteristics of the treatment-naive patients are summarized in Table 1. The 369 treatment-naive patients had mean age of 65.9 ± 12.6 years; 104 patients (28.2%) were males, and 188 patients (50.9%) were treated with pulmonary vasodilators. In the BPA strategy group, patients were older (mean age, BPA vs PEA: 66.5 ± 12.6 years vs 62.5 ± 11.8 years; $P = 0.028$) and had lower mPAP (BPA vs PEA: 37.6 ± 10.4 mm Hg vs 41.4 ± 11.8 mm Hg; $P = 0.016$) compared with the PEA strategy group. There were no significant differences in WHO functional class, 6MWD, BNP level, and estimated glomerular filtration rate (eGFR) at baseline between the BPA strategy group and the PEA strategy group. The baseline characteristics of the on-treatment patients are summarized in Supplemental Table 2. The 690 patients had mean age of 62.1 ± 13.4 years; 208 patients (30.1%) were males, and 388 patients (56.2%) were treated with pulmonary vasodilators. Patients in the BPA strategy group were older (mean age, BPA vs PEA: 63.2 ± 13.1 years vs 57.4 ± 13.6 years; $P < 0.001$) with lower percentage of males (152/561, 27.1% vs 56/129, 43.4%; $P < 0.001$) compared with the PEA strategy group. In the BPA strategy group, the

TABLE 1 Baseline Characteristics of Treatment-Naive Patients Classified Into BPA and PEA Strategy Groups

	All Treatment-Naive Patients (N = 369)	Strategy Group[a]		P Value[b]
		BPA Strategy (n = 313)	PEA Strategy (n = 56)	
Demographics				
Age at diagnosis, y	65.9 ± 12.6	66.5 ± 12.6	62.5 ± 11.8	0.028
Male	104 (28.2)	89 (28.4)	15 (26.8)	0.873
Body mass index, kg/m^2	23.6 ± 4.4	23.7 ± 4.6	23.6 ± 3.5	0.904
Time from diagnosis, days	1 (1-30)	1 (1-29)	1 (1-46)	0.798
Disease severities				
WHO functional class I/II	148 (40.1)	122 (39.0)	26 (46.4)	0.304
n (missing)	369 (0)	313 (0)	56 (0)	
6MWD, m	352 ± 117	349± 116	368 ± 127	0.327
n (missing)	303 (66)	258 (55)	45 (11)	
mPAP, mm Hg	38.2 ± 10.7	37.6 ± 10.4	41.4 ± 11.8	0.016
n (missing)	369 (0)	313 (0)	56 (0)	
PVR, dyn/s/cm^5	675 ± 354	664 ± 361	735 ± 308	0.171
n (missing)	369 (0)	313 (0)	56 (0)	
Cardiac index, m L/min/m^2	2.5 ± 0.7	2.5 ± 0.7	2.4 ± 0.6	0.335
n (missing)	368 (1)	312 (1)	56 (0)	
BNP, mpg/mL	60 (22-180)	60 (22-187)	55 (28-158)	0.797
n (missing)	326 (43)	272 (41)	54 (2)	
Mixed venous oxygen saturation, %	64.4 ± 8.2	64.5 ± 8.3	63.5± 7.9	0.394
n (missing)	332 (37)	279 (34)	53 (3)	
eGFR, mL/min/1.73 m^2	63.4 ± 16.6	63.3 ± 16.2	63.9 ± 18.7	0.811
n (missing)	288 (81)	242 (71)	46 (10)	
History and comorbidities associated with CTEPH				
History of acute venous thromboembolism	144 (39.0)	126 (40.3)	18 (32.1)	0.299
Intravenous device	8 (2.2)	6 (1.9)	2 (3.6)	0.349
Varicose veins	14 (3.8)	14 (4.5)	0 (0.0)	0.141
Thromboembolic risk	228 (61.8)	198 (63.3)	30 (53.6)	0.181
Hypercoagulable disorder	18 (4.9)	14 (4.5)	4 (7.1)	0.496
Active cancer/history of cancer	28 (7.6)	24 (7.7)	4 (7.1)	1.00
Previous stroke/transient ischemic attack	6 (1.6)	6 (1.9)	0 (0.0)	0.597
Hemiplegia/paraplegia	3 (0.8)	3 (1.0)	0 (0.0)	1.00
Use of antipsychotics	28 (7.6)	25 (8.0)	3 (5.4)	0.783
Thyroid disease or hormone replacement therapy	18 (4.9)	16 (5.1)	2 (3.6)	1.0
Inflammatory bowel disease	2 (0.5)	2 (0.6)	0 (0.0)	1.000
COPD/ILD	13 (3.5)	11 (3.5)	2 (3.6)	1.00
Anticoagulants				
Warfarin	128 (34.7)	107 (34.2)	21 (37.5)	0.649
DOACs	233 (63.1)	198 (63.3)	35 (62.5)	1.00
Dabigatran	2 (0.5)	2 (0.6)	0 (0.0)	1.00
Rivaroxaban	83 (22.5)	74 (23.6)	9 (16.1)	0.296
Apixaban	79 (21.4)	67 (21.4)	12 (21.4)	1.00
Edoxaban	69 (18.7)	55 (17.6)	14 (25)	0.195
No oral anticoagulants	8 (2.2)	8 (2.6)	0 (0.0)	0.613
Pulmonary vasodilators				
Any pulmonary vasodilator,	188 (50.9)	162 (51.8)	26 (46.4)	0.472
PDE-5 inhibitors/sGC stimulators	169 (45.8)	143 (45.7)	26 (46.4)	1.00
Riociguat	165 (44.7)	139 (44.4)	26 (46.4)	0.884
Prostacyclin analog, PGI$_2$ receptor agonists	34 (9.2)	28 (8.9)	6 (10.7)	0.621
Selexipag	18 (4.9)	17 (5.4)	1 (1.8)	0.331
Endothelin receptor antagonists	19 (5.1)	17 (5.4)	2 (3.6)	0.750

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Categorization of all treatment-naive patients according to strategy of reperfusion therapy during follow-up. [b]Comparison between BPA and PEA strategy groups, P < 0.05 statistically significant.

6MWD = 6-minute walk distance; BNP = brain natriuretic peptide; BPA = balloon pulmonary angioplasty; COPD/ILD = chronic obstructive pulmonary disease/interstitial lung disease; CTEPH = chronic thromboembolic pulmonary hypertension; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; mPAP = mean pulmonary artery pressure; PEA = pulmonary endarterectomy; PDE = phosphodiesterase; PGI2 = prostaglandin-I2; PVR = pulmonary vascular resistance; sGC = soluble guanylate cyclase; WHO = World Health Organization.

catheter-based mPAP (mean BPA vs PEA: 27.2 $\pm$ 10.8 mm Hg vs 22.7 $\pm$ 7.2 mm Hg; $P < 0.001$), PVR (BPA vs PEA: 366 $\pm$ 281 dyn/s/cm^5 vs 291 $\pm$ 205 dyn/s/cm^5; $P < 0.001$), and cardiac index (BPA vs PEA: 2.8 $\pm$ 0.7 L/min/m^{2}vs 2.6 $\pm$ 0.6 L/min/m^2; $P = 0.001$) at registration were higher compared with the PEA strategy group. In the BPA strategy group, patients were more frequently treated with antipsychotics (BPA vs PEA: 65 [11.6%] vs 2 [1.6%]; $P < 0.001$), pulmonary vasodilators (BPA vs PEA: 331 [59.0%] vs 57 [44.2%]; $P = 0.003$), and non–vitamin K antagonists (BPA vs PEA: 292 [52.0%] vs. 40 [31.0%]; $P < 0.001$) compared with the PEA strategy group.

PRIMARY OUTCOME: MORBIDITY AND MORTALITY EVENTS IN TREATMENT-NAIVE PATIENTS.

Among the treatment-naive patients, morbidity and mortality events occurred in 12 patients in the BPA strategy group and 2 patients in the PEA strategy group. Kaplan-Meier–estimated proportions of morbidity and mortality were 1.9% (95% CI: 0.8%-4.4%) at 1 year, 6.1% (95% CI: 3.1%-11.9%) at 3 years, and 10.2% (95% CI: 5.2%-19.5%) at 5 years in the BPA strategy group, and 0% at 1 year, 0% at 3 years, and 16.1% (95% CI: 4.3%-50.6%) at 5 years in the PEA strategy group (Figure 2A). The estimated proportions of all-cause death were 0% at 1 year, 1.7% (95% CI: 0.4%-7.2%) at 3 years, and 1.7% (95% CI: 0.4%-7.2%) at 5 years in the BPA strategy group (Figure 2B). There were no deaths in the PEA strategy group.

SECONDARY OUTCOMES: FUNCTIONAL CLASS, EXERCISE TOLERANCE, AND PULMONARY HEMODYNAMICS IN TREATMENT-NAIVE PATIENTS.

Table 2 shows the results of the treatment-naive patients. Follow-up period from baseline was 615 (Q1-Q3: 311-997) days. In the BPA strategy group, the number (percentage) of patients with WHO functional class I or II increased from 122 (39.0%) to 276 (88.2%) ($P < 0.001$), and 6MWD increased from 344 $\pm$ 114 m to 405 $\pm$ 118 m ($P < 0.001$), showing significant improvements. Of the 56 patients in the PEA strategy group, 22 (39.3%) underwent BPA during the follow-up period. In the PEA strategy group, the number of patients with WHO functional class I or II increased from 26 (46.4%) to 49 (87.5%) ($P < 0.001$), and 6MWD increased from 351 $\pm$ 116 m to 400 $\pm$ 115 m ($P < 0.001$), also showing significant improvements. mPAP, PVR, mixed venous oxygen saturation, and BNP were also improved at follow-up compared with baseline in both groups. Cardiac index was significantly improved in the BPA strategy group (baseline to follow-up: 2.5 $\pm$ 0.7

L/min/m^2 to 2.7 $\pm$ 0.7 L/min/m^2; $P < 0.001$) but was not improved in the PEA strategy group (2.4 $\pm$ 0.6 to 2.5 $\pm$ 0.5 L/min/m^2; $P = 0.343$).

EXPLORATORY OUTCOMES: SYMPTOMATIC VENOUS THROMBOEMBOLISM AND RELEVANT LABORATORY TESTS IN TREATMENT-NAIVE PATIENTS.

Symptomatic venous thromboembolism occurred in 2 patients in the BPA strategy group and 1 patient in the PEA strategy group. Kaplan-Meier–estimated proportions of symptomatic venous thromboembolism were 0.7% (95% CI: 0.2%-2.8%) at 1 year, 0.7% (95% CI: 0.2%-2.8%) at 3 years, and 0.7% (95% CI: 0.2%-2.8%) at 5 years in the BPA strategy group, and 2.0% (95% CI: 0.3%-13.6%) at 1 year, 2.0% (95% CI: 0.3%-13.6%) at 3 years, and 2.0% (95% CI: 0.3%-13.6%) at 5 years in the PEA strategy group (Figure 2E). The eGFR was significantly improved in the BPA strategy group (baseline to follow-up: 63.3 $\pm$ 16.2 mL/min/1.73 m^2 to 65.5 $\pm$ 17.1 mL/min/1.73m^2; $P = 0.002$) but was not improved in the PEA strategy group (63.9 $\pm$ 18.7 mL/min/1.73m^2 to 61.8 $\pm$ 20.7 mL/min/1.73m^2; $P = 0.306$) (Table 2).

OUTCOMES IN PROPENSITY SCORE–MATCHED POPULATION OF TREATMENT-NAIVE PATIENTS.

To compare the BPA strategy group with the PEA strategy group in the treatment-naive patients, a propensity score matching analysis was performed to minimize selection bias. The variables used for matching were the number of classes of pulmonary vasodilators at baseline, age at diagnosis, and mPAP at baseline. The standard mean differences before and after propensity score matching are shown in Supplemental Figure 1. The propensity score–matched population showed no significant differences in the proportions of morbidity and mortality events and symptomatic venous thromboembolism between the BPA strategy group and the PEA strategy group (Supplemental Figure 2). The clinical outcome measures including functional class, exercise tolerance, pulmonary hemodynamics, and key laboratory tests are shown in Table 3. The eGFR was significantly improved in the BPA strategy group compared with the PEA strategy group. Reduction in mPAP was inferior in the BPA strategy group than in the PEA strategy group, but changes in the other clinical outcome measures were not significantly different between the BPA strategy group and the PEA strategy group.

MISSING DATA.

Missing data were reported in Tables 2 and 3 for the BPA strategy group and the PEA strategy group, respectively. The proportion of missing data at follow-up was similar between

FIGURE 2 Kaplan-Meier Cumulative Event Curves for the Treatment-Naive Patients
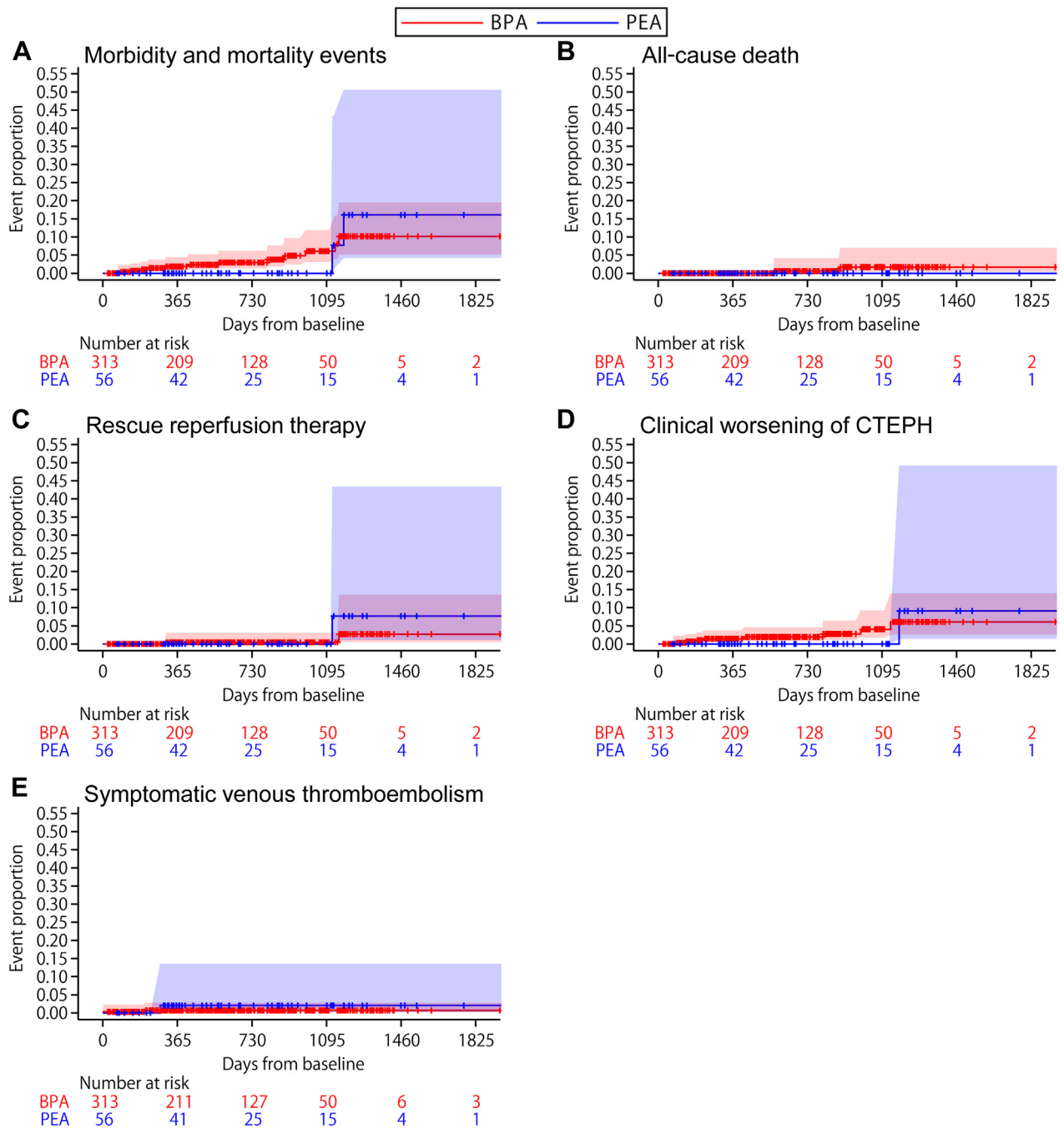
The figures show (A) morbidity and mortality events, (B) all-cause mortality, (C) rescue mechanical reperfusion therapy (BPA or PEA), (D) clinical worsening of CTEPH characterized by decreased 6MWD and worsening of WHO functional class, and (E) symptomatic venous thromboembolism. Red = BPA strategy group. Blue = PEA strategy group. Shaded areas = 95% CIs. 6MWD = 6-minute walk distance; WHO = World Health Organization; other abbreviations as in Figure 1.

TABLE 2 Comparison of Clinical Outcome Measures at Baseline and at Follow-Up in Treatment-Naive Patients

| | | All Treatment-Naive Patients (N = 369) | | | | Strategy Group[a] | | | | | | | |
| | | | | | | BPA Strategy (n = 313) | | | | PEA Strategy (n = 56) | | | |

Follow-up period from baseline, d		615 (311-997)				614 (302-967)				619 (367-1,106)			
BPA during follow-up		335 (90.8)				313 (100.0)[d]				22 (39.3)[d]			
PEA as initial reperfusion therapy		49 (13.3)				0 (0.0)				49 (87.5)			

	Baseline	Follow-Up	Change[b]	P Value[c]	Baseline	After Intervention	Change[b]	P Value[c]	Baseline	After Operation	Change[b]	P Value[c]
WHO functional class I/II	148 (40.1)	325 (88.1)	177 (48.0)	<0.001	122 (39.0)	276 (88.2)	154 (49.2)	<0.001	26 (46.4)	49 (87.5)	23 (41.1)	<0.001
n (missing)	369 (0)				313 (0)				56 (0)			
6MWD, m	345 ± 114	405 ± 117	60 ± (97	<0.001	344 ± 114	405 ± 118	62 ± 100	<0.001	351 ± 116	400 ± 115	49 ± 80	<0.001
n (missing)	252 (117)				213 (100)				39 (17)			
mPAP, mm Hg	38.2 ± 10.6	22.9 ± 7.0	−15.4 ± 10.7	<0.001	37.6 ± 10.4	23.0 ± 7.0	−14.6 ± 10.4	<0.001	41.8 ± 11.1	22.0 ± 7.0	−19.9± 11.4	<0.001
n (missing)	363 (6)				310 (3)				53 (3)			
PVR, dyn/s/cm⁵	677 ± 356	299 ± 157	−378 ± 346	<0.001	665 ± 362	300 ± 155	−365 ± 352	<0.001	743 ± 314	293 ± 172	−450 ± 302	<0.001
n (missing)	363 (6)				310 (3)				53 (3)			
Cardiac index, L/min/m²	2.5 ± 0.7	2.7 ± 0.7	0.2 ± 0.7	<0.001	2.5 ± 0.7	2.7 ± 0.7	0.2 ± 0.7	<0.001	2.4 ± 0.6	2.5 ± 0.5	0.1 ± 0.6	0.343
n (missing)	360 (9)				307 (6)				53 (3)			
BNP, median (Q1-Q3), pg/mL	60 (23-180)	22 (12-48)	−108 (239)	<0.001	60 (21-190)	21 (11-45)	−112 (245)	<0.001	55 (28-158)	31 (17-62)	−89 ± 209	0.001
n (missing)	325 (44)				271 (42)				54 (2)			
Mixed venous oxygen saturation, %	64.3 ± 8.2	69.1 ± 6.6	4.8 ± 8.3	<0.001	64.5 ± 8.2	69.2 ± 6.0	4.7 ± 8.1	<0.001	63.4 ± 8.0	68.5 ± 9.2	5.1 ± 9.6	<0.001
n (missing)	314 (55)				266 (47)				48 (8)			
eGFR, mL/min/1.73 m²	63.4 ± 16.6	64.9 ± 17.8	1.5 ± 11.5	0.027	63.3 ± 16.2	65.5 ± 17.1	2.2 ± 11.0	0.002	63.9 ± 18.7	61.8 ± 20.7	−2.1 ± 13.7	0.306
n (missing)	288 (81)				242 (71)				46 (10)			

Values median (Q1-Q3), n (%), or mean ± SD. [a]Categorization of all treatment-naive patients according to strategy of reperfusion therapy during follow-up. [b]Change at follow-up from baseline are described as mean ± SD for continuous data and n (%) for categorical data. [c]Comparison of data between baseline and final follow-up using paired *t* test (parametric variables), Wilcoxon singed-rank test (nonparametric variables), and McNemar test (categorical variables); *P* < 0.05 statistically significant. [d]Of them, BPA as rescue reperfusion therapy is included in 2 patients in the BPA strategy group and in 1 patient in the PEA strategy group.

Abbreviations as in **Table 1**.

groups. Missing data was considered as "missing at random" and missing data imputation was not performed.

OUTCOMES IN ON-TREATMENT PATIENTS. Follow-up period from baseline was 1,136 (684-1,300) days in the outcome analysis of on-treatment patients. Morbidity and mortality events occurred in 34 patients in the BPA strategy group and 5 patients in the PEA strategy group. Kaplan-Meier-estimated morbidity and mortality rates were 1.7% (95% CI: 0.8%-3.3%) at 1 year, 7.4% (95% CI: 5.2%-10.5%) at 3 years, and 9.7% (95% CI: 6.7%-13.8%) at 5 years in the BPA strategy group, and 0.9% (95% CI: 0.1%-6.2%) at 1 year, 4.3% (95% CI: 1.6%-11.0%) at 3 years, and 6.9% (95% CI: 2.7%-17.3%) at 5 years in the PEA strategy group

(Supplemental Figure 3A). The estimated mortality rates were 0.7% (95% CI: 0.2%-2.0%) at 1 year, 3.3% (95% CI: 1.8%-5.8%) at 3 years, and 4.4% (95% CI: 2.5%-7.6%) at 5 years in the BPA strategy group, and 0.9% (95% CI: 0.1%-6.3%) at 1 year, 1.9% (95% CI: 0.5%-7.4%) at 3 years, and 4.6% (95% CI: 1.2%-15.9%) at 5 years in the PEA strategy group (Supplemental Figure 3B). Symptomatic venous thromboembolism occurred in 4 patients in the BPA strategy group and none in the PEA strategy group. Kaplan-Meier-estimated symptomatic venous thromboembolism rates were 0.6% (95% CI: 0.2%-1.9%) at 1 year, 0.9% (95% CI: 0.3%-2.3%) at 3 years, and 0.9% (95% CI: 0.3%-2.3%) at 5 years in the BPA strategy group (Supplemental Figure 3E). The clinical outcome measures including mPAP, PVR, mixed venous

TABLE 3 Comparison of Changes Between BPA Strategy and PEA Strategy After Propensity Score Matching

	Propensity Score-Matched Population of Treatment-Naive Patients (n = 212)			Strategy Group[a]						Difference Between Changes[c]	
				BPA Strategy (n = 157)			PEA Strategy (n = 55)				
Follow-up period from baseline, d	691 (359-1018)			708 (358-1,007)			619 (360-1,116)				
BPA during follow-up	179 (84.4)			157 (100.0)[d]			22 (40.0)[d]				
PEA as initial reperfusion therapy	48 (22.6)			0 (0.0)			48 (87.3)				
	Baseline	Follow-Up	Change[b]	Baseline	After Intervention	Change[b]	Baseline	After Operation	Change[b]	Mean (95% CI)	P Value[c]
WHO functional class I/II	91 (42.9)	189 (89.2)	98 (46.2)	66 (42.0)	141 (89.8)	75 (47.8)	25 (45.5)	48 (87.3)	23 (41.8)		0.638
n (missing)	212 (0)			157 (0)			55 (0)				
6MWD, m	343 ± 116	414 ± 120	72 ± 102	341 ± 117	421 ± 121	80 ± 109	348 ± 115	397 ± 116	50 ± 81	30 (−3 to 64)	0.077
n (missing)	139 (73)			101 (56)			38 (17)				
mPAP, mm Hg	40.6 ± 10.4	23.5 ± 7.5	−17.1 ± 11.2	40.2 ± 10.1	24.0 ± 7.5	−16.2 ± 11.0	41.8 ± 11.2	22.0 ± 7.0	−19.8 ± 11.5	3.6 (0.1 to 7.1)	0.046
n (missing)	207 (5)			155 (2)			52 (3)				
PVR, dyn/s/cm5	726 ± 353	298 ± 156	−428 ± 342	719 ± 365	299 ± 151	−420 ± 354	747 ± 316	297 ± 172	−450 ± 305	30 (−78 to 138)	0.587
n (missing)	207 (5)			155 (2)			52 (3)				
Cardiac index, L/min/m2	2.4 ± 0.6	2.7 ± 0.6	0.2 ± 0.7	2.4 ± 0.6	2.7 ± 0.6	0.3 ± 0.7	2.4 ± 0.6	2.5 ± 0.5	0.1 ± 0.6	0.2 (0.0-0.4)	0.077
n (missing)	205 (7)			153 (4)			52 (3)				
BNP, pg/mL	67 (25-222)	20 (11-48)	-130 (267)	76 (25-247)	18 (9-40)	−145 (286)	55 (28-158)	29 (17-60)	−91 (210)	−55 (−130 to 21)	0.153
n (missing)	187 (25)			134 (23)			53 (2)				
Mixed venous oxygen saturation, %	63.7 ± 8.9	69.1 ± 6.9	5.4 ± 9.4	63.9 ± 9.0	69.3 ± 5.8	5.5 ± 9.3	63.2 ± 8.0	68.3 ± 9.2	5.1 ± 9.7	0.3 (−2.8 to 3.5)	0.839
n (missing)	178 (34)			131± 26			47 (8)				
eGFR, mL/min/1.73 m2	62.9 ± 15.9	64.4 ± 17.6)	1.5 ± 11.0	62.5 ± 14.8	65.3 ± 16.3	2.8± 9.5	63.9 ± 18.7	61.8 ± 20.7	−2.1 ± 13.7	4.9 (0.5-9.3)	0.030
n (missing)	171 (41)			125 (32)			46 (9)				

Values median (Q1-Q3), n (%), or mean ± SD. [a]Categorization of propensity score-matched population of treatment-naive patients according to strategy of reperfusion therapy during follow-up. [b]Changes at follow-up from baseline are described as mean ± SD for continuous data and n (%) for categorical data. [c]Differences between changes in BPA strategy and PEA strategy were tested using unpaired *t* test (continuous variables) and chi-squared test for (categorical variables); *P* < 0.05 statistically significant. [d]Of them, BPA as rescue reperfusion therapy is included in 1 patient in the BPA strategy group and in 1 patient in the PEA strategy group.

Abbreviations as in **Table 1**.

oxygen saturation, and BNP reached the same levels at follow-up in the 2 groups (Supplemental Table 3).

DISCUSSION

This nationwide prospective observational registry in Japan demonstrated that BPA was more frequently the option of choice for reperfusion in older patients. The BPA strategy and the PEA strategy were acceptable in the incidence of morbidity and mortality events and symptomatic venous thromboembolism as well as in long-term outcomes of functional capacity, exercise tolerance, and pulmonary hemodynamics. In the treatment-naive patients, the BPA strategy achieved greater improvement in renal function compared with the PEA strategy (Central Illustration).

In this registry, the proportions of patients treated with the BPA strategy and the PEA strategy were 84.8% and 15.2%, respectively, in treatment-naive patients, and 81.3% and 18.7%, respectively, in on-treatment patients. Several recent reports from Europe and the United States have shown that only 5.3%-10.9% of patients newly diagnosed with CTEPH were treated with BPA,[12,17] suggesting that the situation in Japan is unique. The CTEPH patients enrolled in this Japanese registry were of female preponderance (70.7%) and had a lower prevalence of a history of venous thromboembolism (40.1%), whereas registries in Europe and the United States reported no sex difference and a high frequency of history of venous thromboembolism (Q1-Q3: 69.0%-87.9%).[12,17,21] The average age of the treatment-naive patients in the
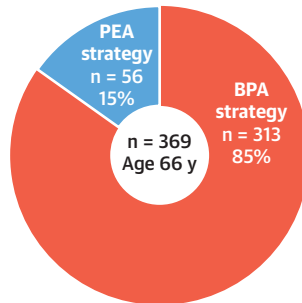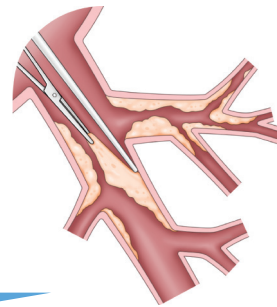
CENTRAL ILLUSTRATION Results From the Japanese Nationwide CTEPH Registry (August 2018 to July 2023)

CTEPH Patients From Japanese Nationwide Registry (August 2018 to July 2023)
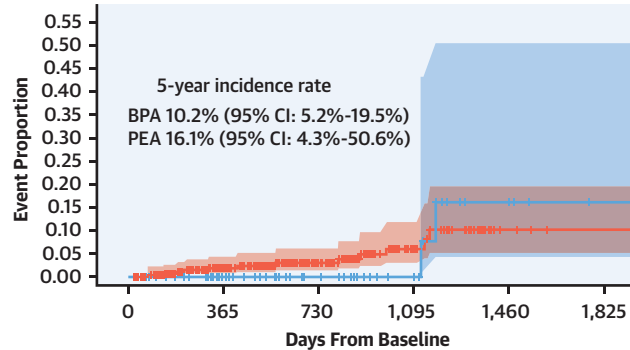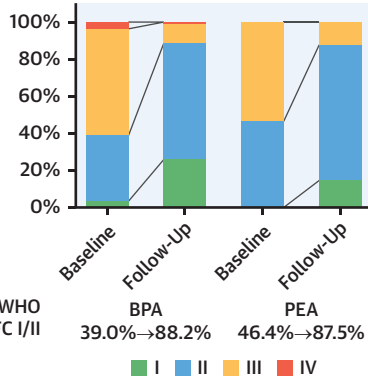
Balloon Pulmonary Angioplasty (BPA)

PEA strategy n = 56 15%
BPA strategy n = 313 85%
n = 369 Age 66 y
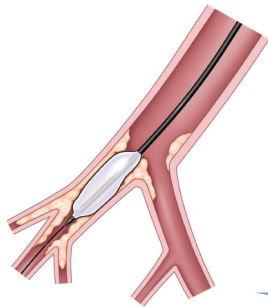
Pulmonary Endarterectomy (PEA)

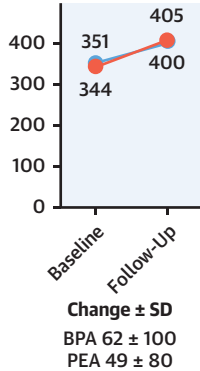median follow-up period: 615 (Q1-Q3: 311-997) days

Morbidity and Mortality Events

5-year incidence rate
BPA 10.2% (95% CI: 5.2%-19.5%)
PEA 16.1% (95% CI: 4.3%-50.6%)

Number at risk
BPA 313   209   128   50   5   2
PEA   56   42   25   15   4   1

WHO Functional Class

WHO FC I/II
BPA 39.0%→88.2%
PEA 46.4%→87.5%

■ I   ■ II   ■ III   ■ IV

6MWD
351
344
405
400
Change ± SD
BPA 62 ± 100
PEA 49 ± 80

mPAP
41.8
37.6
23.0
22.0
Change ± SD
BPA −14.6 ± 10.4
PEA −19.9 ± 11.4

After PSM

eGFR
63.9
62.5
65.3
61.8
Difference between change: 4.9 (95% CI: 0.5-9.3); P = 0.030
Change ± SD
BPA 2.8 ± 9.5
PEA −2.1 ± 13.7

●—● BPA   ●—● PEA
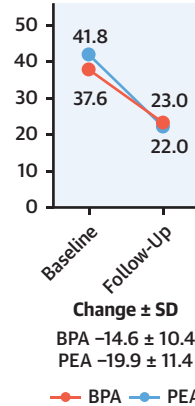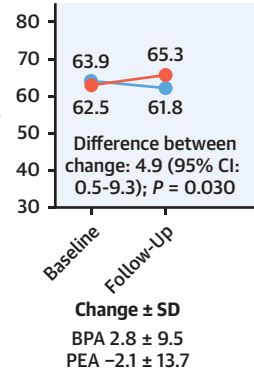
Masaki K, et al. JACC Asia. 2024;4(8):577–589.

The Kaplan-Meier cumulative curve shows morbidity and mortality events for the treatment-naive patients who received the first reperfusion therapy after enrollment. 6MWD = 6-minute walk distance; BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; eGFR = estimated glomerular filtration rate; mPAP = mean pulmonary artery pressure; PEA = pulmonary endarterectomy; PSM = propensity score matching; PVR = pulmonary vascular resistance; WHO = World Health Organization.

Japanese registry was 65.9 years, which was older than that in the other registries. Compared with central type of CTEPH, patients with distal type of CTEPH are predominantly women, have lower risk of acute pulmonary embolism, and have older age.[22] Given the characteristics of CTEPH patients enrolled in the Japanese registry, female preponderance, older age, and lower prevalence of prior venous thromboembolism, these would suggest that Japanese CTEPH patients predominantly have distal type of CTEPH, and they are potentially suitable candidates for BPA.

In the treatment-naive patients, cumulative incidence of morbidities and mortalities was low in both the BPA and the PEA strategy groups. The 3-year mortality rates in the treatment-naive patients were 1.7% in the BPA strategy group and 0% in the PEA strategy group, which are consistent with the international registry that reported mortality rates (mean: 32 months) of 1.8% in the BPA-treated group and 3.5% in the PEA-treated group.[17] The similar results in the Japanese registry to those in international registries suggest that the BPA strategy may be promising in expert BPA centers worldwide.

In the treatment-naive patients, irrespective of reperfusion with BPA or PEA, pulmonary hemodynamics reached the same levels at follow-up, indicating that the effect of reperfusion on subsequent hemodynamics was not associated with the type of reperfusion strategy. In addition, the outcomes of WHO functional class and 6MWD at follow-up after reperfusion therapy were acceptable in both the BPA and PEA strategy groups, supporting the idea that the BPA strategy is an effective treatment for restoring exercise tolerance and activities of daily living in inoperable CTEPH patients. Whereas, in the propensity score-matched population, the reduction in mPAP was greater in the PEA strategy group than in the BPA strategy group, probably because of the treatment characteristics of the PEA strategy, which could provide single-stage treatment, and the BPA strategy, which had some patients in incomplete treatment stage.

A notable finding of the current study is that eGFR showed greater improvement at follow-up in the BPA strategy group than in the PEA strategy group. With a minimally invasive approach, BPA improves pulmonary circulation and consequently ameliorates venous congestion, vital organ perfusion, and blood oxygenation. The pleiotropic effects of BPA on glucose intolerance and nutritional status as well as renal function, in addition to amelioration of right-sided heart failure, have been reported previously.[23,24] The lack of improvement in eGFR in the PEA strategy group may be related to postoperative acute kidney failure, which is reported to be common after PEA, especially in older patients.[25]

In the on-treatment patients who are survivors of initial conditions including reperfusion therapy, the BPA strategy group showed higher mPAP and PVR at registration than the PEA strategy group, because some patients in the BPA strategy group might not complete full BPA stages. Nevertheless, morbidity and mortality rates in the BPA strategy group were as low as those in the PEA strategy group, and the differences in severity of CTEPH were resolved at follow-up, suggesting the efficacy of BPA in on-treatment patients as in treatment-naive patients.

This study contained 125 patients (9.8% of all enrolled patients) without any mechanical reperfusion therapy at the last follow-up (Figure 1, Supplemental Table 4). These patients had a higher percentage of WHO functional class I/II at baseline than those treated with reperfusion therapy (no reperfusion vs reperfusion: 59.2% vs 40.1%; $P < 0.001$), and frequent use of pulmonary vasodilators (66.4%), especially riociguat (55.2%). The final follow-up data of these patients demonstrated 68.8% of WHO functional class I/II, 391 ± 104 m of 6MWD: 26.4 ± 9.3 mm Hg of mPAP, and median: 26p Q1-Q3: 13-61 pg/mL of BNP), suggesting that patients who did not undergo mechanical reperfusion therapy were well controlled with medical therapy alone.

STUDY LIMITATIONS. First, given the observational design of this study, the possibility of residual confounding cannot be completely ruled out when analyzing the association between treatment strategies and clinical outcomes, despite adjustment for the known measured confounders. Second, the current registry lacked information on operability and lesion location. Third, this study was the single-country study, and its generalizability to other countries, where PEA is more often chosen for surgically accessible and borderline patients, should be interpreted with caution. A multinational, large-scale, randomized controlled trial is needed to resolve these limitations and to compare the safety and efficacy of the BPA strategy with the PEA strategy in patients with CTEPH.

CONCLUSIONS

In the present registry, BPA was more frequently the option of choice as reperfusion strategy in older patients with CTEPH. The outcomes of morbidity and

mortality events, pulmonary hemodynamics, and exercise capacity in CTEPH patients treated with the BPA strategy were similar to those treated with the PEA strategy. Reperfusion with the BPA strategy had greater benefit in improving renal function compared with the PEA strategy. BPA performed in specialty centers can be as effective an option as PEA for CTEPH patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The BPA strategy, often used in older patients, is an effective option for CTEPH, with the benefit of greater improvement in renal function than the PEA strategy. Potential benefits gained from expert BPA may be greater for older patients with renal dysfunction when the lesions are optimal for BPA.

TRANSLATIONAL OUTLOOK: Long-term results from international large-scale studies are needed to generalize the outcomes of BPA in this study. In addition, we need randomized controlled trials to compare the safety and efficacy of the BPA strategy with the PEA strategy in CTEPH patients who are uncertain which reperfusion therapy strategy to prefer.

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KEY WORDS pulmonary embolism, pulmonary hypertension, registry, thromboembolism

APPENDIX For a list of the study investigators (collaborators) as well as supplemental tables and figures, please see the online version of this paper.

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