Current Strategies for the Diagnosis and Treatment of Chronic Thromboembolic Pulmonary Hypertension Around the World

Methods

19 countries (Australia, Austria, Belgium, Brazil, Denmark, Finland, Germany, Italy, Japan, the Netherlands, Poland, Russia, Slovakia, Spain, Switzerland, Taiwan, Turkey, the United Kingdom, and the United States).

Data Cleaning:

An initial data report was provided by David Bowers, the consultant statistician to the ICA Board, on 9 November 2017. This was based on a preliminary inspection of the data; proposals were made and advice sought on a small number of cases of missing data, incomplete data, outliers, protocol violations, and clarification of definitions. Responses and guidance were received by 5 December 2017, allowing the data to be cleaned prior to analysis. The main points acted upon were:

a) Two patients were initially included in the registry database but had no recorded diagnosis of CTEPH and no recorded assessment for treatment/intervention. They were therefore excluded from the analysis, so that the final dataset consisted of 1010 patients.

b) Five patients had a date of PEA (operation) earlier than the recorded date of right heart catheterization (diagnosis), making the derived variable “time from diagnosis to PEA” negative. Since PEA would not have been performed without a diagnosis, the “time from diagnosis to PEA” for these patients was set to zero (i.e. diagnosis was assumed to be on the date of operation).

c) Three patients had date of BPA (intervention) earlier than the recorded date of right heart catheterization (diagnosis). The “time from diagnosis to first BPA” was set to zero for these

patients.

d) Several patients had a PVR value of 0. This was treated as missing data.

e) Some unusually high PVR values (from 2000 to 6880 dyn·s·cm^{-5}) and one negative PVR value were advised to be retained.

f) A small number of very low PVR values (below 10 dyn·s·cm^{-5}) were attributed to these values being measured in Wood units. They were therefore multiplied by 80 to convert to dyn·s·cm^{-5}.

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Disclosures

S.G. reports personal fees from Actelion, Bayer, GSK, MSD and Pfizer.

A.M.D. reports personal fees from Actelion, Bayer and MSD.

M.D. reports grants and personal fees from Actelion as well as personal fees from Bayer, M.S.D., Reata and Bellarophon.

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I.M.L. reports grants and personal fees from Actelion and AOPOrphan Pharma, personal fees from MSD and Ferrer and non-financial support from Medtronic.

M.M.M. has acted as a consultant to Actelion and Wexler Surgical.

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K.N., E.F., S.P.H., J.S.O.A., R.Q., R.S.K., G.S. and B.Y. report no conflicts of interest.

Data Availability

This data underlying this article are the property of the International CTEPH Association (ICA). Data will be shared on reasonable request to the corresponding author with permission of the ICA.

TABLE S1. Patient Disposition, by the 34 sites of the CTEPH Registry

Site Num	Name	City	Country	Region	Number of patients	PEA only candidates	Both PEA & BPA candidates	BPA only candidates	Neither candidates	PEA centre *	BPA centre *
2	Papworth Hospital	Cambridge	UK	Europe	66	45	1	7	13	X	X
3	Medical University of Vienna	Vienna	Austria	Europe	38	22	0	15	1	X	X
4	UZ Leuven	Leuven	Belgium	Europe	34	22	2	2	8	X	X
5	Kerckhoff-Klinik	Bad Nauheim	Germany	Europe	253	173	4	51	25	X	X
6	UCSD Medical Centre	La Jolla	USA	AAO	24	22	0	2	0	X	X
7	European Health Centre Otwock	Otwock	Poland	Europe	9	1	1	4	3		X
8	MH Hannover	Hannover	Germany	Europe	3	1	1	1	0		X
9	Sheffield Teaching Hospitals	Sheffield	UK	Europe	35	29	0	0	6		
10	Marmara University	Istanbul	Turkey	Europe	82	82	0	0	0	X	

Site Num	Name	City	Country	Region	Number of patients	PEA only candidates	Both PEA & BPA candidates	BPA only candidates	Neither candidates	PEA centre *	BPA centre *
	Hospital										
11	Kyorin University Hospital	Tokyo	Japan	Japan	14	1	0	13	0		X
12 #	RICP Novosibirsk	Novosibirsk	Russia	Europe	0	0	0	0	0		
13	IRCCS San Matteo	Pavia	Italy	Europe	119	106	0	1	12	X	
14	Hospital Sao Paulo	Sao Paulo	Brazil	AAO	36	18	0	0	18	X	
15	Western Infirmary, Glasgow	Glasgow	UK	Europe	7	1	1	1	4		
16	VU Medical Centre	Amsterdam	Netherlands	Europe	28	21	1	2	4	X	X
18	Chiba University Hospital	Chiba	Japan	Japan	19	14	0	1	4	X	
21	National Taiwan Uni Hospital	Taipei	Taiwan	AAO	18	9	0	3	6	X	X
22	Aarhus University Hospital	Aarhus	Denmark	Europe	3	1	0	0	2	X	

Site Num	Name	City	Country	Region	Number of patients	PEA only candidates	Both PEA & BPA candidates	BPA only candidates	Neither candidates	PEA centre *	BPA centre *
25	Cardiology Research Centre	Moscow	Russia	Europe	26	12	4	10	0	X	X
26	Okayama Medical Centre	Okayama	Japan	Japan	47	0	0	47	0		X
27	Royal Free London NHS Trust	London	UK	Europe	17	3	1	0	13		
28	St Vincent's Hospital	Sydney	Australia	AAO	1	0	0	0	1		X
29	Slovak Medical University	Bratislava	Slovakia	Europe	6	2	0	0	4		
30	University of Maryland	Baltimore	USA	AAO	2	1	0	0	1	X	
31	Hospital Clinic Barcelona	Barcelona	Spain	Europe	18	10	0	0	8	X	
32	HU 12 de Octubre	Madrid	Spain	Europe	2	2	0	0	0	X	
38	Wojewodzki Szpital	Wroclaw	Poland	Europe	15	2	0	8	5		X
43	Kobe University Hospital	Kobe	Japan	Japan	35	10	2	18	5	X	X

Site Num	Name	City	Country	Region	Number of patients	PEA only candidates	Both PEA & BPA candidates	BPA only candidates	Neither candidates	PEA centre *	BPA centre *
44	The Alfred Hospital	Melbourne	Australia	AAO	10	8	0	0	2	X	
45	Uni of Sao Paulo Medical School	Sao Paulo	Brazil	AAO	7	7	0	0	0		
46	Helsinki University Hospital	Helsinki	Finland	Europe	8	8	0	0	0	X	
47	University Hospital of Zurich	Zurich	Switzerland	Europe	3	1	0	0	2	X	
49	Cleveland Clinic	Cleveland	USA	AAO	18	14	1	2	1	X	X
51	Medical University of Warsaw	Warsaw	Poland	Europe	7	1	1	5	0		
				TOTAL:	1010	649	20	193	148		

* Site classified as PEA Centre or BPA Centre based on being a centre at which at least one such procedure has been documented in the registry (CRF 22 or 28) up to the time of baseline analysis, either on one of their own patients or on a patient enrolled by another centre.

This site had recruited but not provided sufficient diagnostic data at the time of the Baseline Analysis datacut, hence no patient entered the analysis.

Table S2. PH Treatment at Diagnosis by Patient Disposition to Intervention, All Regions (n=1010)

	PEA Candidates (n=669)	BPA Candidates (n=213)	Total Candidates, PEA or BPA (n=862)	Neither PEA nor BPA (n=148)
PH-targeted drug treatment, n (%)	175 (26.2%)	116 (54.5%)	282 (37.7%)	80 (54.1%)
of which †				
GCS	43 (24.6%)	59 (50.9%)	98 (34.3%)	37 (46.3%)
PCA	10 (5.7%)	21 (18.1%)	30 (10.6%)	2 (2.5%)
ERA	40 (22.9%)	18 (15.5%)	58 (20.6%)	14 (17.5%)
PDE5i	104 (59.4%)	44 (37.9%)	143 (50.7%)	34 (42.5%)
Other	3 (1.7%)	3 (2.6%)	6 (2.1%)	3 (3.8%)
Single therapy	154 (88.0%)	89 (76.7%)	235 (83.3%)	70 (87.5%)
Double therapy	17 (9.7%)	25 (21.6%)	41 (14.5%)	10 (12.5%)
Triple therapy	4 (2.3%)	2 (1.7%)	6 (2.1%)	0 (0.0%)

PH, pulmonary hypertension; PEA indicates pulmonary endarterectomy; BPA, balloon pulmonary angioplasty; GCS, guanylate cyclase stimulator; PCA, prostacyclin analog; ERA, endothelin receptor antagonist, PDE5i, phosphodiesterase-5 inhibitor.

† Not mutually exclusive. More than one medication class can be prescribed.

Table S3. BPA Patients – Characteristics and Immediate Post-Intervention Experience, by Regions (n=175)

	Japan (n = 77)	Europe/AAO[#] (n = 98)	*P*-value (exploratory)
Sex, n (%) male	15 (19.5%)	43 (43.9%)	0.001
Age at first BPA, years	65 [57.3–75.0]	64.0 [51.0–72.5]	0.194
Time from diagnosis to first BPA (days)	12.0 [4.0–73.3]	165 [82.5–279.5]	< 0.001
Number of BPAs per patients	5.0 [4.0–6.0]	4.0 [3.0–6.0]	0.130
Time between BPA sessions, days	9.5 [7.0–55.0]	49.0 [35.0–79.0]	< 0.001
Last PVR calculated end of last BPA session, $dyn \cdot s \cdot cm^{-5}$	282 [221–356]	318 [265–501]	0.008

Reduction in PVR since diagnosis, dyn·s·cm^{-5}	400 [195–618]	261 [112–435]	0.005
Percentage reduction in PVR since diagnosis	60.2 [38.8–72.2]	41.5 [26.8–56.4]	< 0.001
Treatment with PH-targeted drug on discharge, n (%) *	28 (38.4%)	54 (72.0%)	< 0.001
Patient on oxygen at discharge, n (%) *	50 (68.5%)	5 (5.4%)	< 0.001

Values are expressed as median with first and third quartiles [Q1–Q3] or number and percentage of patients.

BPA indicates balloon pulmonary angioplasty PVR, pulmonary vascular resistance.

* Data were missing for some patients; PH, pulmonary hypertension; # Europe and AAO were put together since AAO included only 5 patients with a BPA procedure and all countries learned this refined technique from Japan.

TABLE S4. Time to death (PH related death) – all patients (N = 39), by region and by intervention

			By region			By intervention	
		All patients (N = 39)	Europe (N = 32)	Japan (N = 2)	AAO (N = 5)	PEA (N = 21)	BPA (no PEA) (N = 3)	No intervention (N = 15)
Time from diagnosis to death (months)	Median	4.44	4.58	9.02	4.44	4.01	10.84	6.01
	Min	0.13	0.13	0.30	1.31	0.13	10.74	0.30
	Max	29.70	29.70	17.74	10.38	21.16	11.96	29.70
		All patients with intervention (N = 24)	Europe (N = 21)	Japan (N = 0)	AAO (N = 3)	PEA (N = 21)	BPA (no PEA) (N = 3)	
Time from procedure to death * (months)	Median	0.79	0.85	-	0.46	0.69	2.07	
	Min	0.00	0.00		0.39	0.00	1.97	
	Max	5.98	5.98		1.25	5.98	3.06	

Values are expressed as median with minimum and maximum. * For BPA patients, time measured from last recorded BPA session

Figures

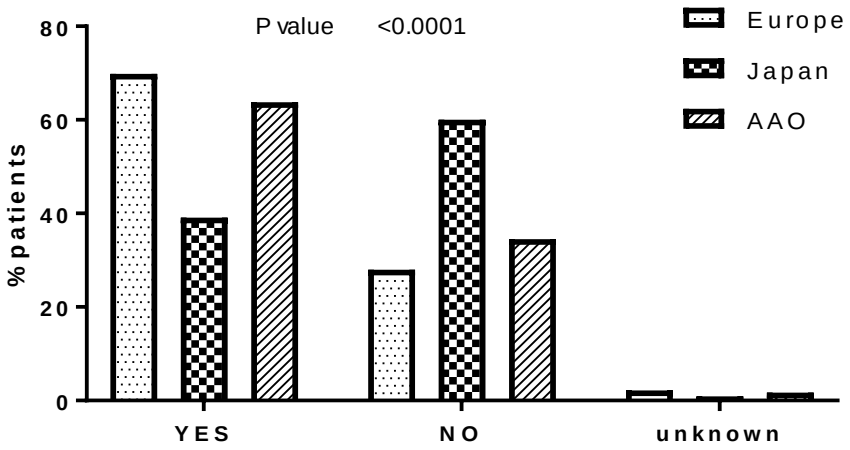

Figure S1. History of acute pulmonary embolism preceding CTEPH, by regions. AAO = America and others. *P*-Value is in the exploratory sense.

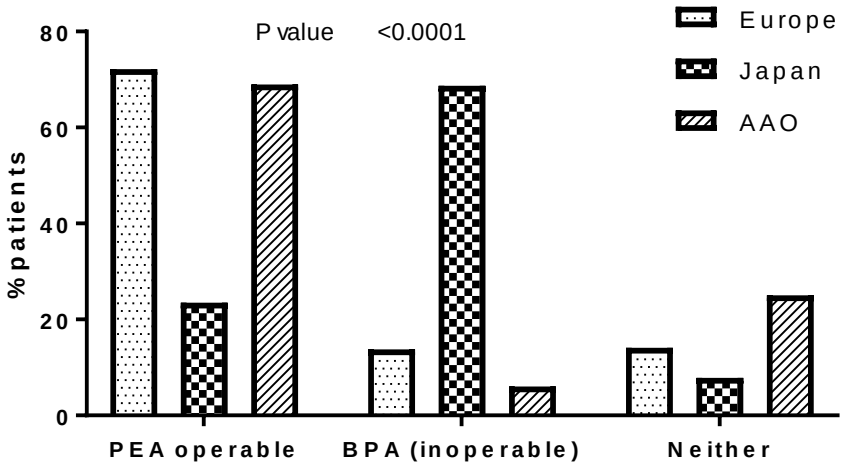

Figure S2. Distribution of patients regarding their disposition to surgery by PEA (pulmonary endarterectomy), intervention with BPA (balloon pulmonary angioplasty) or neither, by regions. AAO = America and others. *P*-Value is in the exploratory sense.

Figure Legends

Supplemental Figure S1. Distribution of patients regarding their disposition to surgery by PEA (pulmonary endarterectomy), intervention with BPA (balloon pulmonary angioplasty) or neither, by regions. AAO = America and others. *P*-Value is in the exploratory sense.

Supplemental Figure S2. History of acute pulmonary embolism preceding CTEPH, by regions. AAO = America and others. *P*-Value is in the exploratory sense.