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
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.
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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.
| Site Num | Site 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          | 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       | Poland  | Europe | 9                 | 1                   | 1                        | 4                   | 3                 | X          |            |
| 8        | MH Hannover                 | Hannover     | Germany | Europe | 3                 | 1                   | 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                 | 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                 | 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                 |            |            |
|          | Glasgow Hospital            |            |         |         |                    |                     |                          |                     |                   |            |            |
| 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                 | 0 X        |            |
| 47      | University Hospital of Zurich | Zurich         | Switzerland | Europe | 3                  | 1                   | 0                        | 0                   | 2                 | 2 X        |            |
| 49      | Cleveland Clinic              | Cleveland      | USA       | AAO    | 18                 | 14                  | 1                        | 2                   | 1                 | 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 data cut, hence no patient entered the analysis.
|                                      | PEA Candidates | BPA Candidates | Total Candidates, Neither PEA nor BPA |
|--------------------------------------|----------------|----------------|---------------------------------------|
|                                      | (n=669)        | (n=213)        | (n=862)                               | (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.s·cm⁻⁵ | 282 [221–356]  | 318 [265–501]         | 0.008                 |
|                                | Median (Q1–Q3) | Median (Q1–Q3) | p-value |
|--------------------------------|----------------|----------------|---------|
| 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, Min: 0.13, Max: 29.70 | Median: 4.58, Min: 0.13, Max: 29.70 | Median: 9.02, Min: 0.30, Max: 17.74 | Median: 4.44, Min: 1.31, Max: 10.38 | Median: 4.01, Min: 0.13, Max: 21.16 | Median: 10.84, Min: 10.74, Max: 11.96 | Median: 6.01, Min: 0.30, Max: 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, Min: 0.00, Max: 5.98 | Median: 0.85, Min: 0.00, Max: 5.98 | - | Median: 0.46, Min: 0.39, Max: 1.25 | Median: 0.69, Min: 0.00, Max: 5.98 | Median: 2.07, Min: 1.97, Max: 3.06 |

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