Supplementary appendix

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Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis

Supplementary material

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Table S1a: Number of available data for each variable in COMPERA

|                        | Classical IPAH n=128 | IPAH with a pulmonary phenotype n=268 | Group 3 PH n=910 |
|------------------------|----------------------|----------------------------------------|-----------------|
| Age, years             | 128 (100%)           | 268 (100%)                             | 910 (100%)      |
| Female                 | 128 (100%)           | 268 (100%)                             | 910 (100%)      |
| BMI, kg/m²             | 128 (100%)           | 268 (100%)                             | 858 (94%)       |
| WHO FC                 | 126 (98%)            | 251 (94%)                              | 867 (95%)       |
| 6MWD, m                | 111 (87%)            | 195 (73%)                              | 662 (73%)       |
| NT-proBNP, ng/L        | 98 (77%)             | 197 (74%)                              | 532 (59%)       |
| BNP, ng/L              | 15 (12%)             | 33 (12%)                               | 180 (20%)       |
| **Pulmonary function** |                      |                                       |                 |
| TLC, % pred            | 103 (81%)            | 228 (85%)                              | 734 (81%)       |
| FVC, % pred            | 113 (88%)            | 235 (88%)                              | 884 (93%)       |
| FEV₁, % pred           | 111 (87%)            | 237 (88%)                              | 855 (94%)       |
| FEV₁/FVC (%)           | 102 (80%)            | 222 (83%)                              | 724 (80%)       |
| DLCO, % pred           | 128 (100%)           | 268 (100%)                             | 578 (64%)       |
| PaO₂, mmHg             | 105 (82%)            | 225 (84%)                              | 828 (91%)       |
| PaCO₂, mmHg            | 107 (84%)            | 223 (83%)                              | 825 (91%)       |
| **Smoking history**    |                      |                                       |                 |
| If ever:               | 116 (91%)            | 268 (100%)                             | 262 (29%)       |
| Pack years             | 27 (68%)             | 194 (72%)                              | 189 (89%)       |
| **Comorbid conditions**|                      |                                       |                 |
| BMI >30 kg/m²          | 128 (100%)           | 268 (100%)                             | 858 (94%)       |
| Hypertension           | 128 (100%)           | 262 (98%)                              | 750 (82%)       |
| Coronary heart disease | 128 (100%)           | 262 (98%)                              | 731 (80%)       |
| Diabetes mellitus      | 128 (100%)           | 261 (97%)                              | 751 (83%)       |
| Atrial fibrillation    | 119 (93%)            | 257 (96%)                              | 853 (94%)       |
| **Haemodynamics**      |                      |                                       |                 |
| RAP, mmHg              | 113 (88%)            | 229 (85%)                              | 837 (92%)       |
| mPAP, mmHg             | 128 (100%)           | 268 (100%)                             | 910 (100%)      |
| PAWP, mmHg             | 128 (100%)           | 268 (100%)                             | 910 (100%)      |
| CI, L/min/m²           | 122 (95%)            | 252 (94%)                              | 861 (95%)       |
| PVR, WU                | 128 (100%)           | 268 (100%)                             | 910 (100%)      |
| SvO₂, %                | 111 (87%)            | 216 (81%)                              | 780 (86%)       |
| **Risk**               | 128 (100%)           | 266 (99%)                              | 898 (99%)       |
Data are shown as n and % of the respective population.

**Definition of abbreviations:** BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; TLC, total lung capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation.
Table S1b: Number of available data for each variable in ASPIRE

| Variable                      | Classical IPAH (i) n=185 | IPAH with a lung phenotype (ii) n=139 | Group 3.1 or 3.2 PH n=375 (iii) |
|-------------------------------|--------------------------|---------------------------------------|---------------------------------|
| Age, years                    | 185 (100%)               | 139 (100%)                            | 375 (100%)                      |
| Female                        | 185 (100%)               | 139 (100%)                            | 375 (100%)                      |
| BMI, kg/m²                    | 178 (96%)                | 133 (96%)                             | 358 (95%)                       |
| WHO FC                        | 185 (100%)               | 139 (100%)                            | 372 (99%)                       |
| ISWD, m                       | 181 (98%)                | 121 (87%)                             | 353 (94%)                       |
| Pulmonary function            |                          |                                       |                                 |
| FEV₁, % pred                  | 183 (99%)                | 139 (100%)                            | 345 (92%)                       |
| FVC, % pred                   | 183 (99%)                | 139 (100%)                            | 344 (92%)                       |
| FEV₁/FVC (%)                  | 183 (99%)                | 139 (100%)                            | 345 (92%)                       |
| DLCO, % pred                  | 185 (100%)               | 139 (100%)                            | 302 (81%)                       |
| Smoking history If ever:      |                          |                                       |                                 |
| Pack years                    | 168 (91%)                | 139 (100%)                            | 0 (0%)                          |
| Haemodynamics                 |                          |                                       |                                 |
| RAP, mmHg                     | 183 (99%)                | 138 (99%)                             | 373 (99%)                       |
| mPAP, mmHg                    | 185 (100%)               | 139 (100%)                            | 375 (100%)                      |
| PAWP, mmHg                    | 185 (100%)               | 139 (100%)                            | 375 (100%)                      |
| CI, L/min/m²                  | 178 (96%)                | 131 (94%)                             | 368 (98%)                       |
| PVR, WU                       | 185 (100%)               | 139 (100%)                            | 375 (100%)                      |
| SvO₂, %                       | 168 (91%)                | 125 (90%)                             | 347 (93%)                       |
| Computed Tomography (CT)      |                          |                                       |                                 |
| CT report available           | 109 (59%)                | 86 (62%)                              | 219 (58%)                       |
| Fibrosis                      | 109 (59%)                | 86 (62%)                              | 219 (58%)                       |
| Fibrosis severity             | 107 (58%)                | 85 (61%)                              | 207 (55%)                       |
| Emphysema                     | 109 (59%)                | 86 (62%)                              | 219 (58%)                       |
| Emphysema severity            | 106 (57%)                | 85 (61%)                              | 210 (56%)                       |
| Medication                    | 167 (90%)                | 138 (99%)                             | 375 (100%)                      |

Data are shown as n and % of the respective population.
Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; ISWD, incremental shuttle walk distance; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation.
### Table S2a: COMPERA baseline characteristics of patients with IPAH excluded from the analysis (i.e., patients belonging neither to classical IPAH nor to the group of patients with IPAH and a lung phenotype)

|                      | Excluded IPAH patients n=1,406 |
|----------------------|----------------------------------|
| **Age, years**       | 72 [60, 78]                      |
| **Female**           | 880 (63%)                        |
| **BMI, kg/m²**       | 28 [25, 33]                      |
| **WHO FC**           |                                  |
| I                    | 4 (0.3%)                         |
| II                   | 189 (14%)                        |
| III                  | 941 (71%)                        |
| IV                   | 197 (15%)                        |
| **6MWD, m**          | 300 [200, 376]                   |
| **NT-proBNP, ng/L**  | 1641 [615, 3674]                 |
| **BNP, ng/L**        | 209 [102, 461]                   |
| **Pulmonary function** |                                 |
| TLC, % pred          | 92 [80, 102]                     |
| FVC, % pred          | 80 [65, 93]                      |
| FEV₁, % pred         | 75 [62, 91]                      |
| DLCO, % pred         | 54 [40, 71]                      |
| PaO₂, mmHg           | 64 [57, 73]                      |
| PaCO₂, mmHg          | 36 [32, 40]                      |
| **Smoking history**  |                                  |
| Ever                 | 302 (35%)                        |
| Never                | 566 (65%)                        |
| Pack years           | 25 [14, 40]                      |
| **Comorbid conditions** |                                |
| BMI >30 kg/m²        |                                  |
| Hypertension         | 538 (39%)                        |
| Coronary heart disease |                                 |
| Diabetes mellitus    | 900 (74%)                        |
| Atrial fibrillation  | 355 (30%)                        |
|                      | 412 (34%)                        |
|                      | 303 (24%)                        |
| **Haemodynamics**    |                                  |
| RAP, mmHg            | 8 [5, 11]                        |
| mPAP, mmHg           | 42 [34, 51]                      |
Table 1

| PAWP, mmHg | CI, L/min/m² | PVR, WU | SvO₂, % |
|------------|-------------|---------|---------|
| 10 [7, 12] | 2.1 [1.7, 2.6] | 8.1 [5.7, 11.7] | 63 [57, 68] |

| Risk (4-strata model)ᵃ | Low | Intermediate-low | Intermediate-high | High |
|------------------------|-----|------------------|------------------|------|
|                        | 88  | 241              | 697              | 365  |
|                        | (6%)| (17%)            | (50%)            | (26%)|

| PH medications | Monotherapy | Combination therapy |
|----------------|-------------|---------------------|
| CCB            | 71 (5%)     | 1149 (82%)          |
| ERA            | 413 (29%)   | 257 (18%)           |
| PDE5i          | 1103 (78%)  |                     |
| sGCs           | 54 (4%)     |                     |
| PPA            | 39 (3%)     |                     |

Categorical data are shown as n and % of the respective population. Continuous data are depicted as median [Q1, Q3].

Definition of abbreviations: BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; 6MWD, 6-minute walking distance; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; TLC, total lung capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation; CCB, calcium channel blocker; ERA endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PPA, prostacyclin pathway agents.
Table S2b: ASPIRE baseline characteristics of patients with IPAH excluded from the analysis

|                                | Excluded IPAH patients n=148 |
|--------------------------------|-----------------------------|
| Age, years                     | 69 [60, 77]                 |
| Female                         | 78 (53%)                    |
| BMI, kg/m²                     | 28.4 [24.3, 32.6]           |
| WHO FC                         |                             |
| I                              | 0 (0%)                      |
| II                             | 15 (10%)                    |
| III                            | 80 (54%)                    |
| IV                             | 52 (35%)                    |
| ISWD, m                        | 80 [20, 180]                |
| Pulmonary function             |                             |
| FVC, % pred                    | 93 [75, 101]                |
| FEV₁, % pred                   | 78 [61, 90]                 |
| FEV₁ / FVC Ratio               | 70 [62, 76]                 |
| DLCO, % pred                   | 30 [23, 36]                 |
| Smoking history                |                             |
| Ever                           | 28 (33%)                    |
| Never                          | 56 (67%)                    |
| Pack years                     | 25 [20, 30]                 |
| Haemodynamics                  |                             |
| RAP, mmHg                      | 11.0 [8.0, 15.0]            |
| mPAP, mmHg                     | 50 [45, 58]                 |
| PAWP, mmHg                     | 11.0 [8.0, 13.0]            |
| CI, L/min/m²                   | 2.1 [1.8, 2.7]              |
| PVR, WU                        | 9.9 [7.4, 12.9]             |
| SvO₂, %                        | 61 [55, 66]                 |
| CT report available            | 80 (54%)                    |
| Fibrosis (any present)         | 28 (35%)                    |
| Fibrosis (by severity)         |                             |
| None                           | 52 (68%)                    |
| Mild                           | 22 (29%)                    |
| Moderate                       | 3 (3.9%)                    |
| Severe                         | 0 (0%)                      |
| Emphysema (any present)        | 24 (30%)                    |
Categorical data are shown as n and % of the respective population. Continuous data are depicted as median [Q1, Q3].

**Definition of abbreviations:** BMI, body mass index; IPAH, idiopathic pulmonary arterial hypertension; PH, pulmonary hypertension; WHO FC, World Health Organization Functional Class; ISWD, incremental shuttle walk distance; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO₂, mixed-venous oxygen saturation; CT, computed tomography; CCB, calcium channel blocker; ERA endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; PPA, prostacyclin pathway agents.

*Oral monotherapy includes PDE5i or ERA or SGCs; oral combination includes ERA in combination with PDE5i or SCGs; PPA +/- oral therapy includes prostanoids either alone or in combination with PDE5i or sGCs +/- ERA.