

Supplementary Figure S1. A) ESC/ERS 4-strata; B) REVEAL Lite 2; and c) RHC risk tools

A)

	Low risk	Intermediate-low	Intermediate-high	High risk
WHO-FC	I, II	-	III	IV
6MWD	>440 m	320-440 m	165-319 m	<165 m
BNP NT-proBNP	<50 ng/l <300 ng/l	50-199 ng/l 300-649 ng/l	200-800 ng/l 650-1100 ng/l	>800 ng/l >1100 ng/l
ESC/ERS 4-strata risk tool - Points assigned - Risk definition	1 Score <1.5	2 Score 1.5 - 2.49	3 Score 2.5 - 3.49	4 Score ≥3.5

B)

	Points assigned				
	-2	-1	0	1	2
eGFR <60 ml/min/1.73 m ² or renal insufficiency			No	Yes	
Systolic BP (mmHg)			≥110	<110	
Heart rate (bpm)			≤95	>95	
WHO-FC		I	II	III	IV
6MWD (m)	≥440	320-440	165-320	<165	
BNP (ng/l) or NT-proBNP (ng/l)	<50 <300		50-200 300-1100	200-800	≥800 ≥1100

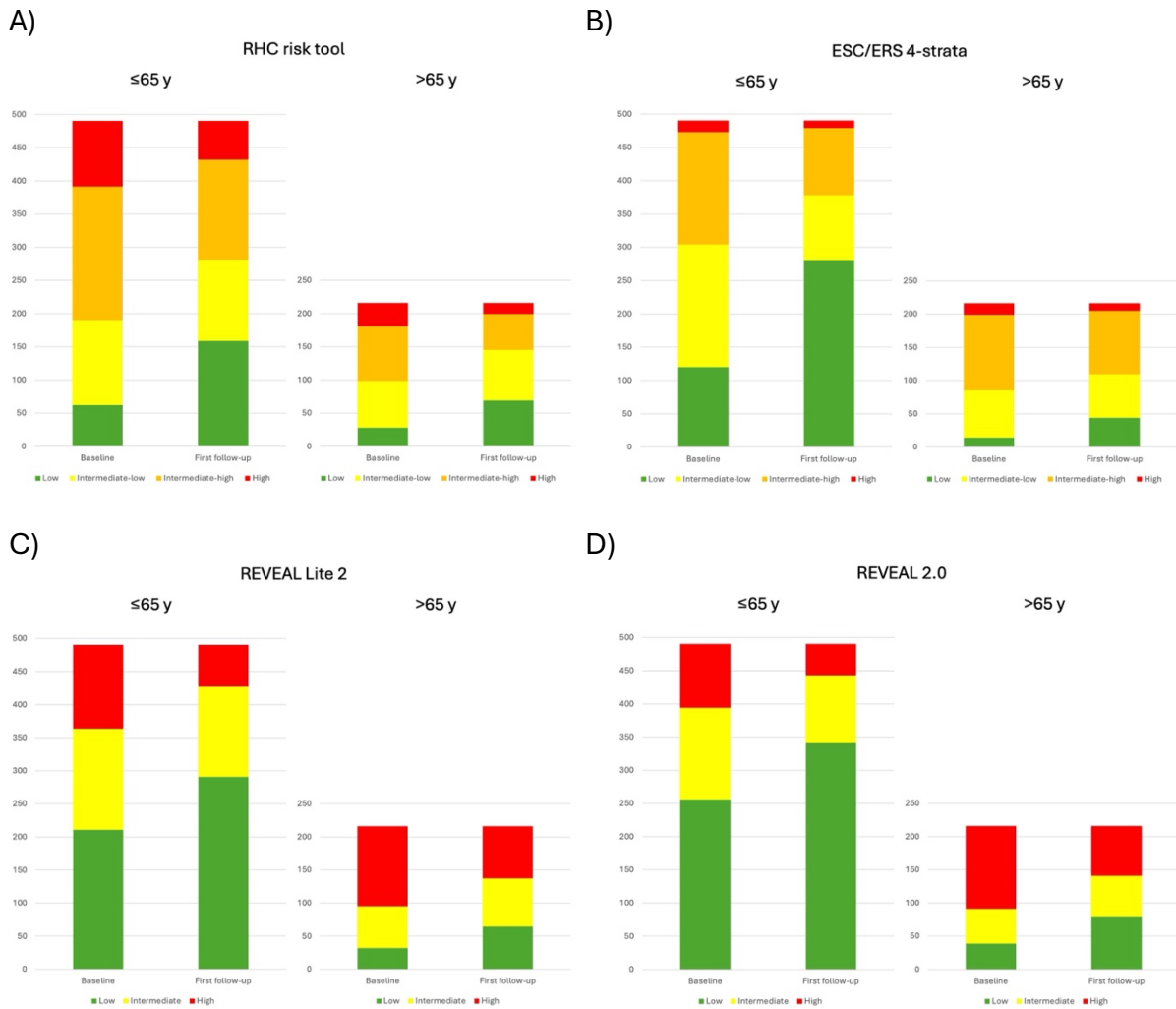
$$\text{REVEAL Lite 2 risk tool} = \text{Sum of the points} + 6 = \begin{cases} 0 - 5 = \text{Low risk} \\ 6 - 7 = \text{Intermediate risk} \\ \geq 8 = \text{High risk} \end{cases}$$

C)

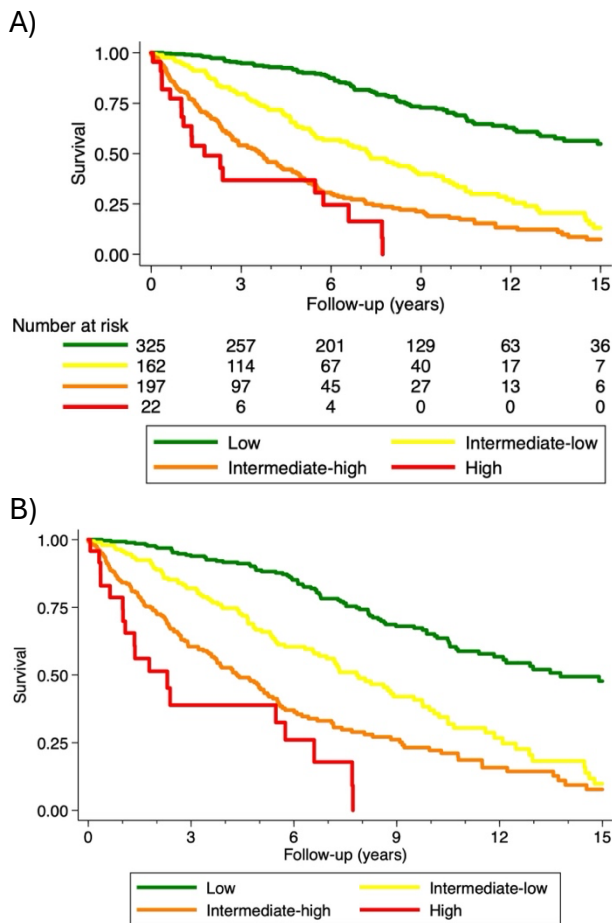
	Low risk	Intermediate-low	Intermediate-high	High risk
RV preload, RAP, mmHg	<8	8 - 9	10 - 14	>14
RV afterload, Ea, mmHg/ml PVR, WU PAC, ml/mmHg	<1.1 <6 >1.5	1.1 - 1.4 6 - 9 >1.1 - 1.5	>1.4 - 1.8 >9 - 14 0.7 - 1.1	>1.8 >14 <0.7
RV pump function, CI, l/min/m ² SVI, ml/m ² CE, ml/mmHg SvO ₂ , %	≥2.5 >38 >1.5 >65	>2.3 - 2.5 >35 - 38 >1.1 - 1.5 >63 - 65	2.0 - 2.3 31 - 35 0.8 - 1.1 60 - 63	<2.0 <31 <0.8 <60
RHC risk tool (3-strata) - Points assigned - Risk definition	1 Score <1.5	2 Score 1.5 - 2.49		3 Score ≥2.5
RHC risk tool (4-strata) - Points assigned - Risk definition	1 Score <1.5	2 Score 1.5 - 2.49	3 Score 2.5 - 3.49	4 Score ≥3.5

Legend. 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; BP: blood bpressure; CE: cardiac efficiency; CI: cardiac index; Ea: pulmonary artery elastance; eGFR: estimated glomerular filtration rate; ERS: European Respiratory Society; ESC: European Society of Cardiology; NT-proBNP: N-terminal pro-BNP; PAC: pulmonary arterial compliance; PVR: pulmonary vascular resistance; RAP: right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC: right heart catheterisation; RV, right ventricle; SVI: stroke volume index; SvO₂: mixed venous oxygen saturation; WHO-FC: World Health Organization functional class; WU: Wood unit.

Supplementary Figure S2. Risk assessment at baseline and at 1st follow-up according to age for the A) RHC risk tool and the recommended risk tools at follow-up: B) ESC/ERS 4-strata, C) REVEAL Lite 2, D) REVEAL 2.0



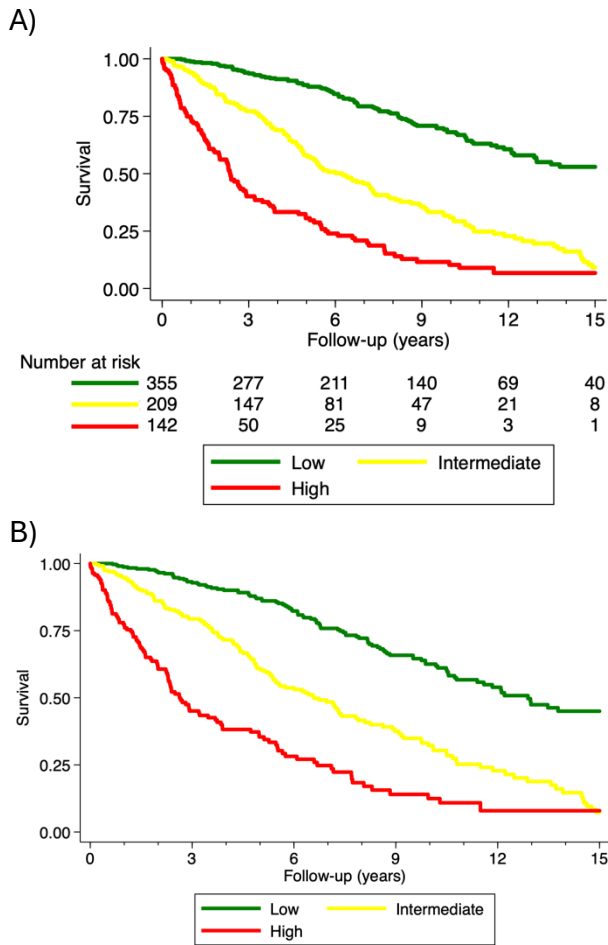
Supplementary Figure S3a. Kaplan Meier curves at 1st follow-up according to ESC/ERS 4-strata risk tool.



Legend. A) unadjusted curves. Pairwise comparisons p-value: low vs intermediate-low: $p < 0.001$; low vs intermediate-high: $p < 0.001$; low vs high: $p < 0.001$; intermediate-low vs intermediate-high: $p < 0.001$; intermediate-low vs high: $p < 0.001$; intermediate-high vs high: $p = 0.062$; B) predicted survival curves for patients aged 55 (the median age of the study cohort) from separate Cox models for the risk strata.

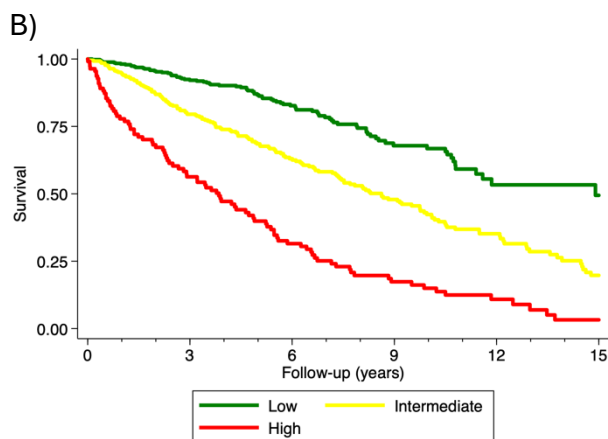
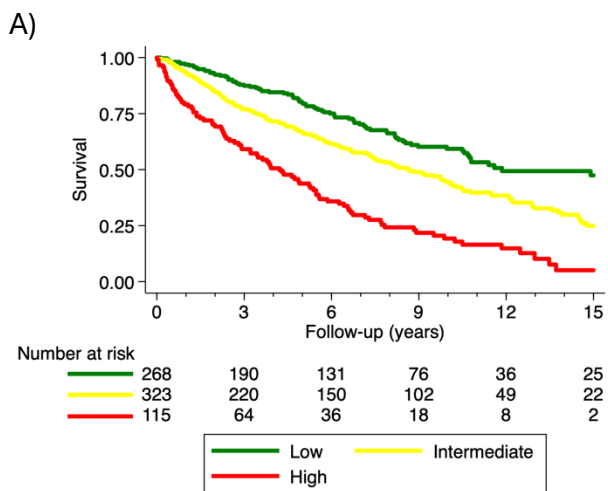
ERS: European Respiratory Society; ESC: European Society of Cardiology

Supplementary Figure S3b. Kaplan Meier curves at 1st follow-up according to REVEAL Lite 2 risk tool.



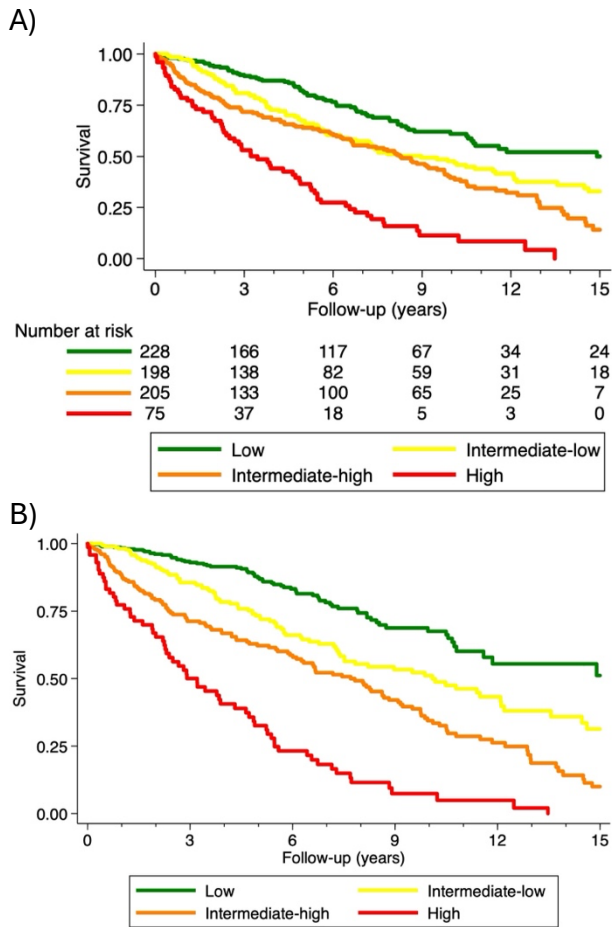
Legend. A) unadjusted curves. Pairwise comparisons p-value: low vs intermediate: $p < 0.001$; low vs high: $p < 0.001$; intermediate vs high: $p < 0.001$; B) predicted survival curves for patients aged 55 (the median age of the study cohort) from separate Cox models for the risk strata. REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management

Supplementary Figure S4a. Kaplan Meier curves at 1st follow-up according to RHC risk tool 3-strata



Legend. A) unadjusted curves. Pairwise comparisons p-value: low vs intermediate: $p < 0.001$; low vs high: $p < 0.001$; intermediate vs high: $p < 0.001$; B) predicted survival curves for patients aged 55 (the median age of the study cohort) from separate Cox models for the risk strata. RHC, right heart catheterization

Supplementary Figure S4b. Kaplan Meier curves at 1st follow-up according to RHC risk tool 4-strata

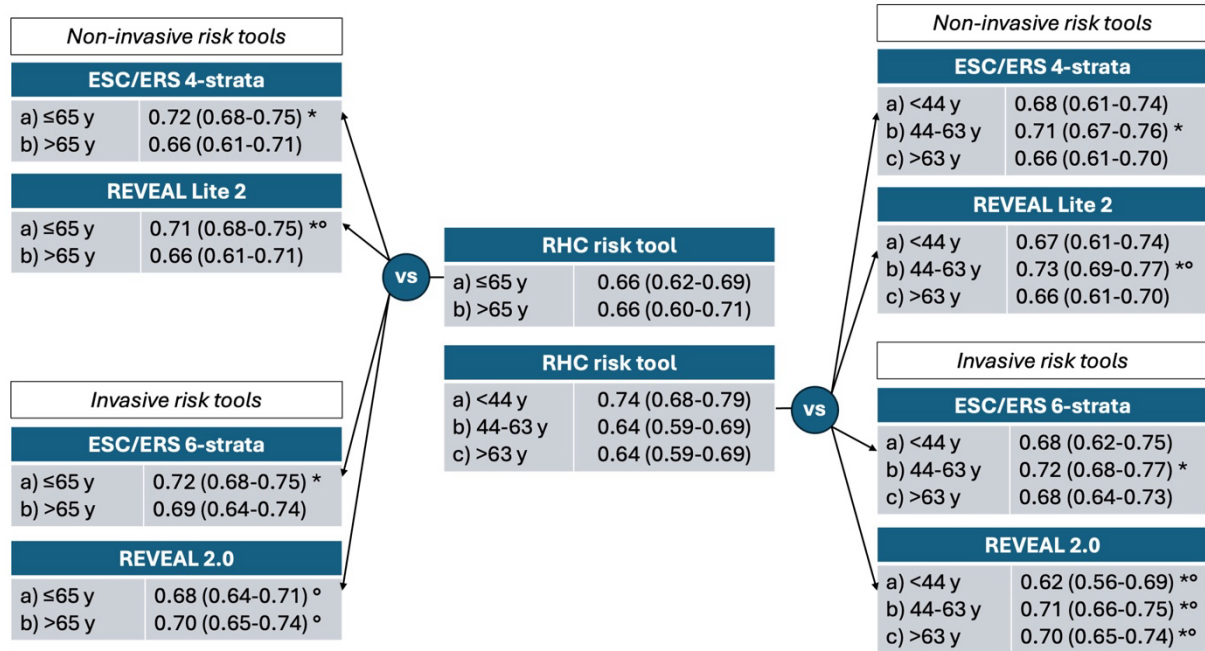


Legend. A) unadjusted curves. Pairwise comparisons p-value: low vs intermediate-low: $p=0.002$; low vs intermediate-high: $p < 0.001$; low vs high: $p < 0.001$; intermediate-low vs intermediate-high: $p = 0.033$; intermediate-low vs high: $p < 0.001$; intermediate-high vs high: $p < 0.001$; B) predicted survival curves for patients aged 55 (the median age of the study cohort) from separate Cox models for the risk strata.

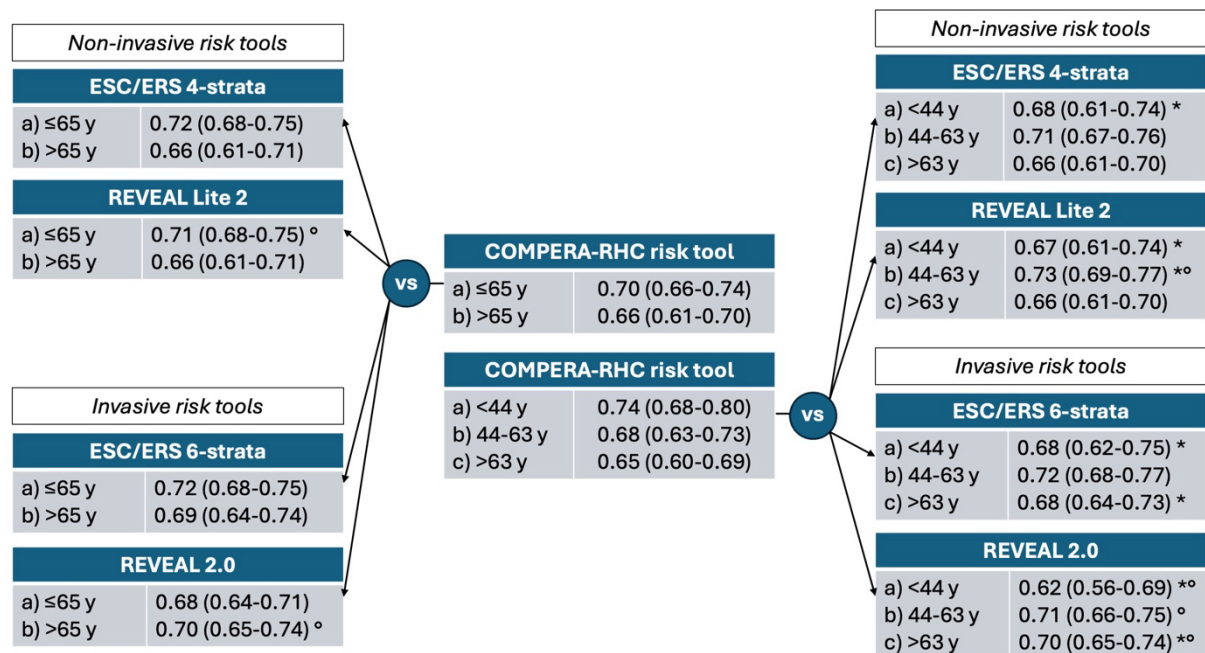
RHC, right heart catheterization

Supplementary Figure S5. C-index of A) RHC and B) COMPERA-RHC risk tools compared to other risk tools, including only patients with at least 2 of the following variables: WHO-FC, 6MWD and BNP/NT-proBNP (n= 672)

A) C-index of RHC risk tool vs other risk tools



B) C-index of COMPERA-RHC risk tool vs other risk tools

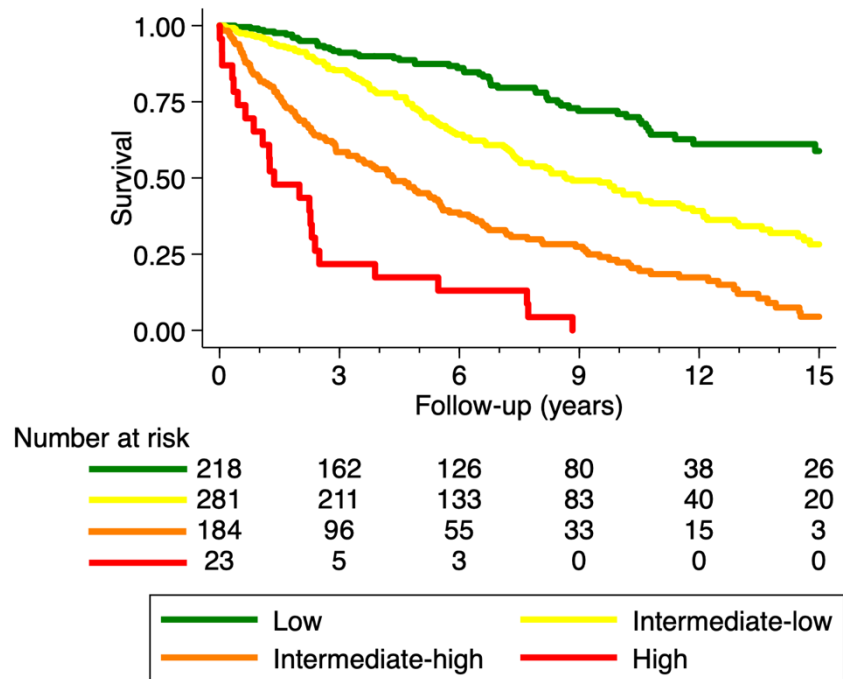


Legend: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization.

* p-value <0.05 vs RHC/COMPERA-RHC risk tool for the same age group

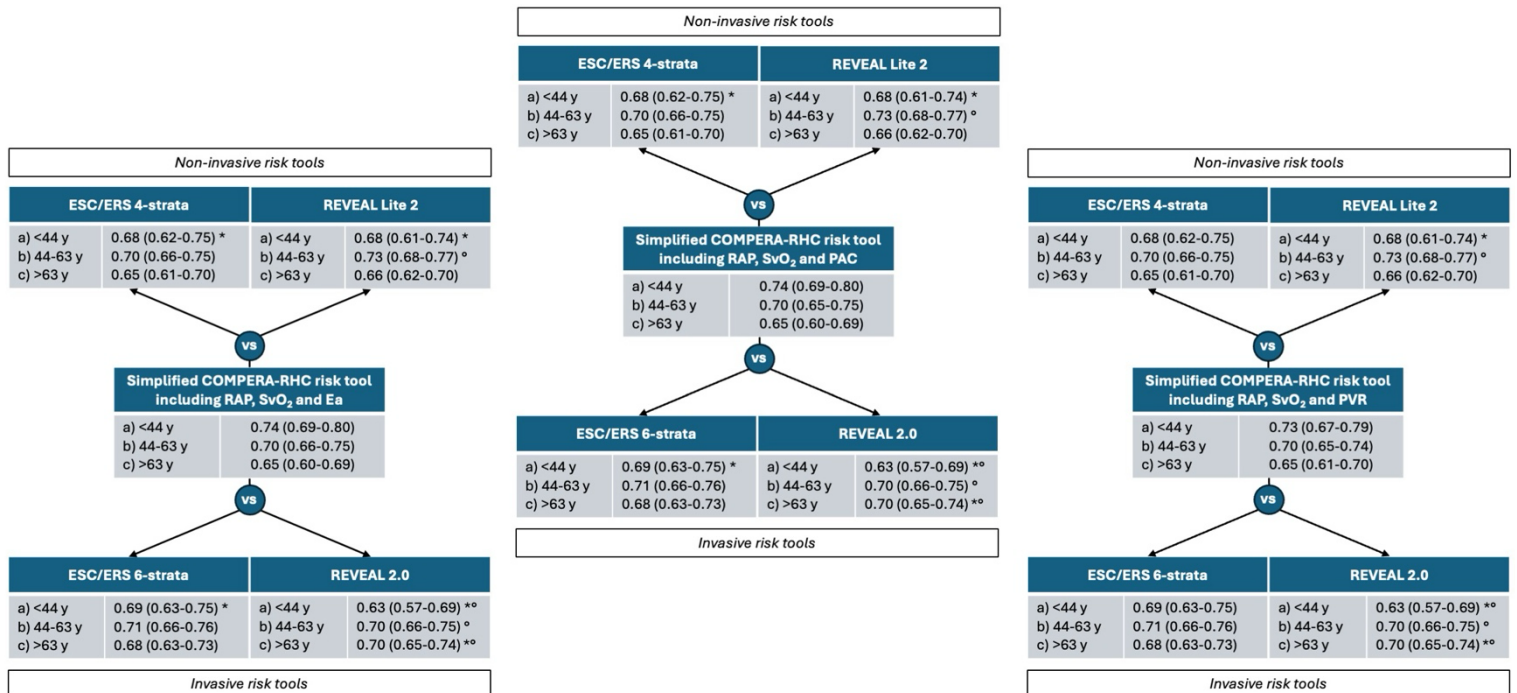
° p-value <0.05 for the corresponding continuous REVEAL score vs RHC/COMPERA-RHC risk tool for the same age group

Supplementary Figure S6. Kaplan Meier curves at 1st follow-up according to COMPERA-RHC risk tool.



Legend. Pairwise comparisons p-value: low vs intermediate-low: $p < 0.001$; low vs intermediate-high: $p < 0.001$; low vs high: $p < 0.001$; intermediate-low vs intermediate-high: $p < 0.001$; intermediate-low vs high: $p < 0.001$; intermediate-high vs high: $p < 0.001$. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; RHC, right heart catheterization

Supplementary Figure S7. C-index of the simplified COMPERA-RHC risk tools compared to other risk tools in the different age categories

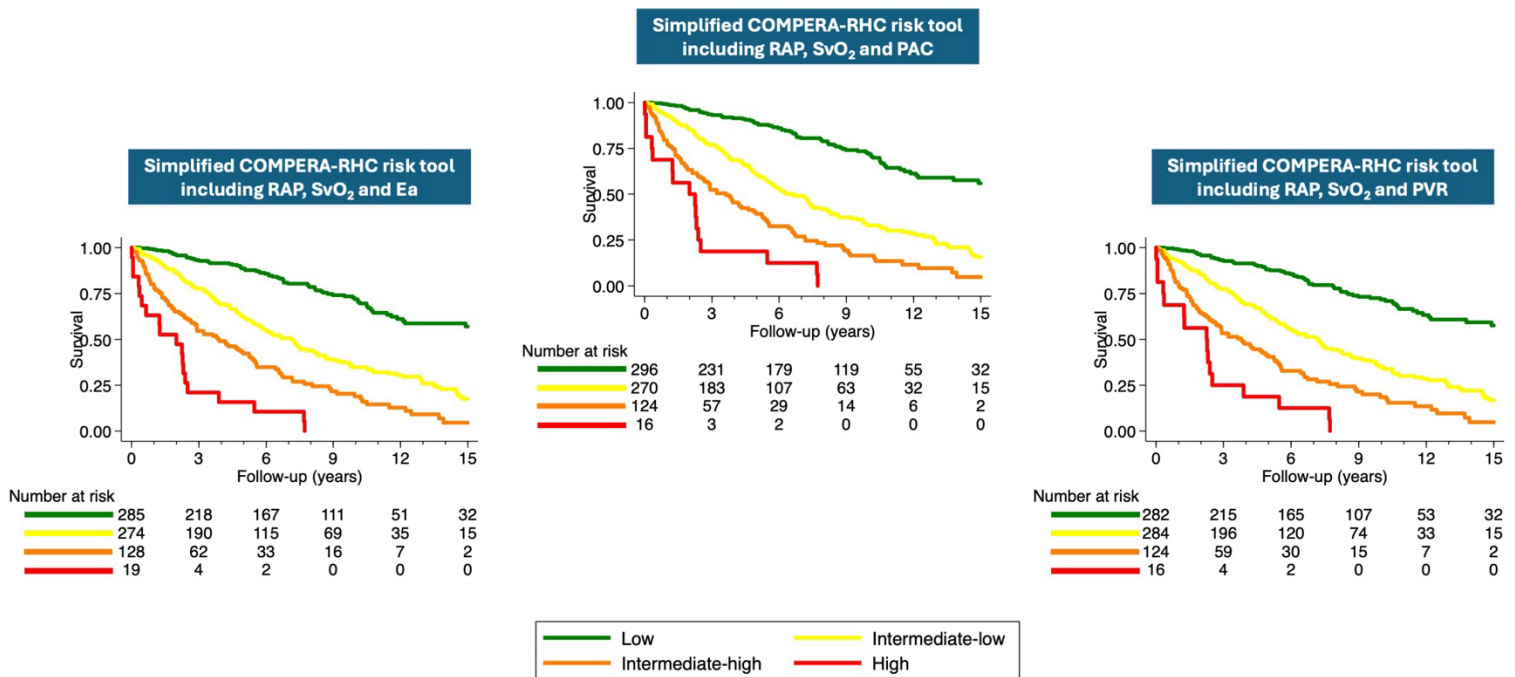


Legend: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; Ea, pulmonary artery elastance; ESC/ERS, European Society of Cardiology/European Respiratory Society; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; SvO₂, mixed venous oxygen saturation.

* p-value <0.05 vs simplified COMPERA-RHC risk tool for the same age group

° p-value <0.05 for the corresponding continuous REVEAL score vs simplified COMPERA-RHC risk tool for the same age group

Supplementary Figure S8. Kaplan Meier curves at 1st follow-up according to the simplified COMPERA-RHC risk tools.



Legend. Pairwise comparisons p-value for all the 3 risk tools: low vs intermediate-low: $p < 0.001$; low vs intermediate-high: $p < 0.001$; low vs high: $p < 0.001$; intermediate-low vs intermediate-high: $p < 0.001$; intermediate-low vs high: $p < 0.001$; intermediate-high vs high: $p < 0.01$.

COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; Ea, pulmonary artery elastance; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SvO₂, mixed venous oxygen saturation.

Supplementary Table S1. Cardiopulmonary comorbidities according to the age at diagnosis.

	All	≤65 y	>65 y	p-value
n	794	534	260	
eGFR, ml/min/1.73m ² (n)	73 (55-89) (n= 768)	80 (65-98) (n= 510)	56 (42-69) (n= 258)	<0.001
Haemoglobin, g/dl	14.2 (12.8-15.9)	14.5 (13-16.1)	13.8 (12.1-15.1)	<0.001
Dysthyroidism, n (%)	158 (20)	94 (18)	64 (25)	0.020
BMI, kg/m ²	24 (21-28)	24 (21-28)	25 (22-29)	0.002
Cardiac comorbidities:				
- Obesity, n (%)	130 (16)	85 (16)	45 (17)	0.619
- Systemic hypertension, n (%)	320 (40)	152 (28)	168 (65)	<0.001
- Diabetes mellitus, n (%)	94 (11)	30 (6)	64 (25)	<0.001
- Coronary artery disease, n (%)	84 (11)	24 (4)	60 (23)	<0.001
- Atrial fibrillation, n (%)	85 (11)	40 (7)	45 (17)	<0.001
Number of cardiac comorbidities, n (%)				<0.001
- 0	361 (45)	310 (58)	51 (20)	
- 1	244 (31)	149 (28)	95 (37)	
- 2	117 (15)	51 (10)	66 (25)	
- 3	55 (7)	16 (3)	39 (15)	
- 4-5	17 (2)	8 (1)	9 (3)	
DLCO, % (n)	51 (34-65) (n= 537)	57 (46-69) (n= 340)	37 (29-51) (n= 197)	<0.001
Pulmonary comorbidity, n (%) *	120 (15)	41 (8)	79 (30)	<0.001

Legend: BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide; eGFR, estimated glomerular filtration rate; HRCT, high resolution computed tomography
 * 257 (32%) patients have only HRCT scan available, and, among these, 27 (11%) patients have signs of mild parenchymal lung disease at HRCT

Supplementary Table S2. PAH treatment strategies according to (A) the age at diagnosis and (B) the age at diagnosis and the study period (before and after 2015, when the ESC/ERS guidelines on PAH were published recommending initial dual oral combination therapy).

(A)

	All	≤65 y	>65 y	p-value
Initial treatment strategy, n (%)				0.492
- <i>Mono</i> :	<u>646 (81)</u>	<u>438 (82)</u>	<u>208 (80)</u>	
• CCB	71 (11)	62 (14)	9 (4)	
• ERA	306 (47)	185 (42)	121 (58)	
• PDE5-I	185 (29)	116 (26.5)	69 (33)	
• Prostacyclin				
▪ IV/SC	63 (10)	59 (13.5)	4 (2)	
▪ Oral/inhalatory	21 (3)	16 (4)	5 (3)	
- <i>Combo</i> :	<u>148 (19)</u>	<u>96 (18)</u>	<u>52 (20)</u>	
• ERA+PDE5-I	142 (96)	91 (95)	51 (98)	
• ERA+PDE5-I+Selexipag	5 (3)	4 (4)	1 (2)	
• PDE5-I+IV/SC prostacyclin	1 (1)	1 (1)	0	
End of study treatment, n (%)				<0.001
- Mono	331 (42)	189 (35)	142 (55)	
- Double combo	304 (38)	200 (38)	104 (40)	
- Triple combo	159 (20)	145 (27)	14 (5)	

(B)

Study period	2003-2015		Since 2015	
	≤65 y	>65 y	≤65 y	>65 y
Age at diagnosis				
Initial treatment strategy, n (%)				
- <i>Mono</i> :	<u>395 (94)</u>	<u>149 (92)</u>	<u>43 (39)</u>	<u>59 (60)</u>
• CCB	47 (12)	9 (6)	15 (35)	0
• ERA	168 (42)	82 (55)	17 (40)	39 (66)
• PDE5-I	105 (27)	49 (33)	11 (25)	20 (34)
• Prostacyclin				
▪ IV/SC	59 (15)	4 (3)	0	0
▪ Oral/inhalatory	16 (4)	5 (3)	0	0
- <i>Combo</i> :	<u>28 (6)</u>	<u>13 (8)</u>	<u>68 (61)</u>	<u>39 (40)</u>
• ERA+PDE5-I	27 (96)	13 (100)	64 (94)	38 (97)
• ERA+PDE5-I+Selexipag	0	0	4 (6)	1 (3)
• PDE5-I+IV/SC prostacyclin	1 (4)	0	0	0
End of study treatment, n (%)				
- Mono	157 (37)	94 (58)	32 (29)	48 (49)
- Double	150 (36)	57 (35)	50 (45)	47 (48)
- Triple	116 (27)	11 (7)	29 (26)	3 (3)

Legend: CCB, calcium channel blockers; ERA, endothelin receptor antagonist; ESC/ERS, European Society of Cardiology/European Respiratory Society; IV/SC, intravenous/subcutaneous; PAH, pulmonary arterial hypertension; PDE5-I, phosphodiesterase type 5 inhibitors

Supplementary Table S3. Baseline ESC/ERS 4-strata, REVEAL Lite 2, 4-strata RHC risk tool and COMPERA-RHC according to the age at diagnosis

	All	≤65 y	>65 y	p-value
n	794	534	260	
ESC/ERS 4-strata baseline risk, n (%)				<0.001
- Low	141 (18)	126 (24)	15 (6)	
- Intermediate-low	286 (36)	195 (36)	91 (35)	
- Intermediate-high	323 (41)	191 (36)	132 (51)	
- High	44 (5)	22 (4)	22 (8)	
Only patients with BNP/NT-proBNP available, n (%)	N= 493	N= 305	N= 188	<0.001
- Low	79 (16)	68 (22)	11 (6)	
- Intermediate-low	210 (43)	138 (45)	72 (38)	
- Intermediate-high	188 (38)	94 (31)	94 (50)	
- High	16 (3)	5 (2)	11 (6)	
Excluding patients with ≥2 missing variables	N= 781	N= 530	N= 251	<0.001
- Low	140 (18)	125 (24)	15 (6)	
- Intermediate-low	274 (35)	192 (36)	82 (33)	
- Intermediate-high	323 (41)	191 (36)	132 (52)	
- High	44 (6)	22 (4)	22 (9)	
REVEAL Lite 2 baseline risk, n (%)				<0.001
- Low	254 (32)	220 (41)	34 (13)	
- Intermediate	235 (30)	165 (31)	70 (27)	
- High	305 (38)	149 (28)	156 (60)	
Only patients with BNP/NT-proBNP values available, n (%)	N= 493	N= 305	N= 188	<0.001
- Low	163 (33)	136 (45)	27 (15)	
- Intermediate	127 (26)	83 (27)	44 (23)	
- High	203 (41)	86 (28)	117 (62)	
Only patients with at least 2 of the following variables: WHO-FC, 6MWD and BNP/NT-proBNP	N= 781	N= 530	N= 251	<0.001
- Low	254 (32)	220 (41)	34 (13)	
- Intermediate	234 (30)	164 (31)	70 (28)	
- High	293 (38)	146 (28)	147 (57)	
RHC risk tool baseline risk, n (%)				0.691
- Low	95 (12)	66 (12)	29 (11)	
- Intermediate-low	217 (27)	139 (26)	78 (30)	
- Intermediate-high	315 (40)	212 (40)	103 (40)	
- High	167 (21)	117 (22)	50 (19)	

COMPERA-RHC risk tool baseline risk, n (%)				<0.001
- Low	60 (8)	48 (9)	12 (4)	
- Intermediate-low	304 (38)	226 (42)	78 (30)	
- Intermediate-high	373 (47)	228 (43)	145 (56)	
- High	57 (7)	32 (6)	25 (10)	

Legend: 6MWD: 6-min walk distance; BNP, brain natriuretic peptide; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N-terminal pro-hormone BNP; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; WHO-FC: World Health Organization functional class

Supplementary Table S4. Baseline characteristics according to the age tertiles identified at first follow-up (<44 y, 44-63 y, and >63 y)

	<44 y	44-63 y	>63 y	p-value
n	245	270	279	
Age, years	33 (27-38)	55 (50-59)	72 (68-76)	
Male gender, n (%)	66 (27)	78 (29)	90 (32)	0.398
PAH aetiology, n (%)	* [†]	* ^{ff}	^{ff} [†]	<0.001
- I/H/D	140 (57)	147 (55)	138 (49)	
- CTD	23 (10)	74 (27)	125 (45)	
- CHD	82 (33)	49 (18)	16 (6)	
WHO-FC, n (%)	* [†]	* ^{ff}	^{ff} [†]	<0.001
- I	16 (7)	6 (2)	4 (2)	
- II	93 (38)	81 (30)	40 (14)	
- III	130 (53)	171 (63)	226 (81)	
- IV	6 (2)	12 (5)	9 (3)	
6MWD, m (n)	451 (377-540) ^{*†} (n= 241)	393 (306-468) ^{*ff} (n= 262)	314 (249-389) ^{ff†} (n= 247)	<0.001
BNP/NT-proBNP, n (%)	n= 133 [†]	n= 160 ^{ff}	n= 200 ^{ff†}	<0.001
- <50/<300 ng/l	47 (35)	45 (28)	22 (11)	
- 50-200/300-650 ng/l	29 (22)	39 (24)	48 (24)	
- 200-800/650-1100 ng/l	26 (20)	30 (19)	45 (22)	
- >800/>1100 ng/l	31 (23)	46 (29)	85 (43)	
HR, bpm	83 (72-90) [†]	80 (73-90) ^{ff}	78 (70-88) ^{ff†}	0.009
RAP, mmHg	6 (4-9)	7 (4-11)	6 (4-10)	0.466
mPAP, mmHg	59 (49-73) ^{*†}	52 (41-62) ^{*ff}	44 (37-53) ^{ff†}	<0.001
sPAP, mmHg	93 (76-112) ^{*†}	86 (67-102) ^{*ff}	75 (62-89) ^{ff†}	<0.001
Ea, mmHg/ml	1.87 (1.23-2.74) [†]	1.74 (1.01-2.49) ^{ff}	1.48 (1.09-2.07) ^{ff†}	<0.001
PAWP, mmHg	7 (6-10) [†]	8 (6-10)	8 (6-10) [†]	0.017
SBP, mmHg	111 (103-124) ^{*†}	122 (110-137) ^{*ff}	130 (115-145) ^{ff†}	<0.001
CI, l/min/m ²	2.4 (2.0-3.1) [†]	2.3 (1.9-2.9)	2.2 (1.9-2.7) [†]	0.030
SVI, ml/m ²	31 (22-40)	29 (23-36)	30 (24-35)	0.151
CE, ml/mmHg	0.84 (0.57-1.30) ^{*†}	0.92 (0.63-1.55) ^{*ff}	1.14 (0.79-1.54) ^{ff†}	<0.001
RV power, mmHg*l/min	138 (107-175) ^{*†}	116 (95-145) ^{*ff}	102 (78-124) ^{ff†}	<0.001
RVSWI, ml*mmHg	20.7 (15.5-28.4) ^{*†}	16.7 (13.0-21.4) ^{*ff}	14.7 (11.7-17.8) ^{ff†}	<0.001
RC product, min	11770 (10168-14354) ^{*†}	10519 (8895-12338) ^{*ff}	9668 (8491-10851) ^{ff†}	<0.001
PVR, WU	12.8 (8.9-19.3) ^{*†}	10.7 (6.8-16.1) ^{*ff}	9.2 (6.7-12.8) ^{ff†}	<0.001
PAC, ml/mmHg	0.94 (0.65-1.40)	0.95 (0.66-1.51)	1.05 (0.77-1.46)	0.086
Systemic arterial saturation, %	96 (93-98) ^{*†}	95 (92-97) [*]	95 (92-97) [†]	0.005
SvO ₂ , %	68.7 (60.5-74) ^{*†}	65.1 (57.7-70.7) ^{*ff}	62.3 (55.6-68.8) ^{ff†}	<0.001
COMPERA 1.0 baseline risk, n (%)	* [†]	* ^{ff}	^{ff} [†]	<0.001
- Low	112 (46)	82 (31)	41 (15)	
- Intermediate	115 (47)	160 (59)	197 (70)	
- High	18 (7)	28 (10)	41 (15)	

REVEAL 2.0 baseline risk, n (%)	*‡	*§§	§§‡	<0.001
- Low	139 (57)	121 (45)	47 (17)	
- Intermediate	68 (28)	78 (29)	65 (23)	
- High	38 (15)	71 (26)	167 (60)	
Bologna baseline risk, n (%)	*‡	*§§	§§‡	<0.001
- Low	80 (33)	47 (17)	16 (6)	
- Intermediate	135 (55)	174 (65)	164 (59)	
- High	30 (12)	49 (18)	99 (35)	
RHC risk tool baseline risk, n (%)				0.268
- Low	28 (14)	46 (17)	40 (14)	
- Intermediate	154 (60)	148 (55)	171 (61)	
- High	63 (26)	76 (28)	68 (25)	
eGFR, ml/min/1.73m ² (n)	90 (79-107) *‡ (n= 233)	70 (57-86) *§§ (n= 258)	57 (43-70) §§‡ (n= 277)	<0.001
Haemoglobin, g/dl	14.6 (13.3-16.2) ‡	14.3 (12.8-16.0) §§	13.9 (12.2-15.1) §§‡	<0.001
Dysthyroidism, n (%)	34 (14) ‡	57 (21)	67 (24) ‡	0.012
BMI, kg/m ²	22 (20-25) *‡	25 (22-29) *	25 (22-29) ‡	<0.001
Cardiac comorbidities:				
- Obesity, n (%)	21 (9) *‡	58 (21) *	51 (18) ‡	<0.001
- Systemic hypertension, n (%)	32 (13) *‡	109 (40) *§§	179 (64) §§‡	<0.001
- Diabetes mellitus, n (%)	3 (1) *‡	25 (9) *§§	66 (24) §§‡	<0.001
- Coronary artery disease, n (%)	4 (2) *‡	20 (7) *§§	60 (22) §§‡	<0.001
- Atrial fibrillation, n (%)	12 (5) ‡	26 (10) §§	47 (17) §§‡	<0.001
Number of cardiac comorbidities, n (%)	*‡	*§§	§§‡	<0.001
- 0	183 (75)	120 (45)	58 (21)	
- 1	52 (21)	92 (34)	100 (36)	
- 2	10 (4)	36 (13)	71 (25)	
- 3	0	14 (5)	41 (15)	
- 4-5	0	8 (3)	7 (3)	
DLCO, % (n)	60 (51-71) *‡ (n= 152)	54 (36-69) *§§ (n= 173)	38 (29-53) §§‡ (n= 212)	<0.001
Pulmonary comorbidity, n (%) *	3 (1) *‡	36 (13) *§§	81 (29) §§‡	<0.001
Initial treatment strategy, n (%)				0.816
- <i>Mono:</i>	<u>202 (82)</u>	<u>220 (81)</u>	<u>224 (80)</u>	
• CCB	35 (17)	27 (12)	9 (4)	
• ERA	79 (39)	95 (43)	132 (59)	
• PDE5-I	53 (26)	61 (28)	71 (31)	
• Prostacyclin				
○ IV/SC	29 (15)	28 (13)	6 (3)	
○ Oral/inhalatory	6 (3)	9 (4)	6 (3)	
- <i>Combo:</i>	<u>43 (18)</u>	<u>50 (19)</u>	<u>55 (20)</u>	
• ERA+PDE5-I	41 (95)	47 (94)	54 (98)	
• ERA+PDE5-I+Selexipag	2 (5)	2 (4)	1 (2)	
• PDE5-I+IV/SC prostacyclin	0	1 (2)	0	

End of study treatment, n (%)	*‡	*ff	ff‡	<0.001
- Mono	77 (31)	108 (40)	146 (52)	
- Double combo	88 (36)	107 (40)	109 (39)	
- Triple combo	80 (33)	55 (20)	24 (9)	

Legend: 6MWD, 6-minute walk distance; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blockers; CE, cardiac efficiency; CHD, congenital heart disease; CI, cardiac index; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; CTD, connective tissue disease; DLCO, diffusing capacity of the lungs for carbon monoxide; Ea, pulmonary artery elastance; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; HR, heart rate; I/H/D, idiopathic/heritable/drug-induced; IV/SC, intravenous/subcutaneous; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE5-I, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; RV, right ventricle; RVSWI, RV stroke work index; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

*ff‡ = p-value <0.05 between respective pairs

Supplementary Table S5. Laboratory and haemodynamic variables at baseline and at 1st follow-up and their absolute changes (Δ) according to the age at diagnosis

	Baseline	1 st follow-up	p Baseline vs 1 st follow-up	Δ	p $\Delta \leq 65$ vs >65 y
eGFR, ml/min/1.73m ²					
a) ≤ 65 y (n= 403)	82 (66-99)	85 (69-100)	0.002	2 (-5-10)	0.038*
b) >65 y (n= 183)	57 (43-73)	58 (43-70)	0.535	-1 (-8-7)	
Haemoglobin, g/dl					
a) ≤ 65 y	14.5 (13.0-16.1)	14.0 (13.0-15.9)	0.001	-0.3 (-1.4-0.9)	0.311
b) >65 y	13.9 (12.3-15.1)	13.3 (12.0-14.5)	<0.001	-0.6 (-1.5-0.6)	
HR, bpm					
a) ≤ 65 y	81 (72-90)	80 (71-90)	0.508	0 (-8-8)	0.909
b) >65 y	77 (70-85)	78 (69-88)	0.563	-1 (-8-8)	
RAP, mmHg					
a) ≤ 65 y	6 (4-10)	7 (4-9)	0.841	0 (-2-3)	0.148
b) >65 y	6 (4-9)	7 (5-9)	0.075	1 (-2-3)	
mPAP, mmHg					
a) ≤ 65 y	56 (44-67)	49 (36-62)	<0.001	-5 (-12-1)	0.227
b) >65 y	43 (37-53)	38 (33-46)	<0.001	-4 (-9-1)	
sPAP, mmHg					
a) ≤ 65 y	90 (71-106)	78 (58-101)	<0.001	-9 (-20-2)	0.644
b) >65 y	71 (62-88)	64 (53-77)	<0.001	-8 (-17-0)	
Ea, mmHg/ml					
a) ≤ 65 y	1.77 (1.12-2.58)	1.19 (0.75-1.91)	<0.001	-0.37 (-0.94 - -0.04)	0.101
b) >65 y	1.44 (1.04-1.99)	1.03 (0.76-1.37)	<0.001	-0.34 (-0.66 - -0.09)	
PAWP, mmHg					
a) ≤ 65 y	8 (6-10)	9 (7-11)	<0.001	1 (-1-3)	0.159
b) >65 y	8 (7-10)	10 (8-12)	<0.001	1 (0-3)	
SBP, mmHg					
a) ≤ 65 y	117 (106-133)	111 (102-122)	<0.001	-5 (-17-5)	0.613
b) >65 y	131 (117-145)	123 (112-140)	<0.001	-7 (-19-7)	
CI, l/min/m ²					
a) ≤ 65 y	2.4 (2.0-3.0)	2.9 (2.4-3.6)	<0.001	0.5 (0-1.1)	0.121
b) >65 y	2.2 (1.9-2.7)	2.8 (2.3-3.3)	<0.001	0.4 (0-0.8)	
SVI, ml/m ²					
a) ≤ 65 y	30 (23-38)	37 (29-46)	<0.001	6 (0-14)	0.229
b) >65 y	30 (25-36)	37 (30-42)	<0.001	5 (1-11)	
CE, ml/mmHg					
a) ≤ 65 y	0.90 (0.61-1.48)	1.33 (0.81-2.09)	<0.001	0.32 (0.02-0.81)	0.216
b) >65 y	1.18 (0.83-1.56)	1.63 (1.21-2.13)	<0.001	0.40 (0.09-0.72)	
RV power, mmHg*l/min					
a) ≤ 65 y	124 (102-161)	135 (106-174)	<0.001	6 (-17-35)	0.203
b) >65 y	101 (78-121)	102 (85-130)	0.008	6 (-14-25)	
RVSWI, ml*mmHg					
a) ≤ 65 y	18.8 (14.1-24.2)	19.5 (15.2-25.6)	0.002	0.9 (-3.1-5.1)	0.088
b) >65 y	15.1 (11.9-17.9)	14.8 (11.6-19.2)	0.349	-0.1 (-2.5-3.4)	
RC product, min					
a) ≤ 65 y	11055 (9374-13085)	10155 (8642-12223)	<0.001	-578 (-2146-912)	0.398
b) >65 y	9642 (8525-10796)	9004 (7819-10138)	<0.001	-683 (-1928-583)	
PVR, WU					
a) ≤ 65 y	11.6 (7.5-17.2)	7.9 (4.3-12.7)	<0.001	-2.8 (-6.2 - -0.7)	0.115

b) >65 y	9.0 (6.5-12.2)	5.7 (4.4-8.2)	<0.001	-2.4 (-4.3 – -1)	
PAC, ml/mmHg					0.111
a) ≤65 y	0.95 (0.65-1.48)	1.38 (0.88-2.06)	<0.001	0.32 (0.01–0.81)	
b) >65 y	1.11 (0.80-1.51)	1.49 (1.11-2.06)	<0.001	0.37 (0.10–0.73)	
SvO ₂ , %					0.145
a) ≤65 y	67.4 (59.0-72.5)	69.3 (62.5-75.0)	<0.001	2.3 (-3.1–7.1)	
b) >65 y	63.3 (56.8-69.1)	68.0 (62.0-72.0)	<0.001	3.4 (-1.2–8.0)	

Legend: CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; eGFR, estimated glomerular filtration rate; HR, heart rate; mPAP, mean pulmonary artery pressure; PAC, pulmonary arterial compliance; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; RV, right ventricle; RVSWI, RV stroke work index; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation
 * = p-value <0.05 also for % Δ comparisons

Supplementary Table S6. Risk stratification at baseline and at 1st follow-up according to ESC/ERS 4-strata, REVEAL Lite 2 and RHC risk tools and respective changes (Δ) according to the age at diagnosis A) including only patients with BNP/NT-proBNP available at 1st follow-up and B) excluding patients with ≥ 2 missing variables at 1st follow-up.

A)

	Baseline	1 st follow-up	p Baseline vs 1 st follow-up	Δ	p $\Delta \leq 65$ vs >65 y
ESC/ERS 4-strata, n (%)					<0.001
a) ≤ 65 y			<0.001	63 (81%)	
- Low	8 (11)	41 (53)			
- Intermediate-low	41 (52)	25 (32)			
- Intermediate-high	28 (36)	11 (14)			
- High	1 (1)	1 (1)			
b) >65 y			0.228	42 (54%)	
- Low	5 (6)	13 (17)			
- Intermediate-low	31 (40)	30 (38)			
- Intermediate-high	36 (46)	29 (37)			
- High	6 (8)	6 (8)			
REVEAL Lite 2, n (%)					0.001
a) ≤ 65 y			0.061	61 (78%)	
- Low	31 (40)	45 (58)			
- Intermediate	23 (29)	19 (24)			
- High	24 (31)	14 (18)			
b) >65 y			0.178	41 (53%)	
- Low	15 (19)	23 (29)			
- Intermediate	18 (23)	21 (27)			
- High	45 (58)	34 (44)			
RHC risk tool, n (%)					0.709
a) ≤ 65 y			<0.001	58 (74%)	
- Low	7 (9)	31 (40)			
- Intermediate-low	23 (29)	26 (33)			
- Intermediate-high	28 (36)	19 (24)			
- High	20 (26)	2 (3)			
b) >65 y			0.004	60 (77%)	
- Low	12 (16)	28 (36)			
- Intermediate-low	29 (37)	31 (40)			
- Intermediate-high	29 (37)	17 (22)			
- High	8 (10)	2 (2)			

B)

	Baseline	1 st follow-up	p Baseline vs 1 st follow-up	Δ	p Δ ≤65 vs >65 y
ESC/ERS 4-strata, n (%)					<0.001
a) ≤65 y			<0.001	353 (74%)	
- Low	119 (25)	272 (57)			
- Intermediate-low	177 (37)	97 (21)			
- Intermediate-high	162 (34)	95 (20)			
- High	17 (4)	11 (2)			
b) >65 y			<0.001	117 (59%)	
- Low	12 (6)	40 (20)			
- Intermediate-low	65 (33)	65 (33)			
- Intermediate-high	106 (54)	81 (41)			
- High	14 (7)	11 (6)			
REVEAL Lite 2, n (%)					<0.001
a) ≤65 y			<0.001	339 (71%)	
- Low	209 (44)	290 (61)			
- Intermediate	149 (31)	126 (27)			
- High	117 (25)	59 (12)			
b) >65 y			<0.001	99 (50%)	
- Low	32 (16)	63 (32)			
- Intermediate	60 (30)	67 (34)			
- High	105 (53)	67 (34)			
RHC risk tool, n (%)					0.001
a) ≤65 y			<0.001	283 (60%)	
- Low	60 (13)	156 (33)			
- Intermediate-low	126 (26)	117 (25)			
- Intermediate-high	196 (41)	147 (31)			
- High	93 (20)	55 (11)			
b) >65 y			<0.001	143 (73%)	
- Low	26 (13)	66 (33)			
- Intermediate-low	67 (34)	71 (36)			
- Intermediate-high	74 (38)	47 (24)			
- High	30 (15)	13 (7)			

Legend: ESC/ERS, European Society of Cardiology/European Respiratory Society; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization.

Supplementary Table S7. Risk stratification at baseline and at 1st follow-up according to ESC/ERS 4-strata and RHC risk tools and respective changes (Δ) according to the age at diagnosis and the initial treatment strategy.

	Baseline	1 st follow-up	p Baseline vs 1 st follow-up	Δ	p $\Delta \leq 65$ vs >65 y
ESC/ERS 4-strata, n (%)					
Initial monotherapy					
a) ≤ 65 y			<0.001	280 (71%)	0.001
- Low	109 (28)	218 (55)			
- Intermediate-low	143 (36)	78 (20)			
- Intermediate-high	131 (33)	90 (23)			
- High	13 (3)	10 (2)			
b) >65 y			0.008	93 (56%)	
- Low	13 (8)	35 (21)			
- Intermediate-low	56 (34)	47 (29)			
- Intermediate-high	87 (52)	75 (45)			
- High	10 (6)	9 (5)			
Initial combination therapy					
a) ≤ 65 y			<0.001	82 (87%)	0.001
- Low	11 (12)	63 (67)			
- Intermediate-low	41 (44)	19 (20)			
- Intermediate-high	38 (40)	11 (12)			
- High	4 (4)	1 (1)			
b) >65 y			0.017	32 (64%)	
- Low	1 (2)	9 (18)			
- Intermediate-low	15 (30)	18 (36)			
- Intermediate-high	27 (54)	21 (42)			
- High	7 (14)	2 (4)			
REVEAL Lite 2, n (%)					
Initial monotherapy					
a) ≤ 65 y			0.002	267 (67%)	<0.001
- Low	186 (47)	227 (57)			
- Intermediate	120 (30)	114 (29)			
- High	90 (23)	55 (14)			
b) >65 y			0.006	78 (47%)	
- Low	30 (18)	48 (29)			
- Intermediate	48 (29)	58 (35)			
- High	88 (53)	60 (36)			
Initial combination therapy					
a) ≤ 65 y			<0.001	78 (83%)	<0.001
- Low	25 (27)	64 (68)			
- Intermediate	33 (35)	22 (23)			
- High	36 (38)	8 (9)			
b) >65 y			0.001	26 (52%)	
- Low	2 (4)	16 (32)			
- Intermediate	15 (30)	15 (30)			
- High	33 (66)	19 (38)			

RHC risk tool, n (%)					
Initial monotherapy					0.003
a) ≤65 y			<0.001	208 (53%)	
- Low	55 (14)	110 (28)			
- Intermediate-low	106 (27)	92 (23)			
- Intermediate-high	162 (41)	137 (35)			
- High	73 (18)	57 (14)			
b) >65 y			0.012	110 (66%)	
- Low	23 (14)	44 (26)			
- Intermediate-low	55 (33)	59 (36)			
- Intermediate-high	66 (40)	49 (30)			
- High	22 (13)	14 (8)			
Initial combination therapy					0.552
a) ≤65 y			<0.001	84 (89%)	
- Low	7 (7)	49 (52)			
- Intermediate-low	22 (23)	30 (32)			
- Intermediate-high	39 (42)	14 (15)			
- High	26 (28)	1 (1)			
b) >65 y			<0.001	43 (86%)	
- Low	5 (10)	25 (50)			
- Intermediate-low	15 (30)	17 (34)			
- Intermediate-high	17 (34)	5 (10)			
- High	13 (26)	3 (6)			

Legend: ESC/ERS, European Society of Cardiology/European Respiratory Society; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization.

Supplementary Table S8. Clinical, laboratory and haemodynamic variables at baseline and at 1st follow-up and their absolute changes (Δ) according to age tertiles.

	Baseline	1 st follow-up	p Baseline vs 1 st follow- up	Δ	p-value $\Delta \leq 65$ vs >65 y
WHO-FC, n (%)					<0.001
a) <44 y			<0.001	149 (64) ^{†*}	
- I	15 (6)	68 (29)			
- II	89 (38)	124 (53)			
- III	124 (53)	41 (17)			
- IV	6 (3)	1 (1)			
b) 44-63 y			<0.001	108 (46) [*]	
- I	6 (2)	28 (2)			
- II	73 (31)	125 (52)			
- III	151 (64)	83 (35)			
- IV	7 (3)	1 (1)			
c) >63 y			<0.001	87 (37) [‡]	
- I	4 (2)	9 (4)			
- II	37 (16)	100 (42)			
- III	189 (80)	125 (53)			
- IV	5 (2)	1 (1)			
6MWD, m					0.003
a) <44 y (n= 228)	453 (384-544)	516 (430-600)	<0.001	46 (5-94) [‡]	
b) 44-63 y (n= 224)	403 (325-484)	452 (357-527)	<0.001	41 (0-82) ^{§§}	
c) >63 y (n= 197)	327 (265-403)	368 (290-434)	<0.001	19 (-7-70) ^{§§†}	
BNP/NT-proBNP, n (%)					0.008
a) <44 y (n=26)			0.023	19 (73) [‡]	
- <50/<300 ng/l	11 (42)	13 (50)			
- 50-200/300-650 ng/l	2 (8)	9 (35)			
- 200-800/650-1100 ng/l	8 (31)	2 (7.5)			
- >800/>1100 ng/l	5 (19)	2 (7.5)			
b) 44-63 y (n=47)			0.250	26 (55)	
- <50/<300 ng/l	13 (28)	21 (45)			
- 50-200/300-650 ng/l	13 (28)	13 (28)			
- 200-800/650-1100 ng/l	15 (32)	8 (17)			
- >800/>1100 ng/l	6 (12)	5 (10)			
c) >63 y (n= 83)			0.273	33 (40) [‡]	
- <50/<300 ng/l	12 (14)	12 (14)			
- 50-200/300-650 ng/l	22 (27)	33 (40)			
- 200-800/650-1100 ng/l	30 (36)	21 (25)			
- >800/>1100 ng/l	19 (23)	17 (21)			
eGFR, ml/min/1.73m ²					0.079
a) <44 y (n= 191)	90 (80-106)	94 (81-110)	0.015	1 (-5-11)	
b) 44-63 y (n= 196)	73 (60-89)	75 (62-92)	0.060	2 (-6-10)	
c) >63 y (n= 199)	58 (44-73)	58 (43-72)	0.559	-1 (-7-7)	
Haemoglobin, g/dl					0.845
a) <44 y	14.6 (13.3-16.1)	14.0 (13.0-16.1)	0.042	-0.2 (-1.8-1)	
b) 44-63 y	14.4 (12.8-16.1)	14.0 (12.9-15.7)	0.005	-0.3 (-1.3-0.6)	
c) >63 y	13.9 (12.4-15.3)	13.5 (12.1-15.0)	<0.001	-0.5 (-1.4-0.6)	
HR, bpm					0.530
a) <44 y	83 (72-91)	80 (72-90)	0.794	0 (-8-10)	
b) 44-63 y	80 (73-90)	80 (70-90)	0.666	0 (-9-7)	

c) >63 y	78 (70-86)	78 (68-87)	0.198	-2 (-9-7)	
RAP, mmHg					0.108
a) <44 y	6 (4-9)	7 (5-9)	0.120	0 (-2-3)	
b) 44-63 y	7 (4-10)	6 (4-9)	0.316	0 (-3-2)	
c) >63 y	6 (4-10)	7 (5-9)	0.131	1 (-2-3)	
mPAP, mmHg					0.384
a) <44 y	59 (49-72)	54 (40-68)	<0.001	-5 (-12-1)	
b) 44-63 y	53 (41-62)	44 (34-58)	<0.001	-6 (-12-0)	
c) >63 y	43 (36-53)	39 (33-46)	<0.001	-4 (-9-0)	
sPAP, mmHg					0.483
a) <44 y	94 (76-112)	86 (64-107)	<0.001	-9 (-20-3)	
b) 44-63 y	87 (67-101)	73 (53-94)	<0.001	-9 (-20-1)	
c) >63 y	71 (61-89)	65 (53-78)	<0.001	-8 (-17-0)	
Ea, mmHg/ml					0.289
a) <44 y	1.89 (1.22-2.76)	1.41 (0.84-2.04)	<0.001	-0.36 (-0.91 - 0.05)	
b) 44-63 y	1.71 (1.00-2.48)	1.06 (0.73-1.70)	<0.001	-0.37 (-0.95 - 0.08)	
c) >63 y	1.44 (1.03-2.01)	1.03 (0.75-1.41)	<0.001	-0.34 (-0.69 - -0.08)	
PAWP, mmHg					0.281
a) <44 y	7 (6-10)	9 (7-11)	<0.001	1 (0-3)	
b) 44-63 y	8 (6-10)	9 (7-11)	<0.001	1 (-1-3)	
c) >63 y	8 (7-10)	10 (8-12)	<0.001	1 (0-3)	
SBP, mmHg					0.036
a) <44 y	112 (103-123)	108 (100-117)	<0.001	-3 (-12-6)*	
b) 44-63 y	122 (111-137)	114 (105-125)	<0.001	-8 (-20-5)*	
c) >63 y	131 (117-145)	123 (111-139)	<0.001	-7 (-21-7)	
CI, l/min/m2					0.070
a) <44 y	2.4 (1.9-3.0)	2.9 (2.3-3.6)	<0.001	0.4 (-0.1-1.1)	
b) 44-63 y	2.4 (1.9-2.9)	2.9 (2.4-3.5)	<0.001	0.6 (0.1-1.1)	
c) >63 y	2.3 (1.9-2.8)	2.8 (2.3-3.3)	<0.001	0.4 (0-0.8)	
SVI, ml/m2					0.247
a) <44 y	31 (22-40)	38 (29-46)	<0.001	5 (-2-14)	
b) 44-63 y	30 (23-37)	37 (30-45)	<0.001	6 (1-14)	
c) >63 y	30 (25-36)	37 (30-43)	<0.001	5 (1-11)	
CE, ml/mmHg					0.123
a) <44 y	0.84 (0.56-1.28)	1.14 (0.73-1.92)	<0.001	0.24 (-0.02-0.74)	
b) 44-63 y	0.93 (0.64-1.62)	1.53 (0.96-2.19)	<0.001	0.36 (0.04-0.86)	
c) >63 y	1.17 (0.82-1.56)	1.62 (1.19-2.16)	<0.001	0.40 (0.08-0.72)	
RV power, mmHg*l/min					0.330
a) <44 y	137 (108-175)	151 (116-185)	0.039	6 (-27-41)	
b) 44-63 y	116 (96-146)	126 (101-158)	<0.001	7 (-12-33)	
c) >63 y	102 (80-123)	102 (86-131)	0.012	4 (-15-24)	
RVSWI, ml*mmHg					0.208
a) <44 y	20.7 (15.5-28.4)	21.3 (16.5-28.1)	0.445	1.0 (-4.8-5.8)	
b) 44-63 y	17.6 (13.3-21.7)	18.2 (14.3-23.3)	<0.001	0.8 (-1.9-4.9)	
c) >63 y	15.0 (11.9-18.1)	15.0 (11.8-19.7)	0.191	0 (-2.4-3.7)	
RC product, min					0.759
a) <44 y	11767 (10177-14384)	10978 (9073-13458)	<0.001	-775 (-2502-1129)	
b) 44-63 y	10557 (8916-12281)	9780 (8246-11272)	<0.001	-399 (-1892-826)	
c) >63 y	9640 (8514-10777)	8929 (7857-10204)	<0.001	-679 (-1926-583)	
PVR, WU					0.197
a) <44 y	12.9 (9.0-19.4)	9.7 (4.9-14.6)	<0.001	-2.8 (-6.2 - -0.4)	
b) 44-63 y	10.6 (6.8-15.8)	6.8 (4.1-10.5)	<0.001	-2.9 (-6.1 - -1.0)	
c) >63 y	9.0 (6.4-12.6)	5.7 (4.3-8.4)	<0.001	-2.3 (-4.4 - -0.9)	
PAC, ml/mmHg					0.274
a) <44 y	0.93 (0.65-1.40)	1.22 (0.83-1.99)	<0.001	0.29 (-0.03-0.72)	

b) 44-63 y	0.96 (0.66-1.53)	1.53 (0.91-2.19)	<0.001	0.34 (0.02-0.86)	
c) >63 y	1.10 (0.79-1.52)	1.49 (1.08-2.06)	<0.001	0.36 (0.09-0.73)	
SvO ₂ , %					0.334
a) <44 y	68.7 (60.4-74.0)	71.0 (64.0-76.1)	<0.001	2.3 (-3.1-7.0)	
b) 44-63 y	65.6 (58.5-71.1)	68.0 (61.5-74.6)	<0.001	2.6 (-2.8-7.1)	
c) >63 y	63.4 (56.6-69.5)	68.0 (61.9-72.0)	<0.001	3.3 (-1.6-7.9)	
ESC/ERS 4-strata, n (%)					<0.001
a) <44 y			<0.001	189 (81%)* ⁺	
- Low	71 (30)	158 (68)			
- Intermediate-low	87 (37)	42 (18)			
- Intermediate-high	69 (29)	31 (13)			
- High	7 (3)	3 (1)			
b) 44-63 y			<0.001	160 (68)*	
- Low	47 (20)	117 (49)			
- Intermediate-low	92 (39)	50 (21)			
- Intermediate-high	89 (37)	62 (26)			
- High	9 (4)	8 (4)			
c) >63 y			<0.001	138 (59%) ⁺	
- Low	16 (7)	50 (21)			
- Intermediate-low	76 (32)	70 (30)			
- Intermediate-high	125 (53)	104 (44)			
- High	18 (8)	11 (5)			
ESC/ERS 4-strata, n (%)					0.001
Only patients with BNP/NT-proBNP available					
a) <44 y			<0.001	23 (88) ⁺	
- Low	4 (15)	19 (73)			
- Intermediate-low	12 (46)	5 (19)			
- Intermediate-high	9 (35)	2 (8)			
- High	1 (4)	0			
b) 44-63 y			<0.001	37 (79) ^{ff}	
- Low	4 (9)	22 (47)			
- Intermediate-low	27 (57)	18 (38)			
- Intermediate-high	16 (34)	6 (13)			
- High	0	1 (2)			
c) >63 y			0.235	45 (54) ^{ff+}	
- Low	5 (6)	13 (16)			
- Intermediate-low	33 (40)	32 (38.5)			
- Intermediate-high	39 (47)	32 (38.5)			
- High	6 (7)	6 (7)			
ESC/ERS 4-strata, n (%)					<0.001
Excluding patients with ≥2 missing variables					
a) <44 y			<0.001	185 (81)* ⁺	
- Low	71 (31)	154 (68)			
- Intermediate-low	83 (37)	42 (18)			
- Intermediate-high	67 (29)	29 (13)			
- High	7 (3)	3 (1)			
b) 44-63 y			<0.001	155 (68)*	
- Low	46 (20)	112 (49)			
- Intermediate-low	89 (39)	50 (22)			
- Intermediate-high	84 (37)	58 (25)			
- High	9 (4)	8 (4)			
c) >63 y			<0.001	130 (60) ⁺	
- Low	14 (7)	46 (21)			

- Intermediate-low	62 (26)	69 (29)		
- Intermediate-high	95 (40)	64 (27)		
- High	47 (20)	23 (10)		
c) >63 y			<0.001	163 (69) †
- Low	31 (13)	75 (32)		
- Intermediate-low	73 (31)	79 (34)		
- Intermediate-high	90 (38)	61 (26)		
- High	41 (18)	20 (8)		

Legend: 6MWD, 6-minute walk distance; BMI, body mass index; BNP, brain natriuretic peptide; CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; eGFR, estimated glomerular filtration rate; ESC/ERS, European Society of Cardiology/European Respiratory Society; HR, heart rate; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; RV, right ventricle; RVSWI, RV stroke work index; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

p-value for % Δ comparisons for continuous variables are all >0.05

*ff† = p-value <0.05 between respective pairs

Supplementary Table S9. Risk recategorization according to RHC risk tool vs ESC/ERS 4 strata risk tool at 1st follow-up with the corresponding age in the (A) overall population and (B) including only patients with BNP/NT-proBNP values available (n= 156). Table (C) shows the number of patients recategorized into a lower or higher risk category by RHC risk tool vs ESC/ERS 4 strata risk tool with the corresponding age.

(A)

n (%)	RHC risk tool low	RHC risk tool intermediate-low	RHC risk tool intermediate-high	RHC risk tool high
ESC/ERS 4-strata low	154 Age: 46 (35-59) y	91 Age: 48 (35-62) y	70 Age: 42 (33-55) y	10 Age: 38 (32-48) y
ESC/ERS 4-strata intermediate-low	49 Age: 69 (56-73) y	50 Age: 67 (56-75) y	48 Age: 46 (34-61) y	15 Age: 39 (33-48) y
ESC/ERS 4-strata Intermediate-high	24 Age: 73 (65-76) y	53 Age: 67 (56-72) y	77 Age: 65 (53-74) y	43 Age: 56 (39-69) y
ESC/ERS 4-strata high	1 Age: 83 y	4 Age: 70 (60-79) y	10 Age: 69 (59-74) y	7 Age: 56 (41-67) y

(B)

n (%)	RHC risk tool low	RHC risk tool intermediate-low	RHC risk tool intermediate-high	RHC risk tool high
ESC/ERS 4-strata low	28 Age: 50 (33-56) y	20 Age: 60 (48-68) y	6 Age: 54 (43-74) y	0 /
ESC/ERS 4-strata intermediate-low	18 Age: 70 (57-76) y	23 Age: 70 (59-77) y	13 Age: 56 (37-62) y	1 73 y
ESC/ERS 4-strata Intermediate-high	13 Age: 75 (66-76) y	11 Age: 70 (65-77) y	13 Age: 71 (60-75) y	3 Age: 64 (35-67) y
ESC/ERS 4-strata high	0 /	3 Age: 78 (63-80) y	4 Age: 76 (71-79) y	0 /

(C)

	Recategorized to lower risk by RHC	Categorized to the same risk	Recategorized to higher risk by RHC	p-value
n [only with BNP/NT-proBNP]	141 (20%) [49 (31%)]	288 (41%) [64 (41%)]	277 (39%) [43 (28%)]	
Age, years [only with BNP/NT-proBNP]	69 (58-74) * ^{ff} 71 (66-77) * ^{ff}	56 (41-68) * ⁺ 59 (50-74) *	46 (35-61) ^{ff+} 59 (43-67) ^{ff}	<0.001 <0.001

Legend: BNP, brain natriuretic peptide; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N-terminal pro-hormone BNP; RHC, right heart catheterization.

Supplementary Table S10. Risk recategorization according to RHC risk tool vs REVEAL Lite 2 risk tool at 1st follow-up with the corresponding age in the (A) overall population and (B) including only patients with BNP/NT-proBNP values available (n= 156). Table (C) shows the number of patients recategorized into a lower or higher risk category by RHC risk tool vs REVEAL Lite 2 risk tool with the corresponding age.

(A)

n (%)	RHC risk tool low	RHC risk tool intermediate	RHC risk tool high
REVEAL Lite 2 low	220 Age: 51 (37-63) y	112 Age: 43 (33-60) y	23 Age: 44 (38-50) y
REVEAL Lite 2 intermediate	78 Age: 67 (55-73) y	98 Age: 57 (40-70) y	33 Age: 44 (33-55) y
REVEAL Lite 2 high	26 Age: 72 (67-76) y	73 Age: 69 (58-77) y	43 Age: 59 (38-70) y

(B)

n (%)	RHC risk tool low	RHC risk tool intermediate	RHC risk tool high
REVEAL Lite 2 low	49 Age: 55 (36-70) y	18 Age: 62 (52-69) y	1 Age: 46 y
REVEAL Lite 2 intermediate	20 Age: 70 (64-77) y	20 Age: 59 (44-73) y	0 /
REVEAL Lite 2 high	21 Age: 72 (68-76) y	24 Age: 72 (63-78) y	3 Age: 60 (35-62) y

(C)

	Recategorized to lower risk by RHC	Categorized to the same risk	Recategorized to higher risk by RHC	p-value
n [only with BNP/NT-proBNP]	177 (25%) [65 (42%)]	361 (51%) [72 (46%)]	168 (24%) [19 (12%)]	
Age, years [only with BNP/NT-proBNP]	69 (58-75) * ^{ff} 71 (65-77) * ^{ff}	54 (39-66) * ⁺ 56 (40-71) *	43 (33-56) ^{ff+} 62 (46-69) ^{ff}	<0.001 <0.001

Legend: BNP, brain natriuretic peptide; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; NT-proBNP, N-terminal pro-hormone BNP; RHC, right heart catheterization.

Supplementary Table S11. Characteristics at 1st follow-up of patients reaching a low risk profile according to ERS/ERS 4-strata and RHC risk tools.

	RHC risk tool low	ESC/ERS 4-strata low	p-value (vs RHC risk tool low)	ESC/ERS 4-strata low, only patients with BNP/NT-proBNP	p-value (vs RHC risk tool low)
n	228	325		54	
Age, years	55 (40-68)	46 (35-59)	<0.001	55 (36-63)	0.471
Male gender, n (%)	54 (24)	105 (32)	0.027	15 (28)	0.529
Aetiology, n (%)	- I/H/D: 129 (56%) - CTD: 77 (34%) - CHD: 22 (10%)	- I/H/D: 200 (62%) - CTD: 55 (17%) - CHD: 70 (21%)	<0.001	- I/H/D: 31 (57%) - CTD: 15 (28%) - CHD: 8 (15%)	0.454
WHO-FC, n (%)			<0.001		<0.001
- I	56 (24)	99 (30)		4 (7)	
- II	134 (59)	226 (70)		50 (93)	
- III	38 (17)	/		/	
- IV	/	/		/	
6MWD, m (n)	509 (420-583) (n= 216)	540 (492-595) (n= 308)	<0.001	526 (450-571) (n= 50)	0.359
BNP/NT-proBNP, n (%)	N= 59	N= 54	<0.001	N= 54	0.001
- <50/<300 ng/l	23 (39)	39 (72)		39 (72)	
- 50-200/300-650 ng/l	24 (41)	15 (28)		15 (28)	
- 200-800/650-1100 ng/l	10 (17)	/		/	
- >800/>1100 ng/l	2 (3)	/		/	
eGFR, ml/min/1.73m ² (n)	85 (66-100) (n= 195)	86 (72-100) (n= 285)	0.211	87 (73-100) (n= 52)	0.387
Haemoglobin, g/dl	13.4 (12.1-14.6)	14 (13-15.4)	<0.001	13.1 (12.1-13.8)	0.261
Dysthyroidism, n (%)	41 (18)	45 (14)	0.186	11 (20)	0.684
BMI, kg/m ²	24 (22-28)	23 (21-27)	0.020	25 (22-29)	0.875
Obesity, n (%)	35 (15)	38 (12)	0.211	14 (26)	0.065
Systemic hypertension, n (%)	100 (44)	116 (36)	0.053	26 (48)	0.569
Diabetes mellitus, n (%)	28 (12)	22 (7)	0.026	8 (15)	0.616
Coronary artery disease, n (%)	17 (7)	17 (5)	0.284	3 (6)	0.774
Atrial fibrillation, n (%)	12 (5)	23 (7)	0.389	1 (2)	0.474
HR, bpm	78 (70-88)	80 (70-90)	0.255	80 (70-90)	0.602
RAP, mmHg	5 (4-7)	6 (4-7)	0.001	5 (4-7)	0.465
mPAP, mmHg	35 (30-40)	41 (33-56)	<0.001	35 (30-44)	0.332
sPAP, mmHg	55 (45-66)	66 (51-90)	<0.001	56 (46-75)	0.285
Ea, mmHg/ml	0.70 (0.56-0.83)	0.89 (0.65-1.44)	<0.001	0.80 (0.63-1.02)	0.001
PAWP, mmHg	9 (7-11)	9 (7-11)	0.580	9 (7-10)	0.452
SBP, mmHg	117 (107-131)	114 (106-130)	0.153	112 (101-136)	0.482
CI, l/min/m ²	3.6 (3.1-4.1)	3.2 (2.7-3.9)	<0.001	3.1 (2.6-3.9)	<0.001
SVI, ml/m ²	45 (41-52)	41 (34-49)	<0.001	40 (36-45)	<0.001
CE, ml/mmHg	2.28 (1.94-2.78)	1.80 (1.13-2.43)	<0.001	1.98 (1.60-2.43)	0.001
RV power, mmHg*U/min	125 (98-153)	133 (106-172)	0.007	116 (87-142)	0.163
RVSWI, ml*mmHg	18.0 (14.9-22.9)	19.5 (15.4-25.9)	0.015	17.2 (13.6-20.5)	0.109
RC product, min	9195 (8142-10729)	9837 (8504-11878)	0.003	9694 (8229-10586)	0.817
PVR, WU	4.0 (3.4-4.9)	5.4 (3.8-9.7)	<0.001	4.6 (3.7-6.5)	0.009
PAC, ml/mmHg	2.28 (1.87-2.95)	1.78 (1.13-2.44)	<0.001	1.96 (1.52-2.40)	0.002
SvO ₂ , %	74.0 (70.0-78.0)	72.0 (67.0-76.6)	<0.001	71.3 (67.0-76.0)	0.008
PAH initial treatment, n (%)			0.007		0.001
- Mono	154 (68)	253 (78)		23 (43)	
- Combo	74 (32)	72 (22)		31 (57)	

PAH end F-UP treatment, n (%)			0.002		0.105
- Mono	107 (47)	120 (37)		17 (32)	
- Double combo	90 (39)	122 (38)		26 (48)	
- Triple combo	31 (14)	83 (25)		11 (20)	
Causes of death, n (%)	71	87	0.368	2	0.377
- HF	36 (51)	45 (52)		/	
- SD	3 (4)	10 (11.5)		/	
- Cancer	11 (15)	10 (11.5)		1 (50)	
- Bleeding	1 (1)	3 (3)		/	
- Infection	6 (8)	10 (11.5)		1 (50)	
- Other	9 (13)	5 (6)		/	
- Unknown	5 (7)	4 (4.5)		/	

Legend: 6MWD, 6-minute walk distance; BMI, body mass index; BNP, brain natriuretic peptide; CE, cardiac efficiency; CHD, congenital heart disease; CI, cardiac index; CTD, connective tissue disease; Ea, pulmonary artery elastance; eGFR, estimated glomerular filtration rate; ESC/ERS, European Society of Cardiology/European Respiratory Society; F-UP, follow-up; HF, heart failure; HR, heart rate; I/H/D, idiopathic/heritable/drug-induced; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; RHC, right heart catheterization; RV, right ventricle; RVSWI, RV stroke work index; SBP, systolic blood pressure; SD, sudden death; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

Supplementary Table S12. Characteristics at 1st follow-up of patients reaching a low risk profile according to REVEAL Lite 2 and RHC risk tools.

	RHC risk tool low	REVEAL Lite 2 low	p-value (vs RHC risk tool low)	REVEAL Lite 2 low, only patients with BNP/NT-proBNP	p-value (vs RHC risk tool low)
n	228	355		68	
Age, years	55 (40-68)	48 (36-62)	<0.001	56 (44-70)	0.477
Male gender, n (%)	54 (24)	114 (32)	0.028	20 (29)	0.338
Aetiology, n (%)	- I/H/D: 129 (56%) - CTD: 77 (34%) - CHD: 22 (10%)	- I/H/D: 212 (60%) - CTD: 69 (19%) - CHD: 74 (21%)	<0.001	- I/H/D: 39 (57%) - CTD: 19 (28%) - CHD: 10 (15%)	0.408
WHO-FC, n (%)			<0.001		0.001
- I	56 (24)	103 (29)		7 (10)	
- II	134 (59)	244 (69)		57 (84)	
- III	38 (17)	8 (2)		4 (6)	
- IV	/	/		/	
6MWD, m (n)	509 (420-583) (n= 216)	525 (464-587) (n= 349)	0.020	500 (423-556) (n= 64)	0.463
BNP/NT-proBNP, n (%)	N= 59	N= 68	0.005	N= 68	0.005
- <50/<300 ng/l	23 (39)	43 (63)		43 (63)	
- 50-200/300-650 ng/l	24 (41)	23 (34)		23 (34)	
- 200-800/650-1100 ng/l	10 (17)	2 (3)		2 (3)	
- >800/>1100 ng/l	2 (3)	/		/	
eGFR, ml/min/1.73m ² (n)	85 (66-100) (n= 195)	86 (72-100) (n= 306)	0.166	85 (69-99) (n= 63)	0.734
Haemoglobin, g/dl	13.4 (12.1-14.6)	14 (12.9-15.2)	<0.001	13.3 (12.1-14.3)	0.300
Dysthyroidism, n (%)	41 (18)	56 (16)	0.485	11 (20)	0.309
BMI, kg/m ²	24 (22-28)	24 (21-27)	0.084	25 (23-29)	0.373
Obesity, n (%)	35 (15)	51 (14)	0.372	14 (26)	0.086
Systemic hypertension, n (%)	100 (44)	129 (36)	0.070	26 (48)	0.641
Diabetes mellitus, n (%)	28 (12)	29 (8)	0.103	8 (15)	0.405
Coronary artery disease, n (%)	17 (7)	25 (7)	0.850	3 (6)	0.977
Atrial fibrillation, n (%)	12 (5)	22 (6)	0.639	1 (2)	0.429
HR, bpm	78 (70-88)	78 (70-89)	0.834	78 (69-89)	0.690
RAP, mmHg	5 (4-7)	6 (4-7)	<0.001	5 (4-7)	0.483
mPAP, mmHg	35 (30-40)	41 (32-56)	<0.001	33 (30-43)	0.785
sPAP, mmHg	55 (45-66)	66 (50-90)	<0.001	53 (46-71)	0.725
Ea, mmHg/ml	0.70 (0.56-0.83)	0.89 (0.65-1.43)	<0.001	0.77 (0.61-1.03)	0.003
PAWP, mmHg	9 (7-11)	9 (7-11)	0.457	9 (7-11)	0.552
SBP, mmHg	117 (107-131)	116 (107-131)	0.554	116 (105-136)	0.892
CI, l/min/m ²	3.6 (3.1-4.1)	3.1 (2.7-3.8)	<0.001	3.0 (2.6-3.7)	<0.001
SVI, ml/m ²	45 (41-52)	43 (38-50)	<0.001	40 (35-45)	<0.001
CE, ml/mmHg	2.28 (1.94-2.78)	1.82 (1.15-2.43)	<0.001	2.03 (1.58-2.43)	0.001
RV power, mmHg*U/min	125 (98-153)	131 (104-171)	0.026	107 (85-138)	0.008
RVSWI, ml*mmHg	18.0 (14.9-22.9)	19.5 (15.5-25.7)	0.016	16.3 (12.5-20.1)	0.010
RC product, min	9195 (8142-10729)	9837 (8547-11742)	0.001	9751 (8333-10785)	0.356
PVR, WU	4.0 (3.4-4.9)	5.3 (3.9-9.6)	<0.001	4.5 (3.8-6.4)	0.008
PAC, ml/mmHg	2.28 (1.87-2.95)	1.78 (1.14-2.41)	<0.001	2.00 (1.54-2.59)	0.004
SvO ₂ , %	74.0 (70.0-78.0)	71.6 (67.0-76.4)	<0.001	70.0 (65.5-75.5)	<0.001
PAH initial treatment, n (%)			0.008		0.002
- Mono	154 (68)	275 (77)		32 (47)	
- Combo	74 (32)	80 (23)		36 (53)	

PAH end F-UP treatment, n (%)			0.004		0.237
- Mono	107 (47)	131 (37)		24 (35)	
- Double combo	90 (39)	138 (39)		33 (49)	
- Triple combo	31 (14)	86 (24)		11 (16)	
Causes of death, n (%)	71	104	0.185	7	0.224
- HF	36 (51)	57 (55)		2 (29)	
- SD	3 (4)	12 (11)		2 (29)	
- Cancer	11 (15)	9 (9)		1 (14)	
- Bleeding	1 (1)	4 (4)		/	
- Infection	6 (8)	8 (7)		1 (14)	
- Other	9 (13)	5 (5)		/	
- Unknown	5 (7)	9 (9)		1 (14)	

Legend: 6MWD, 6-minute walk distance; BMI, body mass index; BNP, brain natriuretic peptide; CE, cardiac efficiency; CHD, congenital heart disease; CI, cardiac index; CTD, connective tissue disease; Ea, pulmonary artery elastance; eGFR, estimated glomerular filtration rate; F-UP, follow-up; HF, heart failure; HR, heart rate; I/H/D, idiopathic/heritable/drug-induced; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; RHC, right heart catheterization; RV, right ventricle; RVSWI, RV stroke work index; SBP, systolic blood pressure; SD, sudden death; sPAP, systolic pulmonary artery pressure; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

Supplementary Table S13. Added value of haemodynamic variables over non-invasive risk tools at 1st follow-up in the overall population (age-adjusted), and in the different age categories.

	ESC/ERS 4-strata		REVEAL Lite 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
RAP, mmHg	1.08 (1.06-1.11)	<0.001*	1.06 (1.03-1.09)	<0.001*
a) ≤65 y	1.06 (1.02-1.10)	0.005	1.09 (1.05-1.12)	<0.001
b) >65 y	1.09 (1.05-1.14)	<0.001	1.09 (1.04-1.14)	<0.001
a) <44 y	1.15 (1.09-1.21)	<0.001	1.15 (1.09-1.21)	<0.001
b) 44-63 y	1.02 (1.01-1.02)	<0.001 ^t	1.01 (1.01-1.02)	<0.001 ^t
c) >63 y	1.10 (1.05-1.15)	<0.001	1.09 (1.05-1.14)	<0.001
Ea, mmHg/ml	1.18 (1.09-1.27)	<0.001*	1.18 (1.10-1.26)	<0.001*
a) ≤65 y	1.14 (1.04-1.24)	0.006	1.14 (1.05-1.24)	0.002
b) >65 y	1.29 (0.99-1.69)	0.063	1.26 (0.99-1.61)	0.059
a) <44 y	1.28 (1.17-1.41)	<0.001	1.27 (1.16-1.38)	<0.001
b) 44-63 y	1.07 (0.92-1.24)	0.438	1.04 (0.92-1.19)	0.487
c) >63 y	1.19 (0.92-1.53)	0.183	1.20 (0.95-1.51)	0.136
PVR, WU	1.02 (1.01-1.03)	0.001*	1.02 (1.01-1.03)	<0.001*
a) ≤65 y	1.01 (1.00-1.03)	0.112	1.02 (1.01-1.03)	0.033
b) >65 y	1.04 (1.00-1.09)	0.058	1.04 (1.004-1.08)	0.032
a) <44 y	1.05 (1.03-1.07)	<0.001	1.05 (1.03-1.06)	<0.001
b) 44-63 y	1.00 (0.98-1.02)	0.916	1.00 (0.98-1.02)	0.755
c) >63 y	1.03 (0.99-1.07)	0.209	1.03 (0.99-1.07)	0.096
PAC, ml/mmHg	0.78 (0.67-0.90)	0.001*	0.77 (0.67-0.89)	<0.001*
a) ≤65 y	0.85 (0.71-1.02)	0.090	0.84 (0.70-0.99)	0.047
b) >65 y	0.74 (0.58-0.93)	0.011	0.76 (0.60-0.95)	0.017
a) <44 y	0.46 (0.29-0.72)	0.001	0.47 (0.30-0.72)	<0.001
b) 44-63 y	0.92 (0.73-1.15)	0.462	0.92 (0.75-1.13)	0.429
c) >63 y	0.80 (0.64-0.99)	0.038	0.81 (0.66-1.00)	0.052
CI, l/min/m ²	0.79 (0.69-0.91)	0.001*	0.77 (0.67-0.88)	<0.001*
a) ≤65 y	0.81 (0.68-0.96)	0.016	0.79 (0.67-0.94)	0.007
b) >65 y	0.83 (0.66-1.06)	0.131	0.83 (0.66-1.04)	0.102
a) <44 y	0.54 (0.39-0.75)	<0.001	0.55 (0.40-0.76)	<0.001
b) 44-63 y	0.87 (0.69-1.09)	0.226	0.85 (0.68-1.05)	0.128
c) >63 y	0.88 (0.70-1.09)	0.239	0.86 (0.70-1.06)	0.166
SVI, ml/m ²	0.98 (0.97-0.99)	<0.001*	0.98 (0.97-0.99)	0.001*

a) ≤65 y	0.98 (0.97-0.99)	0.005	0.98 (0.97-0.99)	0.014
b) >65 y	0.99 (0.97-1.00)	0.145	0.99 (0.97-1.01)	0.168
a) <44 y	0.95 (0.93-0.98)	<0.001	0.96 (0.93-0.98)	<0.001
b) 44-63 y	0.98 (0.97-1.00)	0.075	0.98 (0.97-1.00)	0.096
c) >63 y	0.99 (0.97-1.01)	0.265	0.99 (0.97-1.01)	0.325
CE, ml/mmHg	0.73 (0.62-0.85)	<0.001*	0.73 (0.62-0.85)	<0.001*
a) ≤65 y	0.88 (0.72-1.06)	0.175	0.87 (0.72-1.05)	0.144
b) >65 y	0.71 (0.55-0.91)	0.008	0.72 (0.56-0.92)	0.010
a) <44 y	0.40 (0.25-0.64)	<0.001	0.41 (0.26-0.65)	<0.001
b) 44-63 y	0.94 (0.73-1.21)	0.636	0.96 (0.76-1.22)	0.758
c) >63 y	0.77 (0.61-0.97)	0.026	0.78 (0.63-0.98)	0.034
SvO ₂ , %	0.97 (0.96-0.98)	<0.001*	0.97 (0.96-0.99)	<0.001*
a) ≤65 y	0.97 (0.95-0.98)	<0.001	0.97 (0.95-0.98)	<0.001
b) >65 y	0.98 (0.97-1.00)	0.069	0.99 (0.97-1.01)	0.187
a) <44 y	0.94 (0.92-0.96)	<0.001	0.94 (0.92-0.96)	<0.001
b) 44-63 y	0.98 (0.96-0.99)	0.023	0.98 (0.96-1.00)	0.051
c) >63 y	0.99 (0.97-1.00)	0.122	0.98 (0.97-1.01)	0.228

Legend: CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; ESC/ERS, European Society of Cardiology/European Respiratory Society; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation

t = time varying covariate

* Age-adjusted

Supplementary Table S14. Added value of haemodynamic variables over non-invasive risk tools at 1st follow-up in the overall population (age-adjusted), and in the different age categories, including only patients with at least 2 of these variables: WHO-FC, 6MWD and BNP/NT-proBNP (n= 672)

	ESC/ERS 4-strata		REVEAL Lite 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
RAP, mmHg	1.09 (1.06-1.11)	<0.001*	1.06 (1.03-1.10)	<0.001*
a) ≤65 y	1.06 (1.02-1.10)	0.002	1.05 (1.01-1.09)	0.023
b) >65 y	1.10 (1.05-1.15)	<0.001	1.09 (1.04-1.14)	<0.001
a) <44 y	1.15 (1.09-1.22)	<0.001	1.15 (1.09-1.21)	<0.001
b) 44-63 y	1.02 (1.01-1.03)	0.006 ^t	1.02 (1.01-1.03)	0.004 ^t
c) >63 y	1.11 (1.06-1.16)	<0.001	1.10 (1.05-1.15)	<0.001
Ea, mmHg/ml	1.17 (1.08-1.27)	<0.001*	1.18 (1.10-1.26)	<0.001*
a) ≤65 y	1.14 (1.04-1.25)	0.005	1.14 (1.05-1.25)	0.002
b) >65 y	1.24 (0.93-1.66)	0.139	1.25 (0.97-1.61)	0.087
a) <44 y	1.28 (1.17-1.41)	<0.001	1.29 (1.16-1.42)	<0.001
b) 44-63 y	1.06 (0.91-1.24)	0.433	1.00 (0.89-1.14)	0.947
c) >63 y	1.15 (0.87-1.50)	0.322	1.18 (0.92-1.51)	0.191
PVR, WU	1.02 (1.01-1.04)	0.001*	1.02 (1.01-1.04)	<0.001*
a) ≤65 y	1.01 (1.00-1.03)	0.083	1.02 (1.00-1.03)	0.026
b) >65 y	1.04 (1.00-1.09)	0.079	1.05 (1.00-1.09)	0.029
a) <44 y	1.05 (1.03-1.07)	<0.001	1.05 (1.03-1.06)	<0.001
b) 44-63 y	1.00 (0.98-1.02)	0.916	1.00 (0.98-1.02)	0.898
c) >63 y	1.00 (0.98-1.02)	0.857	1.03 (0.99-1.07)	0.094
PAC, ml/mmHg	0.76 (0.65-0.89)	0.001*	0.75 (0.65-0.87)	<0.001*
a) ≤65 y	0.84 (0.69-1.02)	0.081	0.83 (0.69-1.00)	0.054
b) >65 y	0.73 (0.57-0.93)	0.012	0.74 (0.58-0.94)	0.015
a) <44 y	0.45 (0.28-0.71)	0.001	0.46 (0.30-0.71)	0.001
b) 44-63 y	0.91 (0.71-1.16)	0.454	0.94 (0.75-1.19)	0.628
c) >63 y	0.80 (0.64-0.99)	0.042	0.80 (0.65-1.00)	0.052
CI, l/min/m ²	0.79 (0.68-0.91)	0.001*	0.76 (0.66-0.88)	<0.001*
a) ≤65 y	0.79 (0.66-0.94)	0.010	0.77 (0.64-0.92)	0.004
b) >65 y	0.82 (0.64-1.06)	0.131	0.81 (0.64-1.03)	0.087
a) <44 y	0.54 (0.38-0.75)	<0.001	0.55 (0.40-0.76)	<0.001
b) 44-63 y	0.84 (0.66-1.08)	0.179	0.80 (0.63-1.02)	0.066
c) >63 y	0.87 (0.69-1.10)	0.245	0.85 (0.68-1.06)	0.152
SVI, ml/m ²	0.98 (0.97-0.99)	0.001*	0.98 (0.97-0.99)	0.001*

a) ≤65 y	0.98 (0.97-0.99)	0.005	0.98 (0.97-0.99)	0.012
b) >65 y	0.99 (0.97-1.01)	0.308	0.99 (0.97-1.01)	0.294
a) <44 y	0.95 (0.93-0.98)	<0.001	0.96 (0.93-0.98)	<0.001
b) 44-63 y	0.98 (0.96-1.00)	0.077	0.99 (0.97-1.01)	0.236
c) >63 y	0.99 (0.98-1.01)	0.503	0.99 (0.98-1.01)	0.521
CE, ml/mmHg	0.74 (0.62-0.87)	<0.001*	0.73 (0.62-0.85)	<0.001*
a) ≤65 y	0.87 (0.71-1.06)	0.159	0.86 (0.71-1.05)	0.151
b) >65 y	0.70 (0.54-0.92)	0.011	0.71 (0.55-0.93)	0.011
a) <44 y	0.39 (0.24-0.63)	<0.001	0.40 (0.25-0.65)	<0.001
b) 44-63 y	0.94 (0.72-1.22)	0.630	0.98 (0.76-1.28)	0.934
c) >63 y	0.77 (0.61-0.98)	0.036	0.78 (0.62-0.99)	0.042
SvO ₂ , %	0.97 (0.96-0.98)	<0.001*	0.97 (0.96-0.99)	<0.001*
a) ≤65 y	0.97 (0.95-0.98)	<0.001	0.97 (0.95-0.98)	<0.001
b) >65 y	0.98 (0.96-1.00)	0.043	0.98 (0.96-1.00)	0.089
a) <44 y	0.94 (0.92-0.96)	<0.001	0.94 (0.92-0.96)	<0.001
b) 44-63 y	0.98 (0.96-0.99)	0.046	0.98 (0.96-1.00)	0.075
c) >63 y	0.98 (0.96-1.00)	0.095	0.98 (0.96-1.00)	0.129

Legend: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

* Age-adjusted

Supplementary Table S15. Added value of haemodynamic variables in patients at low-risk at 1st follow-up according to non-invasive risk tools in the overall population (age-adjusted), and in the different age categories

	ESC/ERS 4-strata (n= 325)		REVEAL Lite 2 (n= 355)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
RAP, mmHg	1.15 (1.08-1.23)	<0.001*	1.15 (1.08-1.22)	<0.001*
a) ≤65 y	1.15 (1.08-1.22)	<0.001	1.15 (1.08-1.22)	<0.001
b) >65 y	0.78 (0.57-1.07)	0.117	0.78 (0.57-1.07)	0.319
a) <44 y	1.14 (1.05-1.24)	0.003	1.17 (1.08-1.27)	<0.001
b) 44-63 y	1.19 (1.07-1.32)	0.001	1.15 (1.03-1.27)	0.010
c) >63 y	0.82 (0.62-1.10)	0.194	0.92 (0.75-1.12)	0.391
Ea, mmHg/ml	1.44 (1.21-1.72)	<0.001*	1.46 (1.23-1.72)	<0.001*
a) ≤65 y	1.48 (1.25-1.77)	<0.001	1.48 (1.24-1.75)	<0.001
b) >65 y	0.07 (0.01-1.06)	0.055	0.64 (0.22-1.93)	0.434
a) <44 y	1.56 (1.27-1.93)	<0.001	1.58 (1.28-1.95)	<0.001
b) 44-63 y	1.61 (1.12-2.31)	0.010	1.61 (1.13-2.28)	0.008
c) >63 y	0.12 (0.01-1.16)	0.066	0.61 (0.21-1.78)	0.366
PVR, WU	1.06 (1.03-1.09)	0.001*	1.06 (1.03-1.08)	<0.001*
a) ≤65 y	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.08)	<0.001
b) >65 y	0.69 (0.45-1.07)	0.095	0.93 (0.78-1.11)	0.437
a) <44 y	1.07 (1.04-1.11)	<0.001	1.07 (1.04-1.10)	<0.001
b) 44-63 y	1.06 (1.01-1.11)	0.048	1.06 (1.01-1.12)	0.017
c) >63 y	0.71 (0.49-1.02)	0.061	0.92 (0.78-1.09)	0.332
PAC, ml/mmHg	0.78 (0.67-0.90)	0.035*	0.75 (0.59-0.95)	0.015*
a) ≤65 y	0.70 (0.54-0.92)	0.009	0.69 (0.53-0.90)	0.007
b) >65 y	1.94 (0.98-3.87)	0.058	1.13 (0.72-1.78)	0.580
a) <44 y	0.41 (0.24-0.71)	0.001	0.42 (0.25-0.72)	0.002
b) 44-63 y	0.86 (0.62-1.17)	0.330	0.83 (0.59-1.16)	0.277
c) >63 y	1.81 (0.94-3.48)	0.078	1.15 (0.75-1.77)	0.518
CI, l/min/m ²	0.77 (0.59-1.00)	0.051*	0.74 (0.57-0.96)	0.023*
a) ≤65 y	0.68 (0.51-0.90)	0.008	0.64 (0.49-0.86)	0.003
b) >65 y	1.44 (0.71-2.91)	0.316	1.18 (0.66-2.10)	0.575
a) <44 y	0.50 (0.32-0.79)	0.003	0.51 (0.33-0.78)	0.002
b) 44-63 y	0.87 (0.60-1.28)	0.496	0.84 (0.57-1.26)	0.408
c) >63 y	1.33 (0.66-2.68)	0.420	1.10 (0.61-1.96)	0.757
SVI, ml/m ²	0.98 (0.96-1.01)	0.141*	0.98 (0.96-1.00)	0.067*

a) ≤65 y	0.97 (0.95-0.99)	0.024	0.97 (0.95-0.99)	0.012
b) >65 y	1.04 (0.98-1.10)	0.175	1.01 (0.97-1.06)	0.549
a) <44 y	0.95 (0.92-0.98)	0.003	0.95 (0.92-0.99)	0.006
b) 44-63 y	0.99 (0.96-1.02)	0.580	0.99 (0.96-1.02)	0.397
c) >63 y	1.04 (0.98-1.10)	0.234	1.01 (0.96-1.06)	0.757
CE, ml/mmHg	0.73 (0.62-0.85)	<0.001*	0.70 (0.54-0.91)	0.008*
a) ≤65 y	0.65 (0.49-0.88)	0.006	0.65 (0.49-0.87)	0.004
b) >65 y	1.96 (0.88-4.37)	0.098	1.31 (0.75-2.29)	0.349
a) <44 y	0.34 (0.19-0.60)	<0.001	0.36 (0.21-0.63)	<0.001
b) 44-63 y	0.84 (0.58-1.22)	0.373	0.81 (0.55-1.20)	0.294
c) >63 y	1.91 (0.96-3.81)	0.066	1.27 (0.75-2.15)	0.380
SvO ₂ , %	0.94 (0.91-0.96)	<0.001*	0.94 (0.91-0.97)	<0.001*
a) ≤65 y	0.93 (0.90-0.95)	<0.001	0.93 (0.91-0.96)	<0.001
b) >65 y	0.96 (0.86-1.06)	0.428	0.95 (0.88-1.03)	0.184
a) <44 y	0.91 (0.87-0.95)	<0.001	0.91 (0.87-0.95)	<0.001
b) 44-63 y	0.94 (0.90-0.98)	0.005	0.95 (0.92-0.99)	0.021
c) >63 y	0.97 (0.89-1.07)	0.569	0.96 (0.90-1.03)	0.279

Legend: CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; ESC/ERS, European Society of Cardiology/European Respiratory Society; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation

* Age-adjusted

Supplementary Table S16. Added value of haemodynamic variables in patients at low-risk at 1st follow-up according to non-invasive risk tools in the overall population (age-adjusted), and in the different age categories, including only patients with at least 2 of these variables: WHO-FC, 6MWD and BNP/NT-proBNP

	ESC/ERS 4-strata low risk (n= 312)		REVEAL Lite 2 low-risk (n= 353)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
RAP, mmHg	1.16 (1.09-1.24)	<0.001*	1.15 (1.08-1.22)	<0.001*
a) ≤65 y	1.15 (1.08-1.22)	<0.001	1.15 (1.08-1.22)	<0.001
b) >65 y	0.91 (0.66-1.25)	0.564	0.95 (0.77-1.16)	0.598
a) <44 y	1.15 (1.06-1.25)	0.001	1.17 (1.08-1.27)	<0.001
b) 44-63 y	1.18 (1.05-1.32)	0.004	1.15 (1.03-1.27)	0.010
c) >63 y	0.92 (0.69-1.24)	0.583	0.95 (0.78-1.16)	0.602
Ea, mmHg/ml	1.47 (1.23-1.75)	<0.001*	1.48 (1.26-1.74)	<0.001*
a) ≤65 y	1.49 (1.24-1.78)	<0.001	1.50 (1.26-1.77)	<0.001
b) >65 y	0.08 (0.01-1.31)	0.077	0.64 (0.21-1.91)	0.423
a) <44 y	1.55 (1.26-1.92)	<0.001	1.60 (1.31-1.97)	<0.001
b) 44-63 y	1.60 (1.09-2.35)	0.015	1.63 (1.15-2.31)	0.006
c) >63 y	0.12 (0.01-1.01)	0.051	0.62 (0.22-1.80)	0.381
PVR, WU	1.06 (1.03-1.09)	<0.001*	1.06 (1.03-1.09)	<0.001*
a) ≤65 y	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
b) >65 y	0.72 (0.48-1.10)	0.127	0.93 (0.78-1.10)	0.404
a) <44 y	1.07 (1.03-1.11)	<0.001	1.07 (1.04-1.11)	<0.001
b) 44-63 y	1.06 (1.00-1.12)	0.039	1.07 (1.01-1.12)	0.012
c) >63 y	0.72 (0.51-1.02)	0.063	0.91 (0.77-1.08)	0.278
PAC, ml/mmHg	0.72 (0.56-0.94)	0.017*	0.71 (0.56-0.91)	0.006*
a) ≤65 y	0.68 (0.52-0.91)	0.009	0.67 (0.51-0.88)	0.004
b) >65 y	2.13 (0.88-5.16)	0.094	1.09 (0.68-1.75)	0.711
a) <44 y	0.42 (0.25-0.73)	0.002	0.40 (0.23-0.68)	0.001
b) 44-63 y	0.85 (0.60-1.22)	0.375	0.81 (0.58-1.14)	0.232
c) >63 y	2.03 (0.98-4.21)	0.058	1.11 (0.71-1.74)	0.650
CI, l/min/m ²	0.70 (0.53-0.93)	0.013*	0.69 (0.54-0.90)	0.005*
a) ≤65 y	0.65 (0.48-0.88)	0.006	0.62 (0.47-0.83)	0.001
b) >65 y	1.04 (0.45-2.40)	0.934	1.03 (0.56-1.91)	0.914
a) <44 y	0.52 (0.33-0.81)	0.004	0.48 (0.31-0.74)	0.001
b) 44-63 y	0.87 (0.57-1.34)	0.528	0.82 (0.55-1.23)	0.343
c) >63 y	0.95 (0.42-2.15)	0.893	0.95 (0.51-1.76)	0.873

SVI, ml/m ²	0.98 (0.96-1.00)	0.068*	0.98 (0.96-1.00)	0.021*
a) ≤65 y	0.97 (0.95-1.00)	0.028	0.97 (0.95-0.99)	0.006
b) >65 y	1.03 (0.96-1.10)	0.456	1.00 (0.96-1.06)	0.846
a) <44 y	0.95 (0.92-0.99)	0.006	0.95 (0.92-0.98)	0.002
b) 44-63 y	0.99 (0.96-1.03)	0.708	0.99 (0.96-1.02)	0.380
c) >63 y	1.01 (0.95-1.08)	0.688	0.99 (0.95-1.05)	0.825
CE, ml/mmHg	0.67 (0.50-0.90)	0.008*	0.66 (0.51-0.86)	0.002*
a) ≤65 y	0.64 (0.47-0.87)	0.005	0.63 (0.47-0.85)	0.002
b) >65 y	2.36 (0.94-5.90)	0.067	1.19 (0.65-2.17)	0.574
a) <44 y	0.35 (0.20-0.62)	<0.001	0.34 (0.19-0.59)	<0.001
b) 44-63 y	0.84 (0.56-1.26)	0.398	0.80 (0.54-1.17)	0.250
c) >63 y	2.00 (0.94-4.27)	0.071	1.16 (0.66-2.03)	0.602
SvO ₂ , %	0.94 (0.91-0.96)	<0.001*	0.94 (0.92-0.97)	<0.001*
a) ≤65 y	0.93 (0.90-0.96)	<0.001	0.93 (0.91-0.96)	<0.001
b) >65 y	0.93 (0.83-1.05)	0.243	0.95 (0.87-1.02)	0.164
a) <44 y	0.91 (0.87-0.95)	<0.001	0.91 (0.88-0.95)	<0.001
b) 44-63 y	0.95 (0.91-0.99)	0.020	0.95 (0.91-0.99)	0.013
c) >63 y	0.97 (0.88-1.07)	0.576	0.97 (0.90-1.04)	0.358

Legend: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CE, cardiac efficiency; CI, cardiac index; Ea, pulmonary artery elastance; ESC/ERS, European Society of Cardiology/European Respiratory Society; NT-proBNP, N-terminal pro-hormone BNP; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation; WHO-FC, world health organization functional class.

* Age-adjusted

Supplementary Table S17. C-indexes and AIC of the COMPERA-RHC risk tool and of different simplified models including only 3 haemodynamic parameters.

	C-index	AIC
COMPERA-RHC risk tool – with 8 haemodynamic variables	0.688	3962
COMPERA-RHC risk tool – with only 3 haemodynamic variables:		
• RAP, Ea, and:		
- CI	0.690*	3963
- SVI	0.684*	3976
- CE	0.679*	3980
- SvO ₂	0.698	3949
• RAP, PVR, and:		
- CI	0.685*	3969
- SVI	0.686*	3974
- CE	0.675*	3988
- SvO ₂	0.693*	3957
• RAP, PAC, and:		
- CI	0.694	3957
- SVI	0.689*	3968
- CE	0.681*	3977
- SvO ₂	0.704*	3944

Legend: AIC, Akaike information criterion; CE, cardiac efficiency; CI, cardiac index; COMPERA, comparative, prospective registry of newly initiated therapies for pulmonary hypertension; Ea, pulmonary artery elastance; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SVI, stroke volume index; SvO₂, mixed venous oxygen saturation.

* p-value <0.05 for the comparison between the simplified COMPERA-RHC risk model including RAP, PAC and SvO₂ vs the other simplified COMPERA-RHC risk models