Περιστατικό 17: Σύγχρονη θεραπευτική προσέγγιση σε ασθενή με πνευμονική αρτηριακή υπέρταση

Αναστασία Ανθη

Β΄ Κλινική Εντατικής Θεραπείας & Διακλινικό Ιατρείο Πνευμονικής Υπέρτασης Π.Γ.Ν. «ΑΤΤΙΚΟΝ»

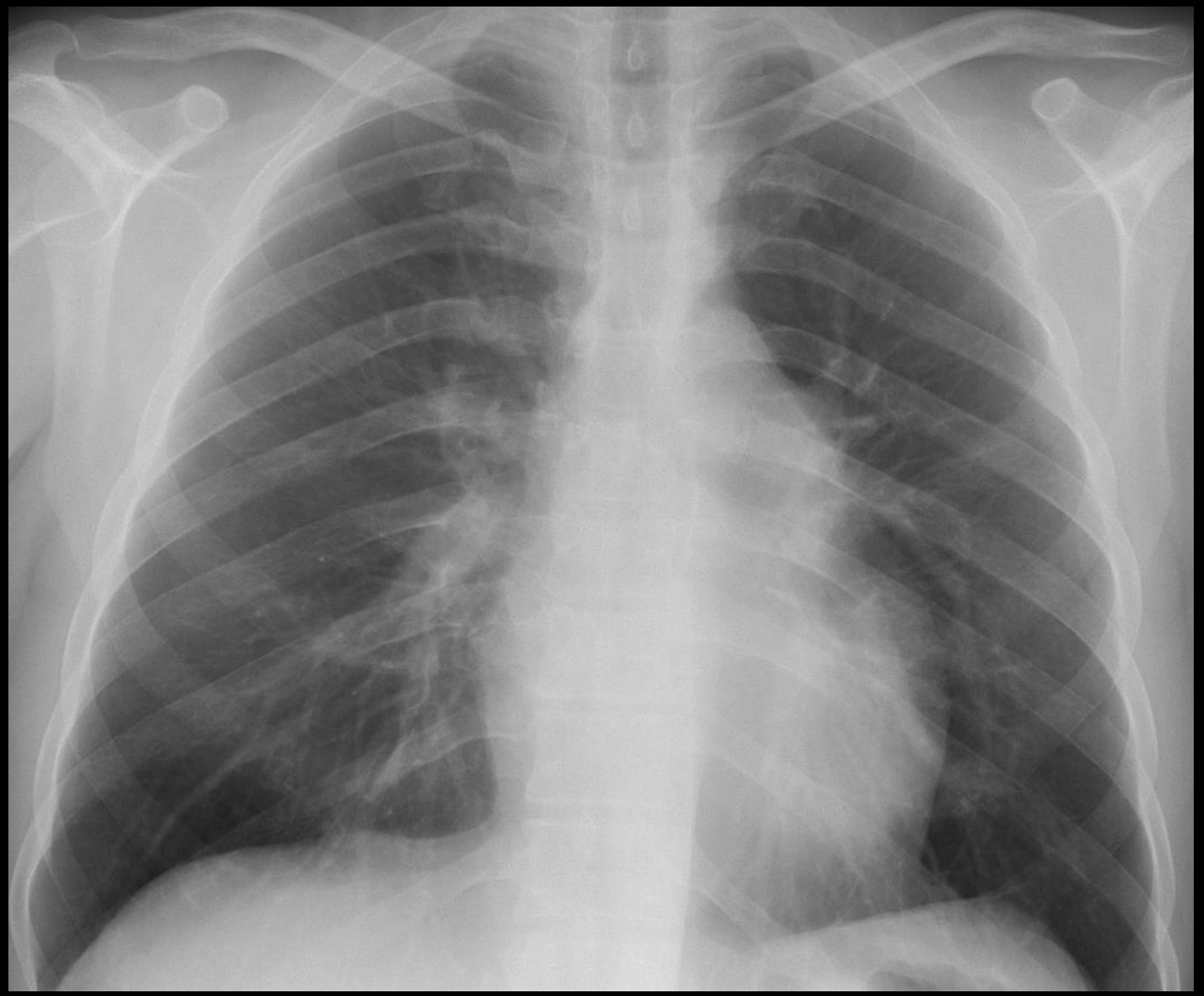
Ανδρας, 47 ετών, καπνιστής

Ατομικό αναμνηστικό: μή αξιοσημείωτο

Εισάγεται σε πνευμονολογική κλινική λόγω σοβαρής αιμόπτυσης

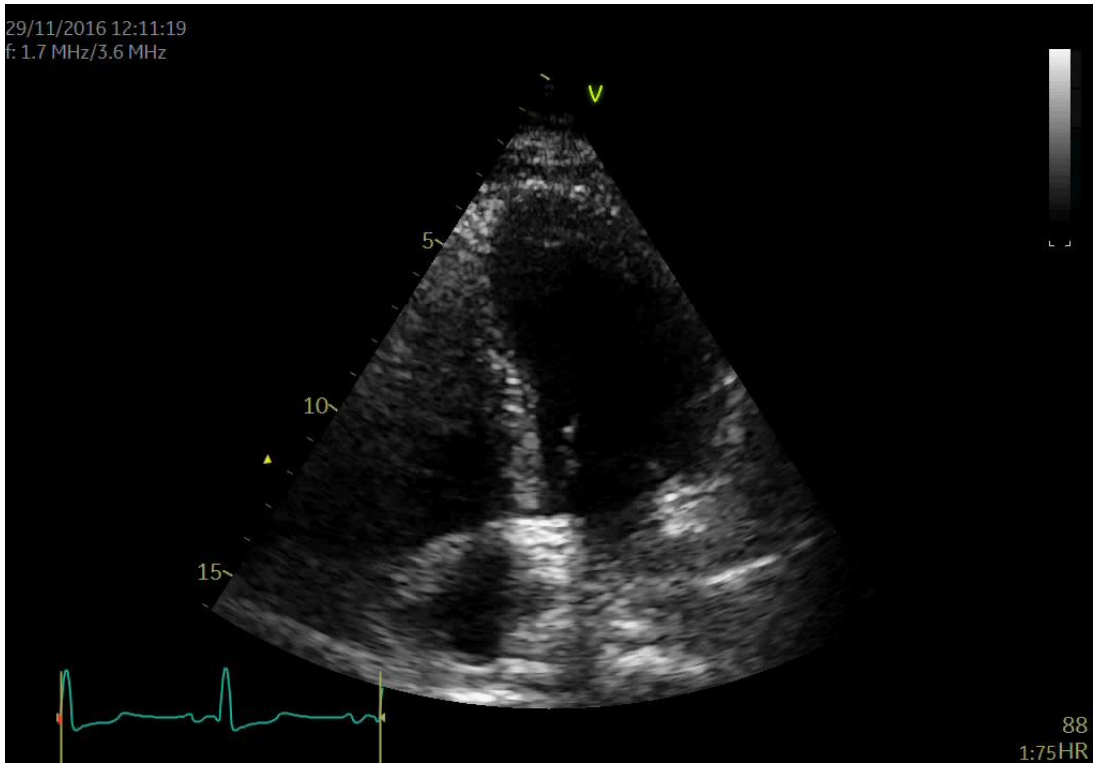
CT θώρακος: χωρίς ευρήματα απο το πνευμονικό παρέγχυμα
Βρογχοσκόπηση: αρνητική

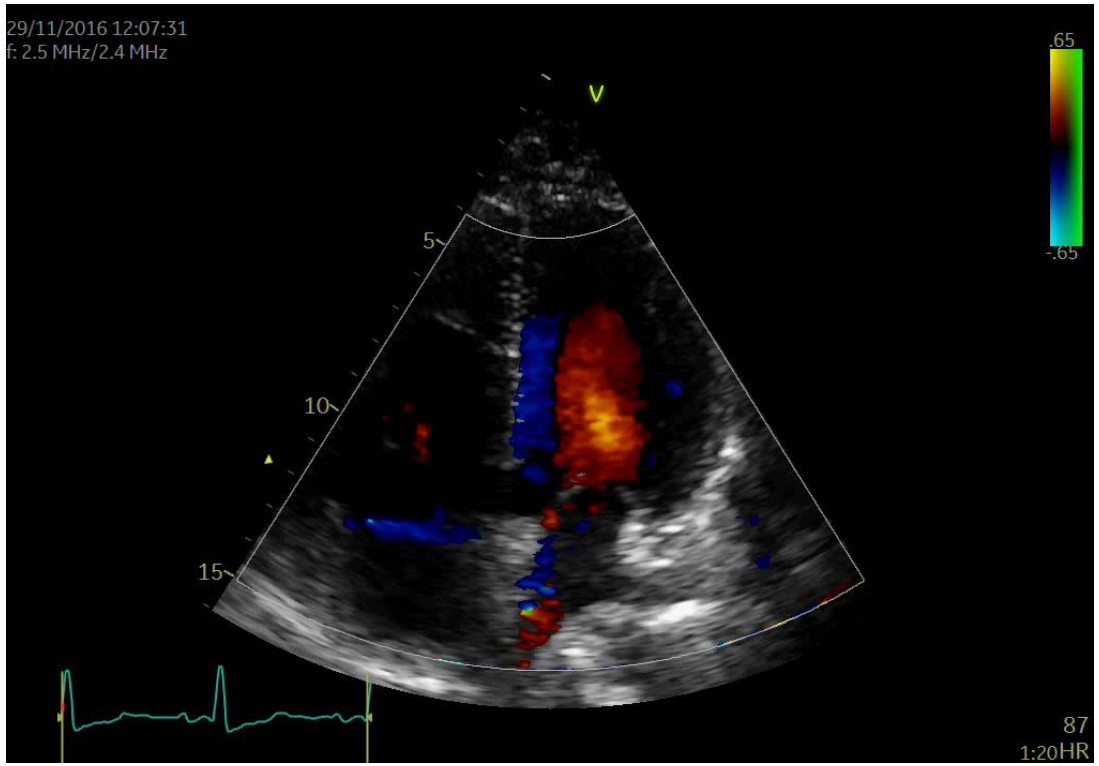
Παραπέμπεται λόγω παθολογικού υπερηχογραφήματος καρδιάς
TVR=4,7 m/sec, SPAP= 90mmHg, TAPSE= 17mm

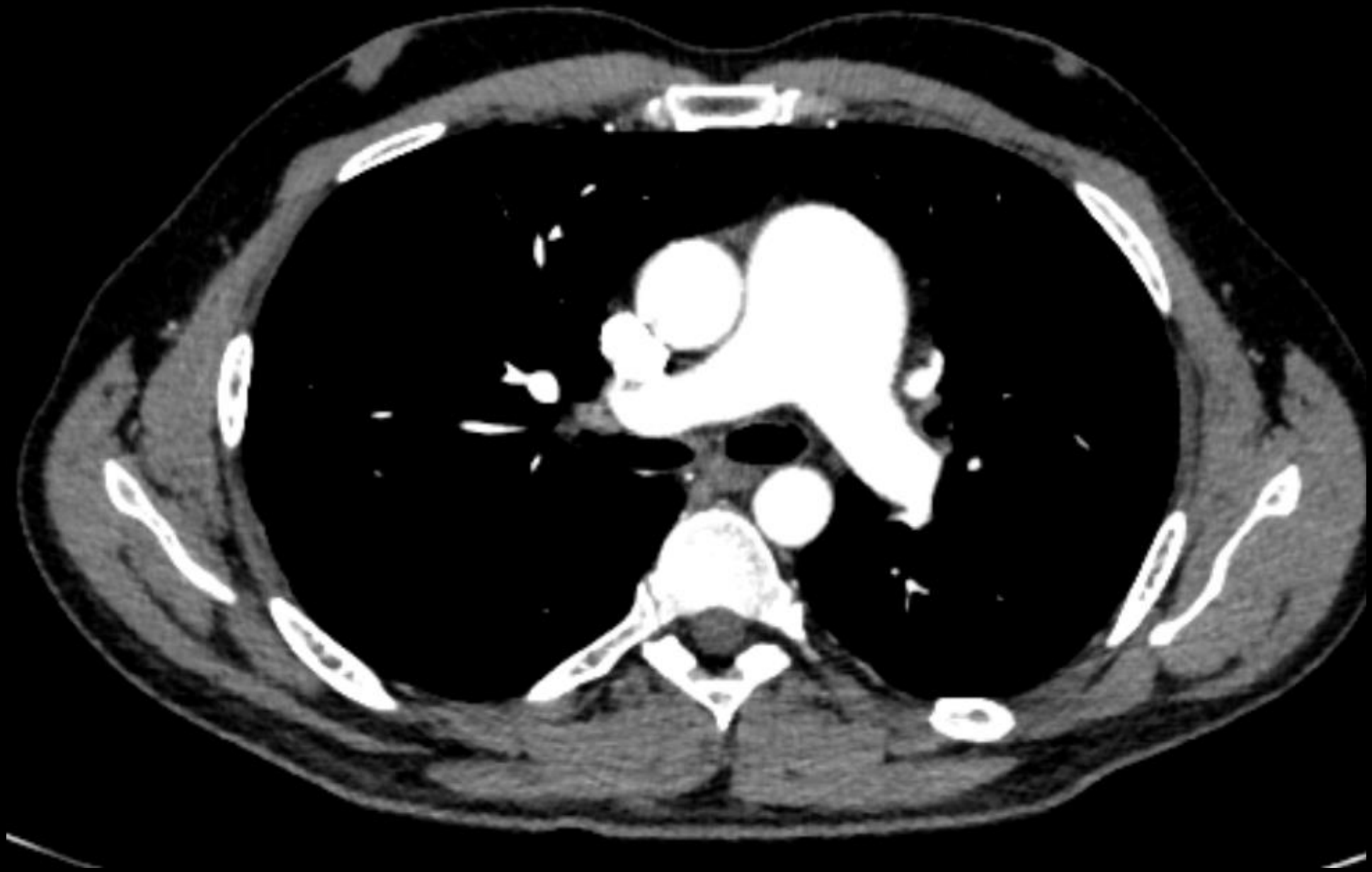


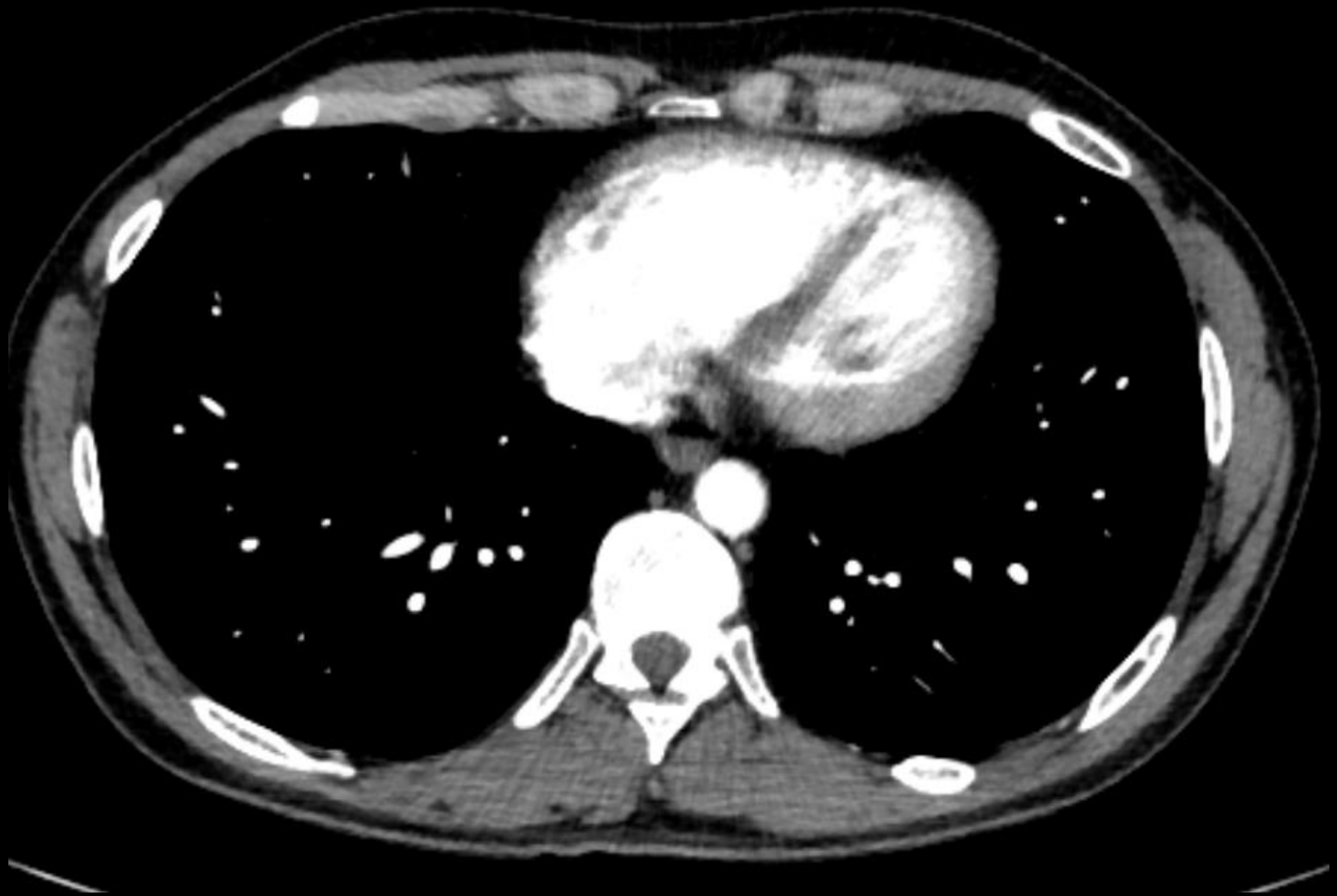
Triplex καρδιάς

TVR=4,7 m/sec, SPAP= 90mmHg, TAPSE= 17mm, S=10cm/sec







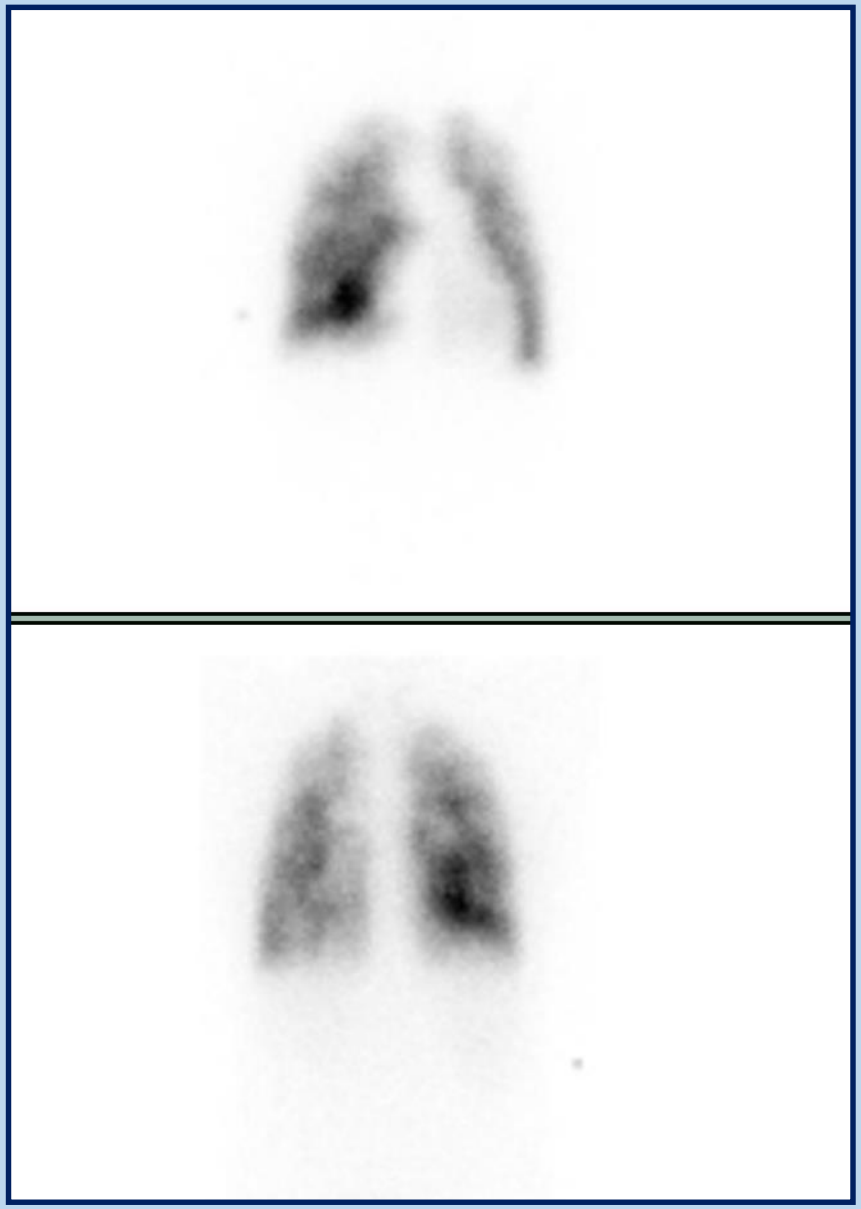


NYHA II late
6MWT=500m
BNP: 55 ng/l

PFT's
FEV1: 2,78L (86%)
FVC: 3,44L (92%)
FEV1/FVC: 81%
DLCO: 75%

Ανοσολογικός/κολλαγονικός έλεγχος : (-)

Scanning αιμάτωσης πνευμόνων

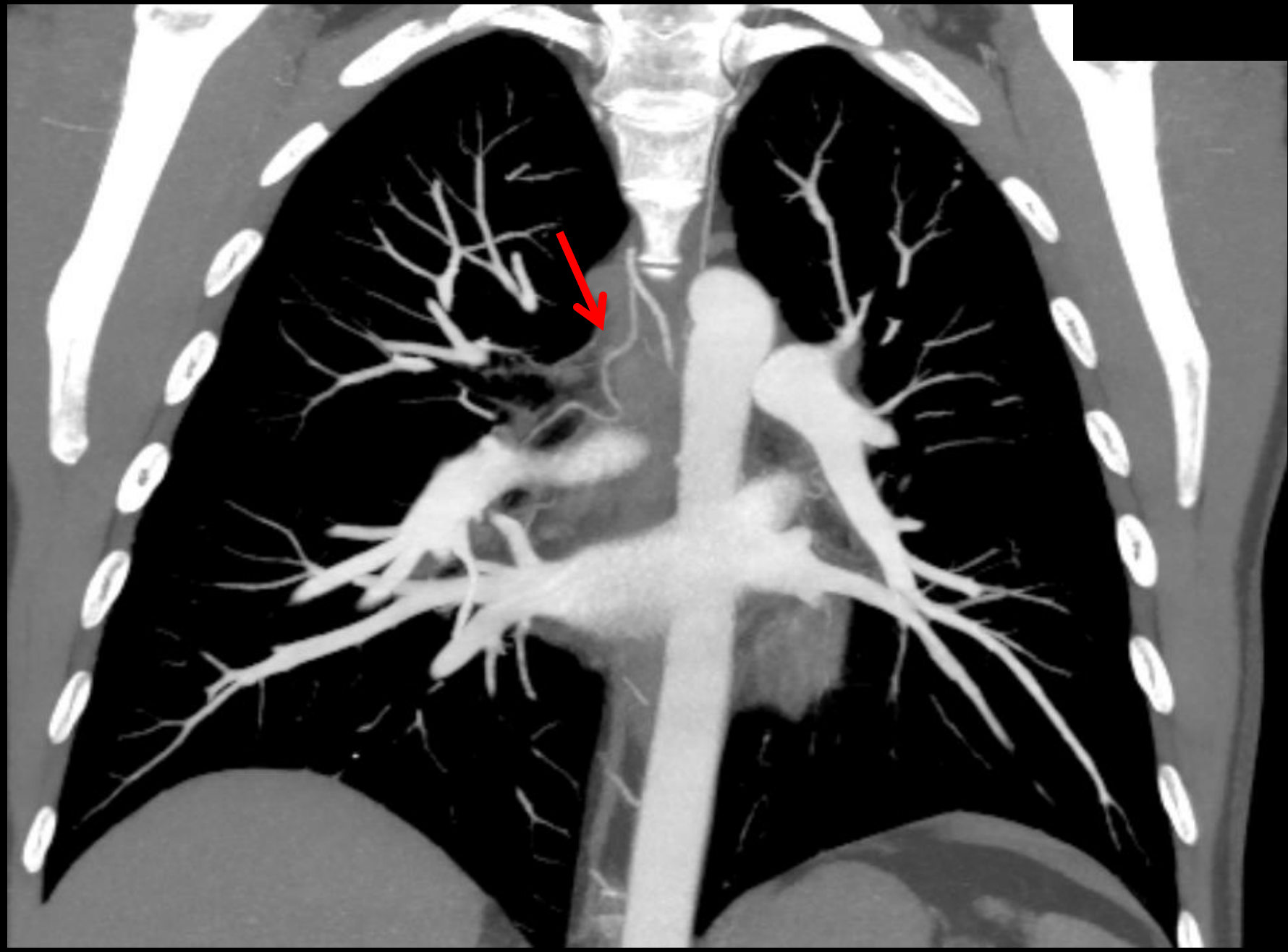


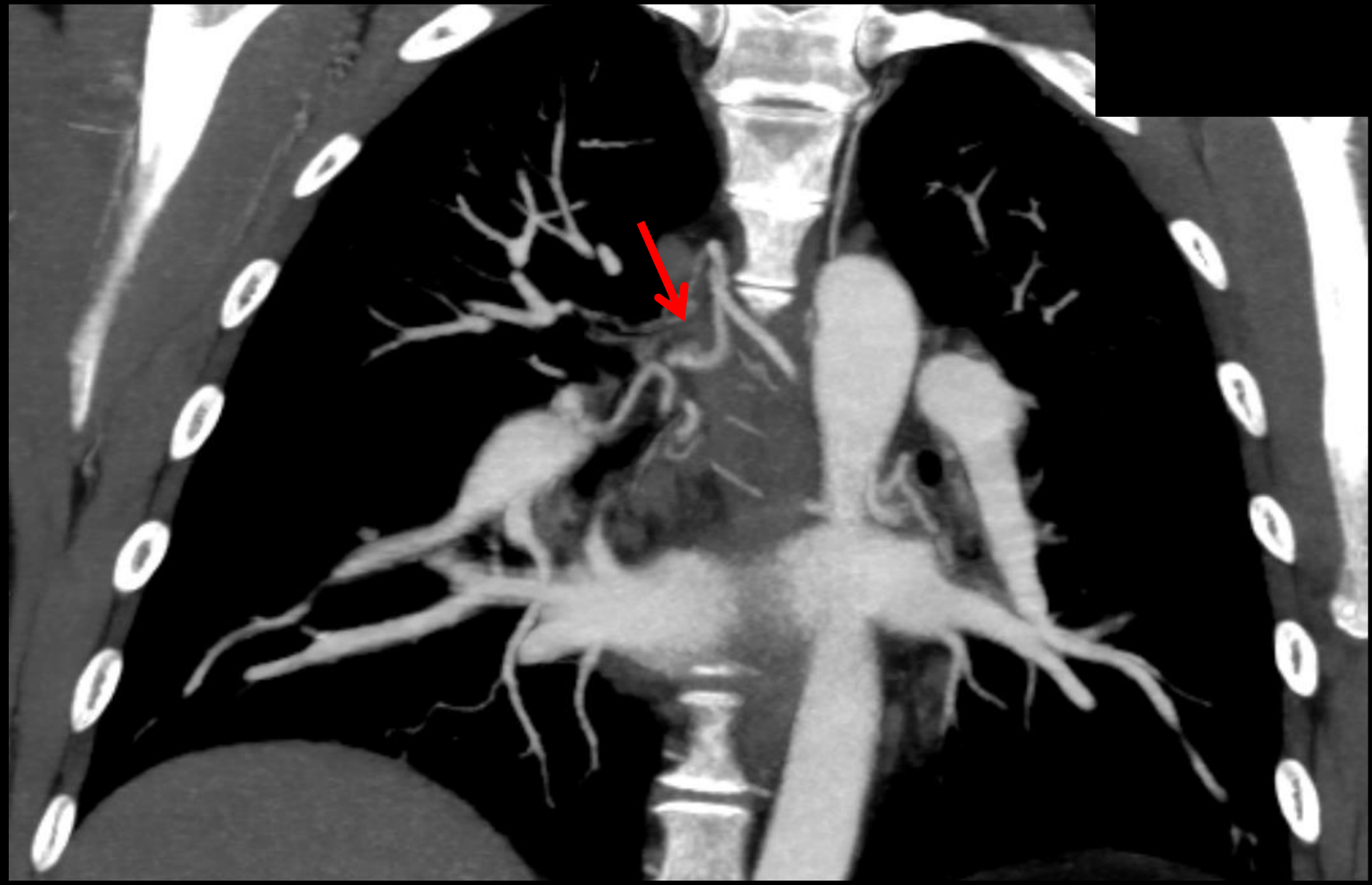
Right Heart Catheterization

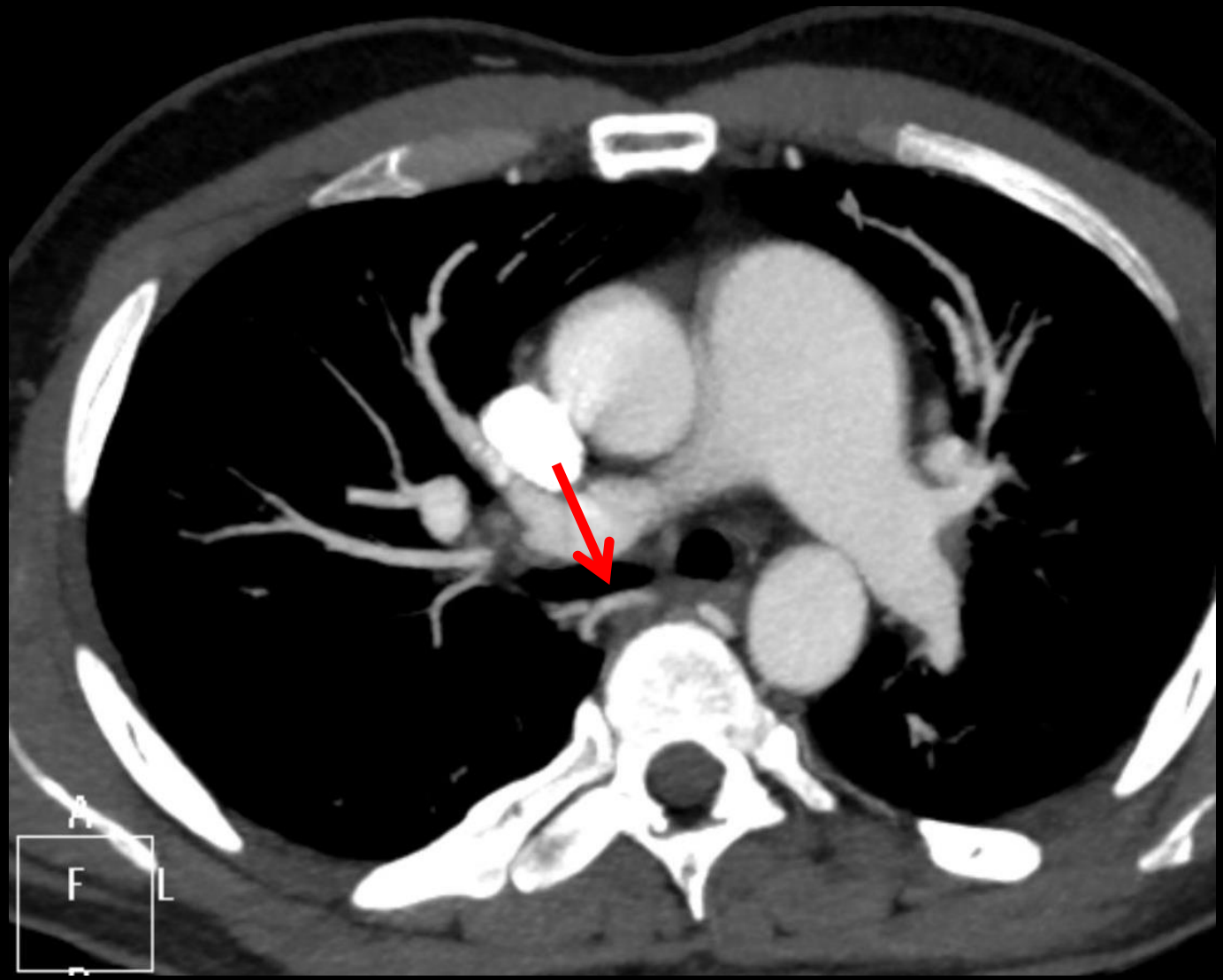
2016

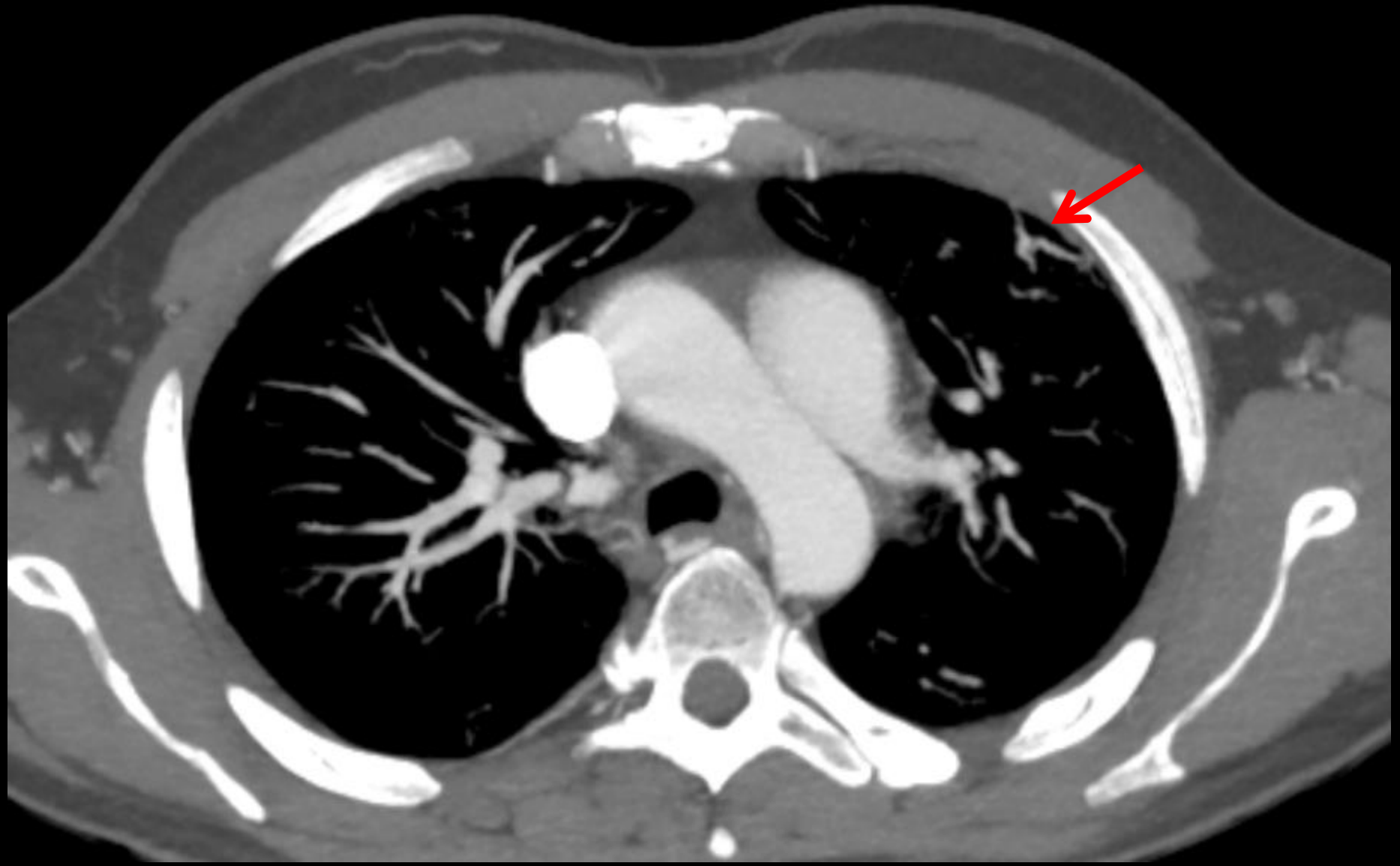
RAP	2	mmHg
PAP	66/29/41	mmHg (S/D/M)
PAWP	4	mmHg
CO	4,4	l/min
CI	2,6	l/min/m^2
PVR	8,4	Wood Units
SvO2	77	%

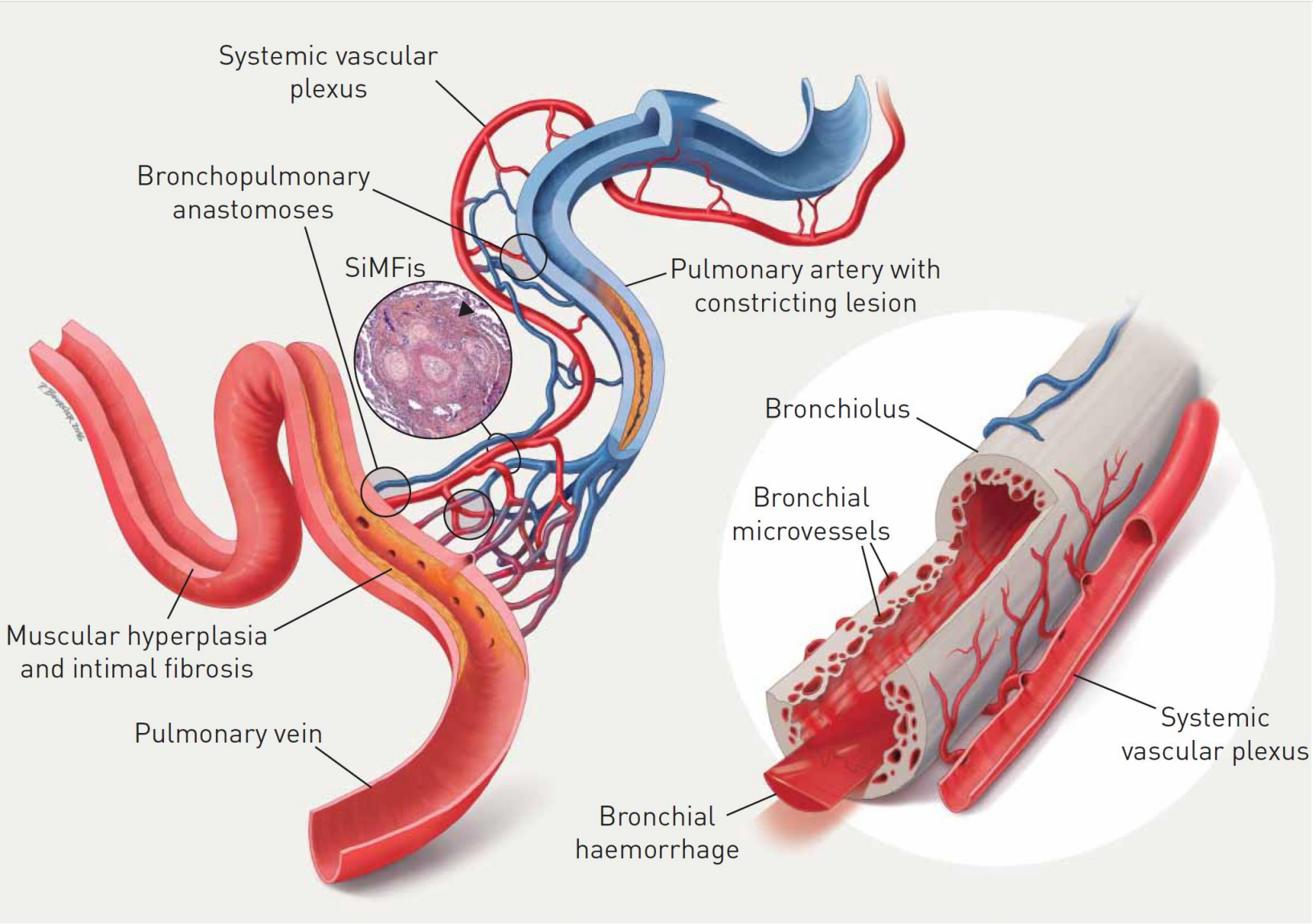
Test αγγειοδραστικότητας με ενδοφλέβια εποπροστενόλη: αρνητικό



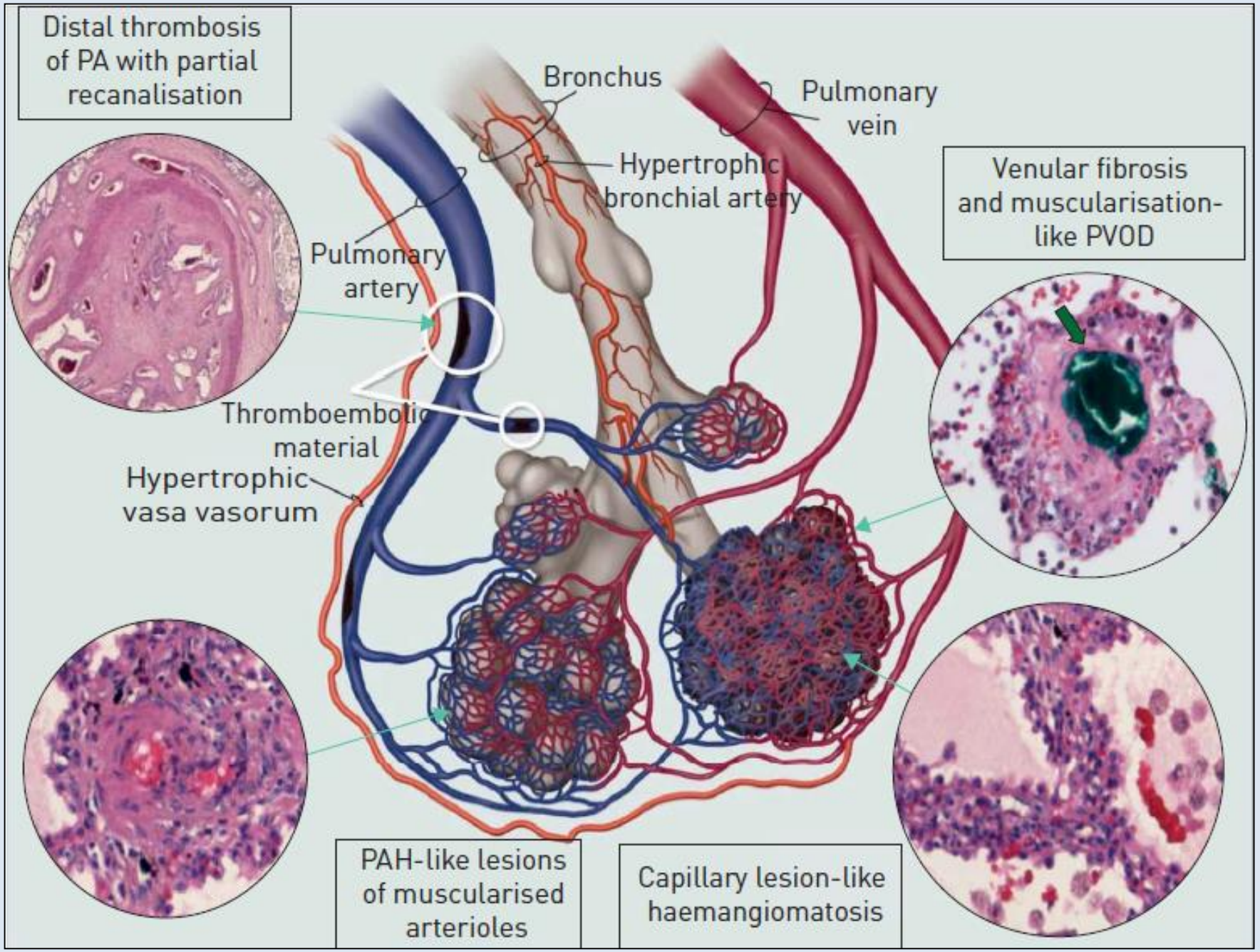



A
F
L





Eur Respir J 2016; 48: 1668–1681


Distal thrombosis of PA with partial recanalisation
Bronchus
Pulmonary vein
Hypertrophic bronchial artery
Venular fibrosis and muscularisation-like PVOD
Pulmonary artery
Thromboembolic material
Hypertrophic vasa vasorum
PAH-like lesions of muscularised arterioles
Capillary lesion-like haemangiomatosis

Η Θεραπευτική προσέγγιση του ασθενή με πνευμονική αρτηριακή υπέρταση γίνεται με βάση:

1. **Τη WHO-FC και την 6λεπτη δοκιμασία βάδισης**
2. **Το υπερηχογράφημα καρδιάς**
3. **Τις αιμοδυναμικές παραμέτρους απο τον δεξιό καρδιακό καθετηριασμό**
4. **Την αξιολόγηση του κινδύνου με συνδυασμό πολλών παραμέτρων**

Η Θεραπευτική προσέγγιση του ασθενή με πνευμονική αρτηριακή υπέρταση γίνεται με βάση:

1. **Τη WHO-FC και την 6λεπτη δοκιμασία βάδισης**
2. **Το υπερηχογράφημα καρδιάς**
3. **Τις αιμοδυναμικές παραμέτρους απο τον δεξιό καρδιακό καθετηριασμό**
4. **Την αξιολόγηση του κινδύνου με συνδυασμό πολλών παραμέτρων**

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

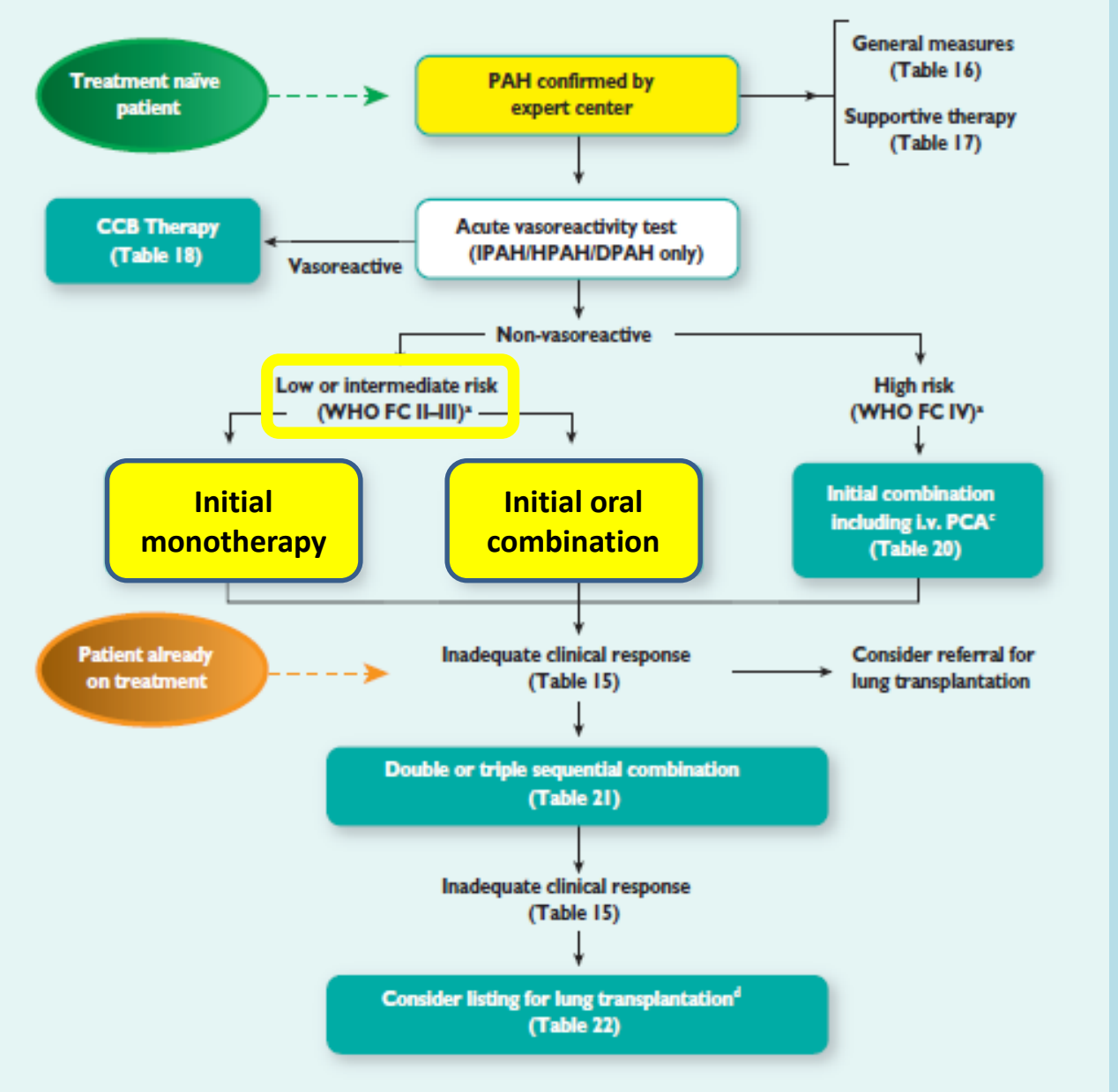
ESC/ERS PH guidelines 2015

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent √	Present
Progression of symptoms	No	√ Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III √	IV
6MWD	>440 m √	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml √	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericard √ effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65% √	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

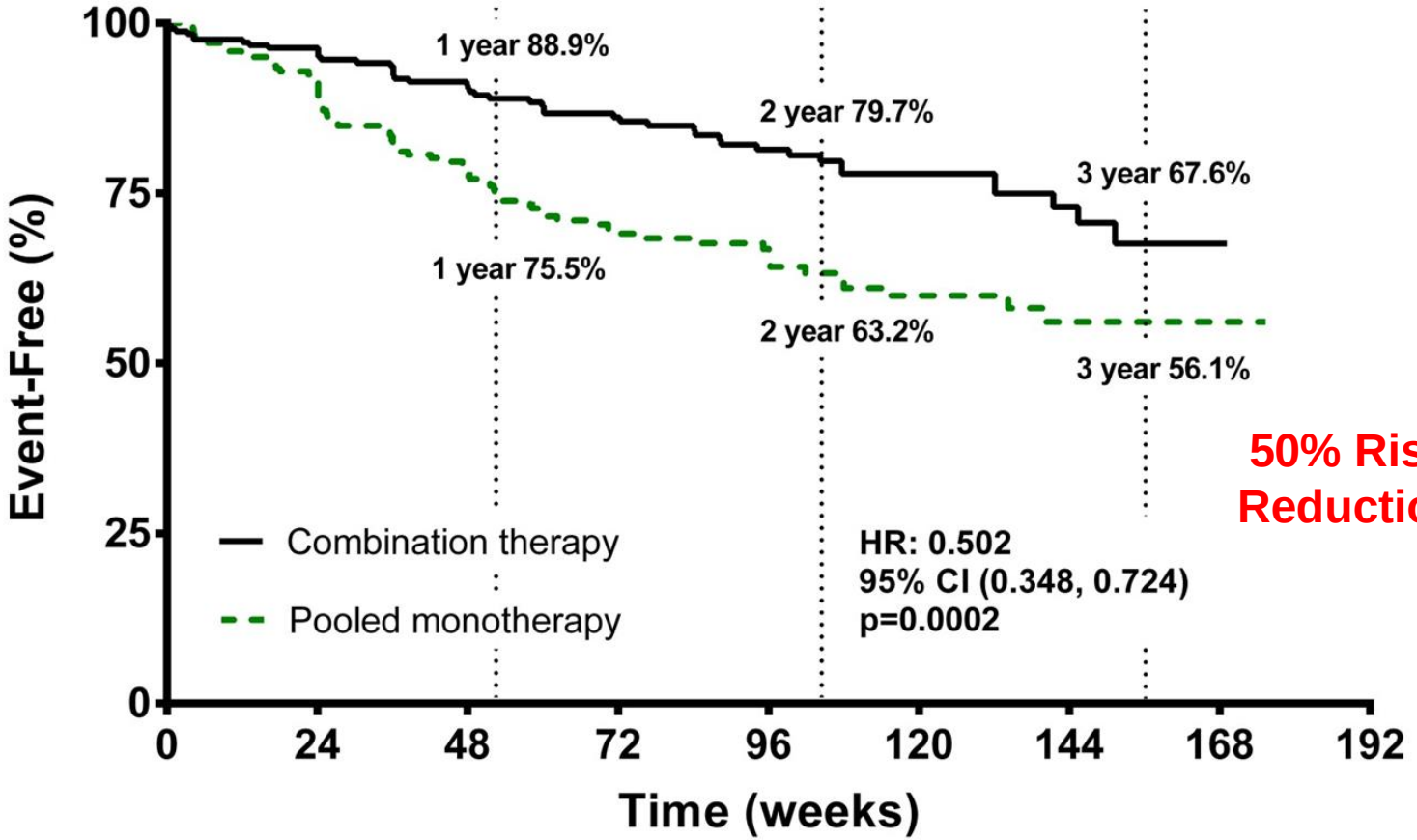
ESC/ERS PH guidelines 2015

Evidence based treatment algorithm for PAH patients



PH guidelines 2015

Ambition study: upfront combination therapy with ambrisentan/ tadalafil reduced the risk of morbidity/mortality

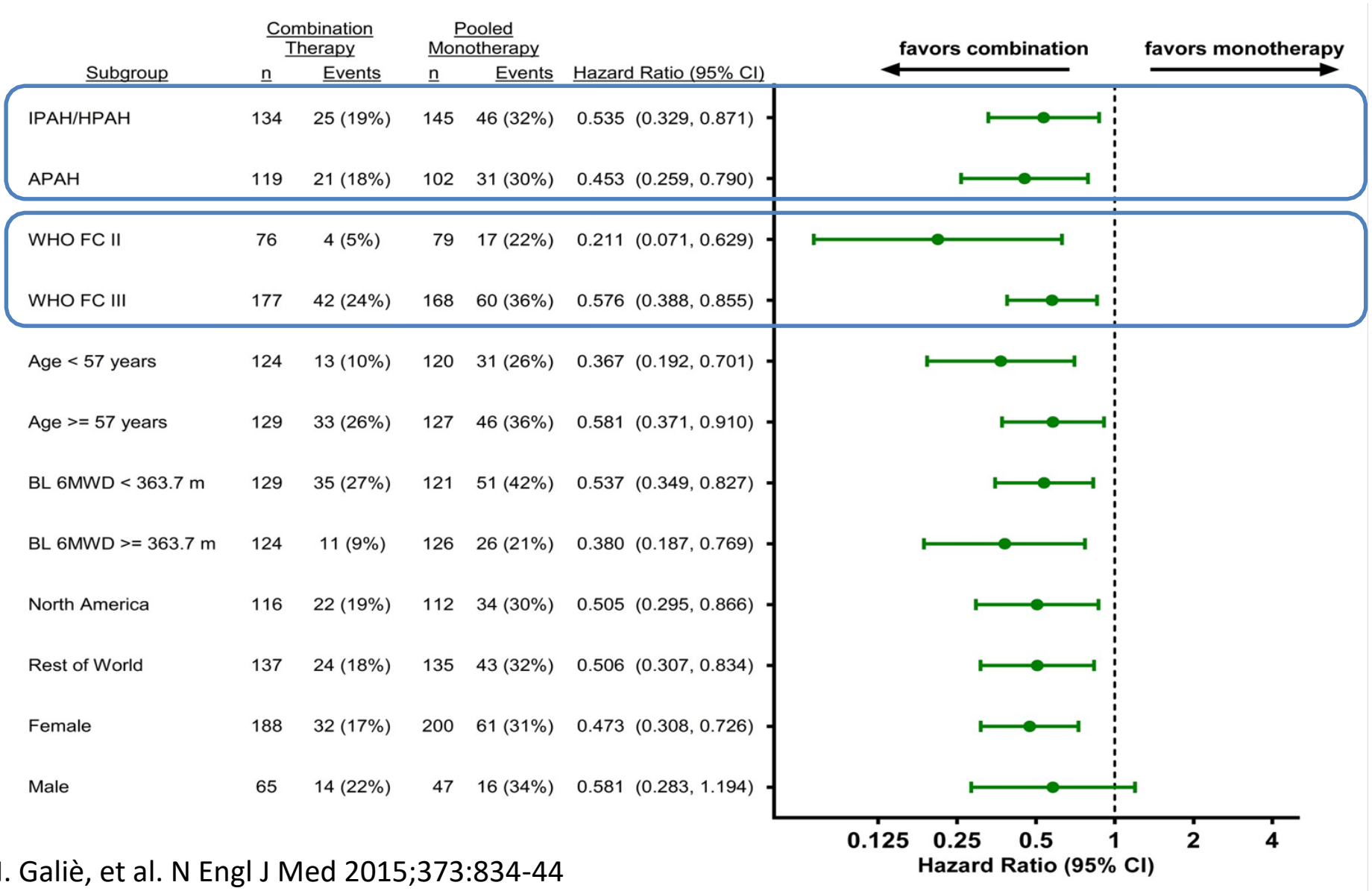


50% Risk Reduction

Number at risk:								
Combination:	253	229	186	145	106	71	36	4
Pooled monotherapy:	247	209	155	108	77	49	25	5

N. Galiè, et al. N Engl J Med 2015;373:834-44

Ambition study: upfront combination therapy with ambrisentan/ tadalafil



Subgroup	Combination Therapy n	Combination Therapy Events	Pooled Monotherapy n	Pooled Monotherapy Events	Hazard Ratio (95% CI)
IPAH/HPAH	134	25 (19%)	145	46 (32%)	0.535 (0.329, 0.871)
APAH	119	21 (18%)	102	31 (30%)	0.453 (0.259, 0.790)
WHO FC II	76	4 (5%)	79	17 (22%)	0.211 (0.071, 0.629)
WHO FC III	177	42 (24%)	168	60 (36%)	0.576 (0.388, 0.855)
Age < 57 years	124	13 (10%)	120	31 (26%)	0.367 (0.192, 0.701)
Age >= 57 years	129	33 (26%)	127	46 (36%)	0.581 (0.371, 0.910)
BL 6MWD < 363.7 m	129	35 (27%)	121	51 (42%)	0.537 (0.349, 0.827)
BL 6MWD >= 363.7 m	124	11 (9%)	126	26 (21%)	0.380 (0.187, 0.769)
North America	116	22 (19%)	112	34 (30%)	0.505 (0.295, 0.866)
Rest of World	137	24 (18%)	135	43 (32%)	0.506 (0.307, 0.834)
Female	188	32 (17%)	200	61 (31%)	0.473 (0.308, 0.726)
Male	65	14 (22%)	47	16 (34%)	0.581 (0.283, 1.194)

N. Galiè, et al. N Engl J Med 2015;373:834-44

Right Heart Catheterization

2016

RAP	2	mmHg
PAP	66/29/41	mmHg (S/D/M)
PAWP	4	mmHg
CO	4,4	l/min
CI	2,6	l/min/m^2
PVR	8,4	Wood Units
SvO2	77	%

Test αγγειοδραστικότητας με ενδοφλέβια εποπροστενόλη: αρνητικό

Right Heart Catheterization

	2016	2017	
RAP	2	4	mmHg
PAP	66/29/41	63/29/40	mmHg (S/D/M)
PAWP	4	7	mmHg
CO	4,4	6,4	l/min
CI	2,6	3,7	l/min/m^2
PVR	8,4	5,1	Wood Units
SvO2	77	77	%

Test αγγειοδραστικότητας με ενδοφλέβια εποπροστενόλη: αρνητικό

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent √	Present
Progression of symptoms	No	√ Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III √	IV
6MWD	>440 m √	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml √	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericard √ effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65% √	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

ESC/ERS PH guidelines 2015

Risk assessment in pulmonary arterial hypertension

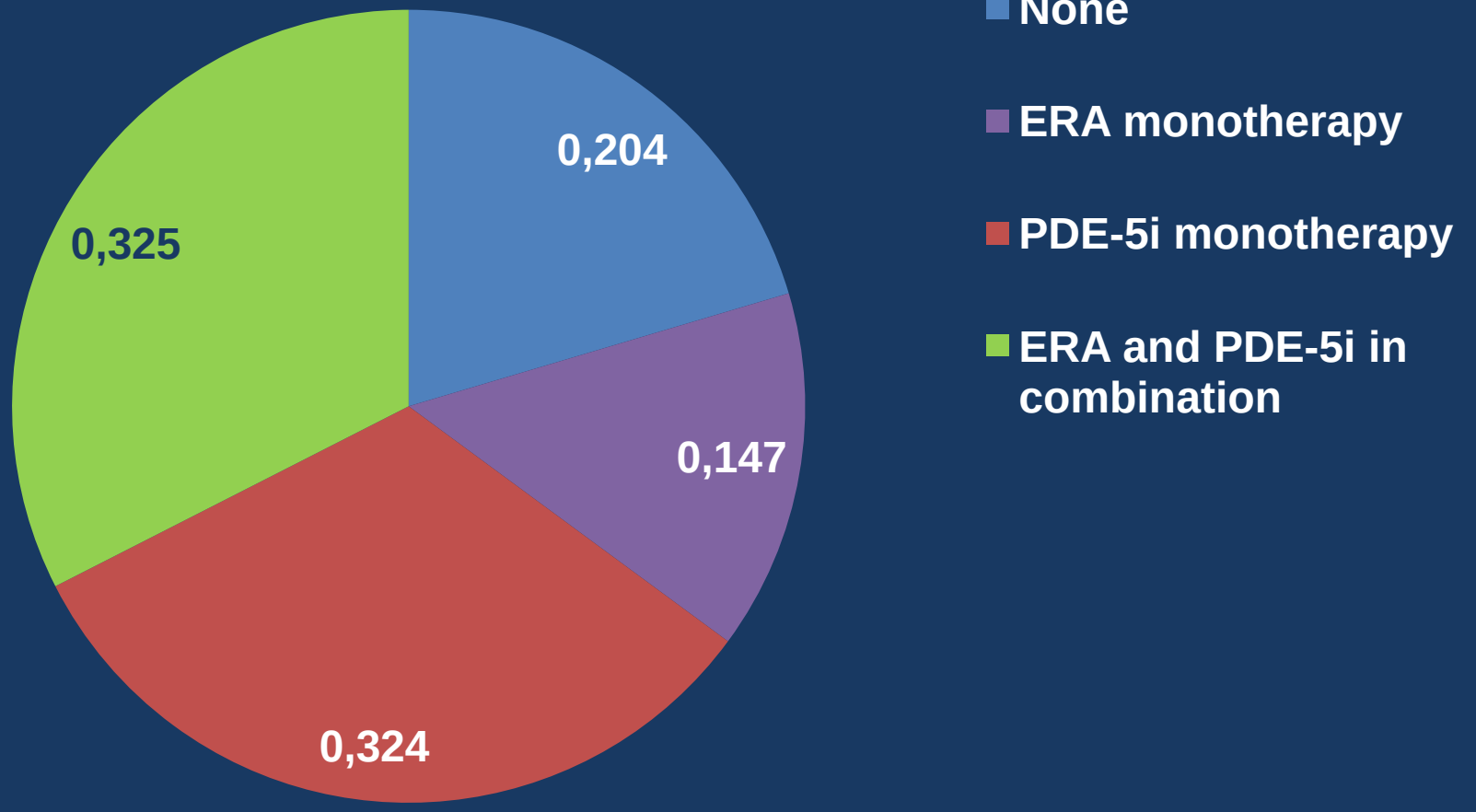
Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

ESC/ERS PH guidelines 2015

Griphon study: Selexipag for the Treatment of PAH

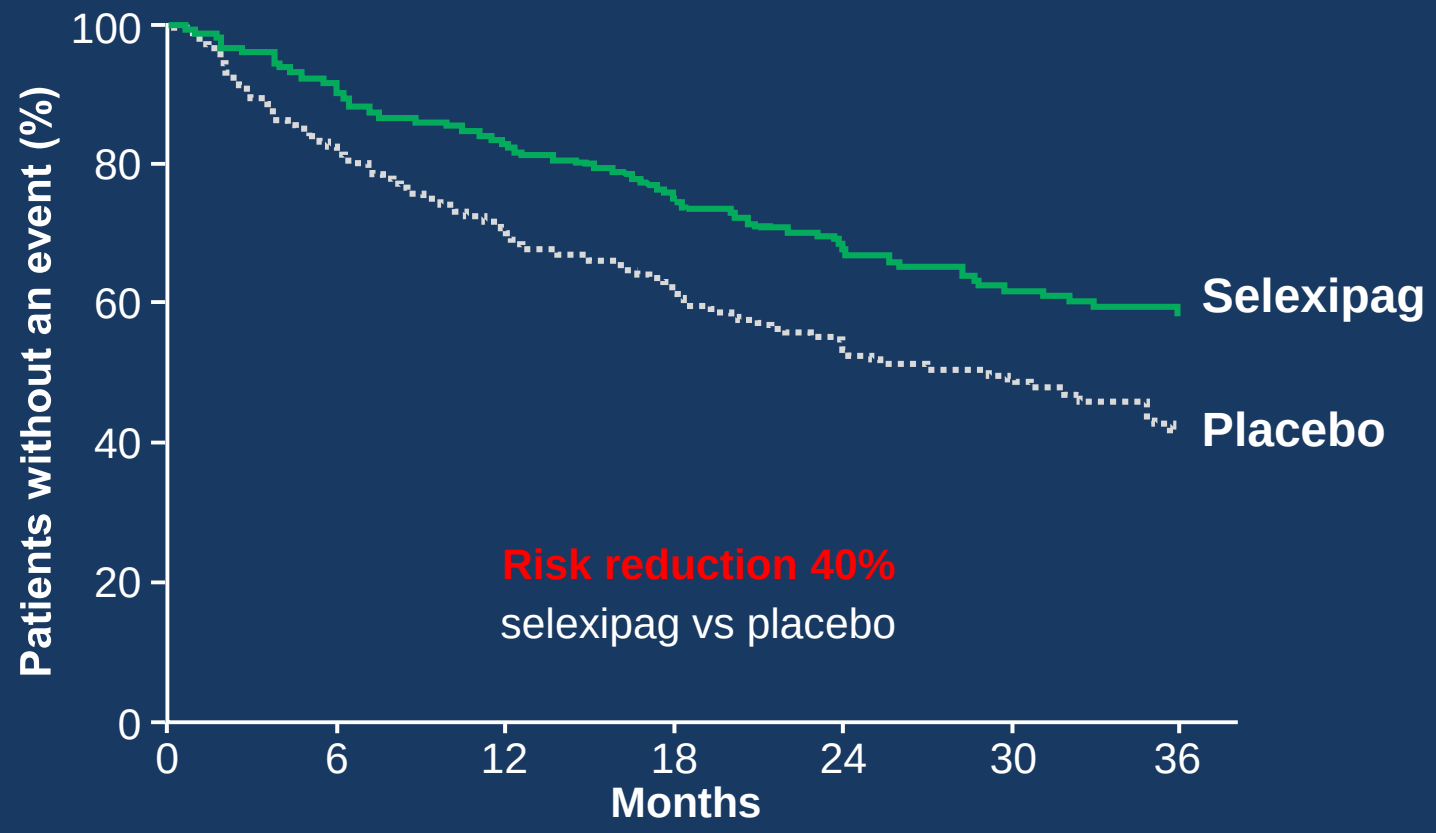
Patient demographics: Background PAH medications

Total number of patients: 1156



Sitbon O, *et al. New Engl J Med* 2015; 373:2522-33.

Griphon study: Time to first morbidity or mortality event (primary endpoint)

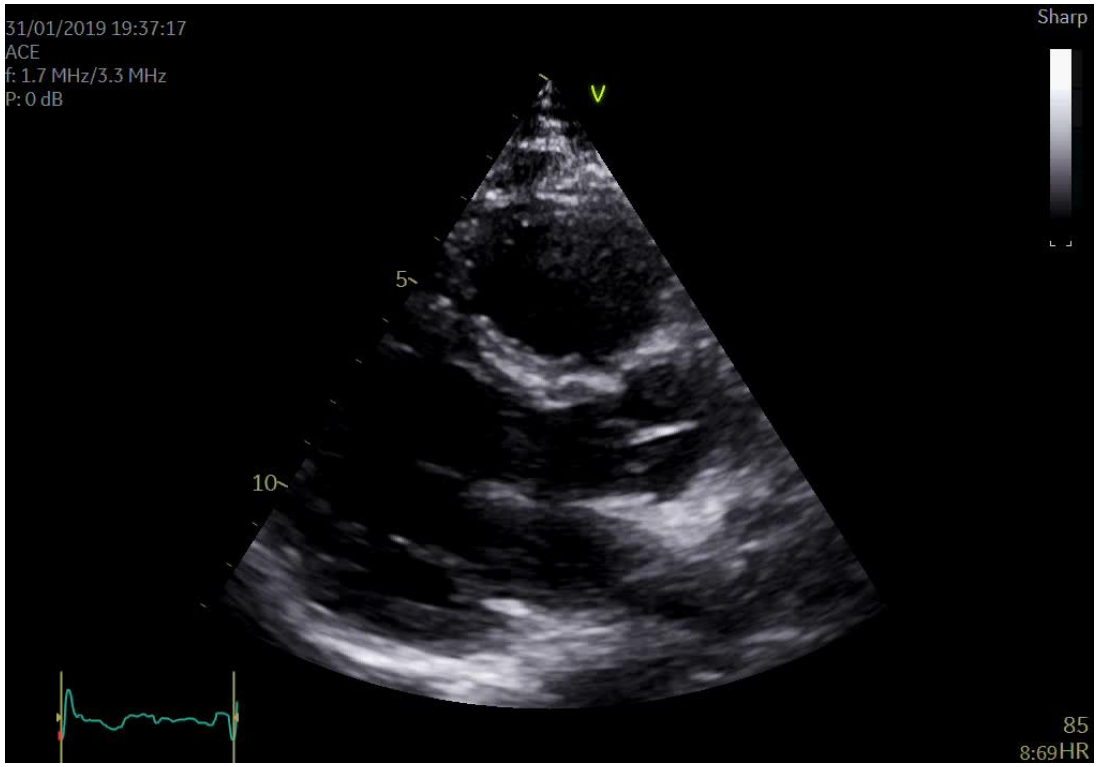


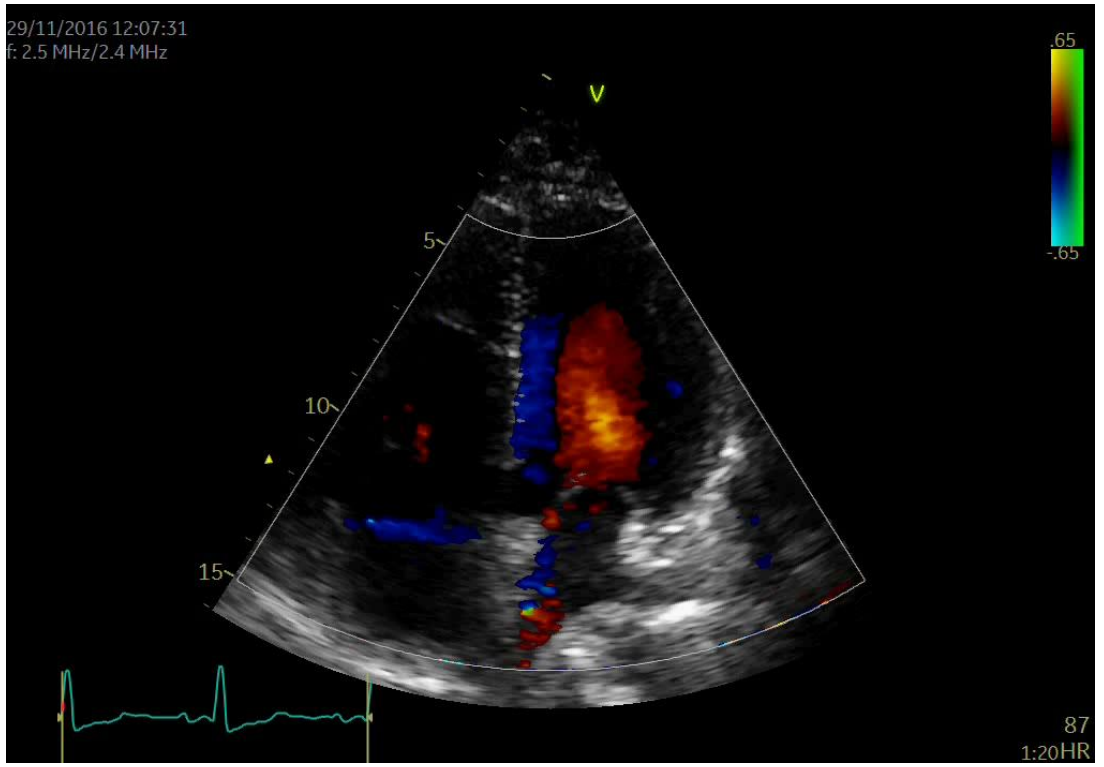
No. at risk							
Placebo	582	433	347	220	149	88	28
Selexipag	574	455	361	246	171	101	40

Sitbon O, *et al. New Engl J Med* 2015; 373:2522-33.

Triplex καρδιάς

TVR=3,8 m/sec, SPAP= 60mmHg, TAPSE= 23mm, S=15cm/sec

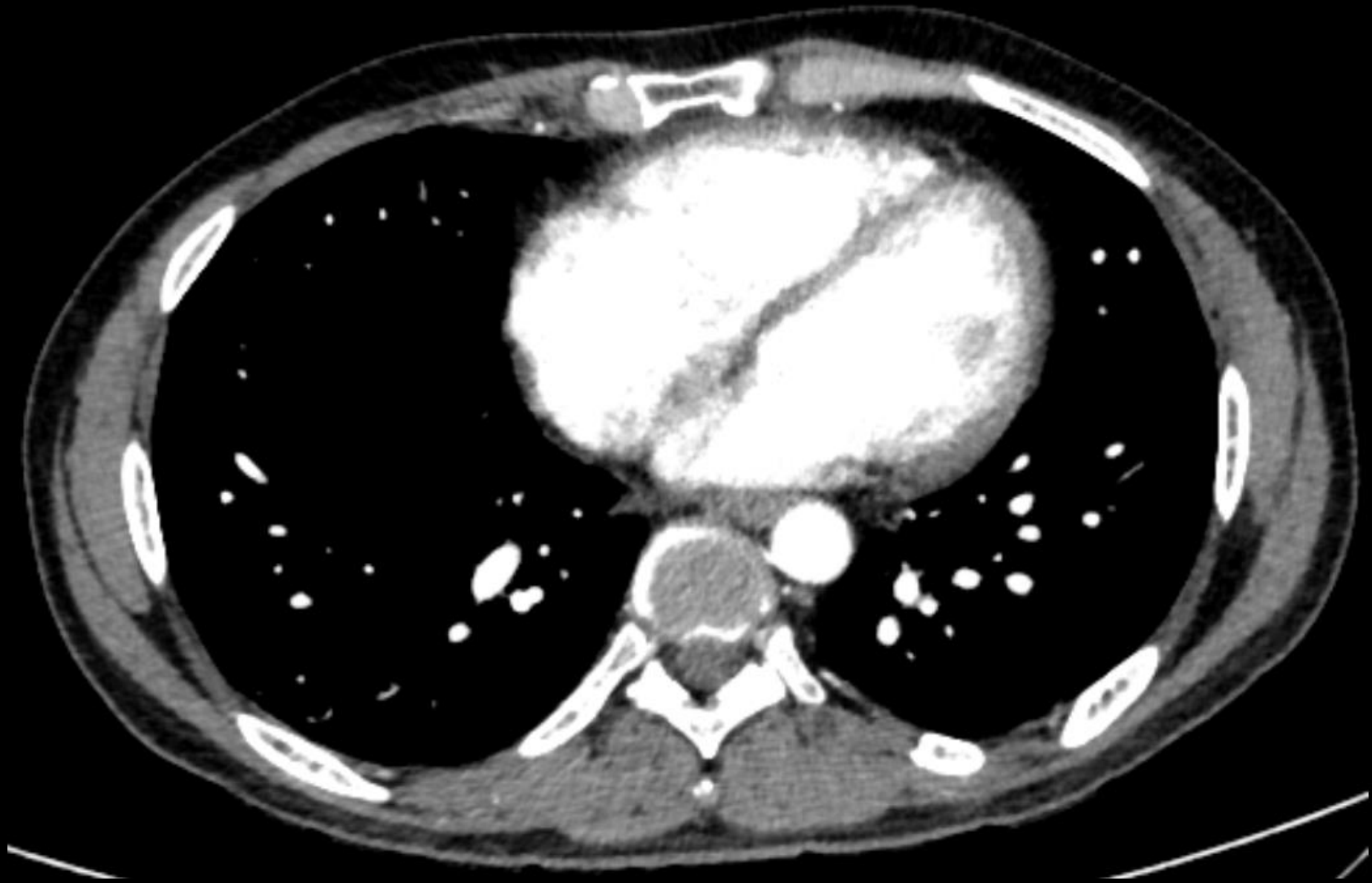




Right Heart Catheterization

	2016	2017	2019	
RAP	2	4	2	mmHg
PAP	66/29/41	63/29/40	57/22/34	mmHg (S/D/M)
PAWP	4	7	5	mmHg
CO	4,4	6,4	6,2	l/min
CI	2,6	3,7	3,6	l/min/m²
PVR	8,4	5,1	4,7	Wood Units
SvO2	77	77	79	%

Test αγγειοδραστικότητας με ενδοφλέβια εποπροστενόλη: αρνητικό



Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

ESC/ERS PH guidelines 2015

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

ESC/ERS PH guidelines 2015

Risk assessment in pulmonary arterial hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

PH guidelines 2015

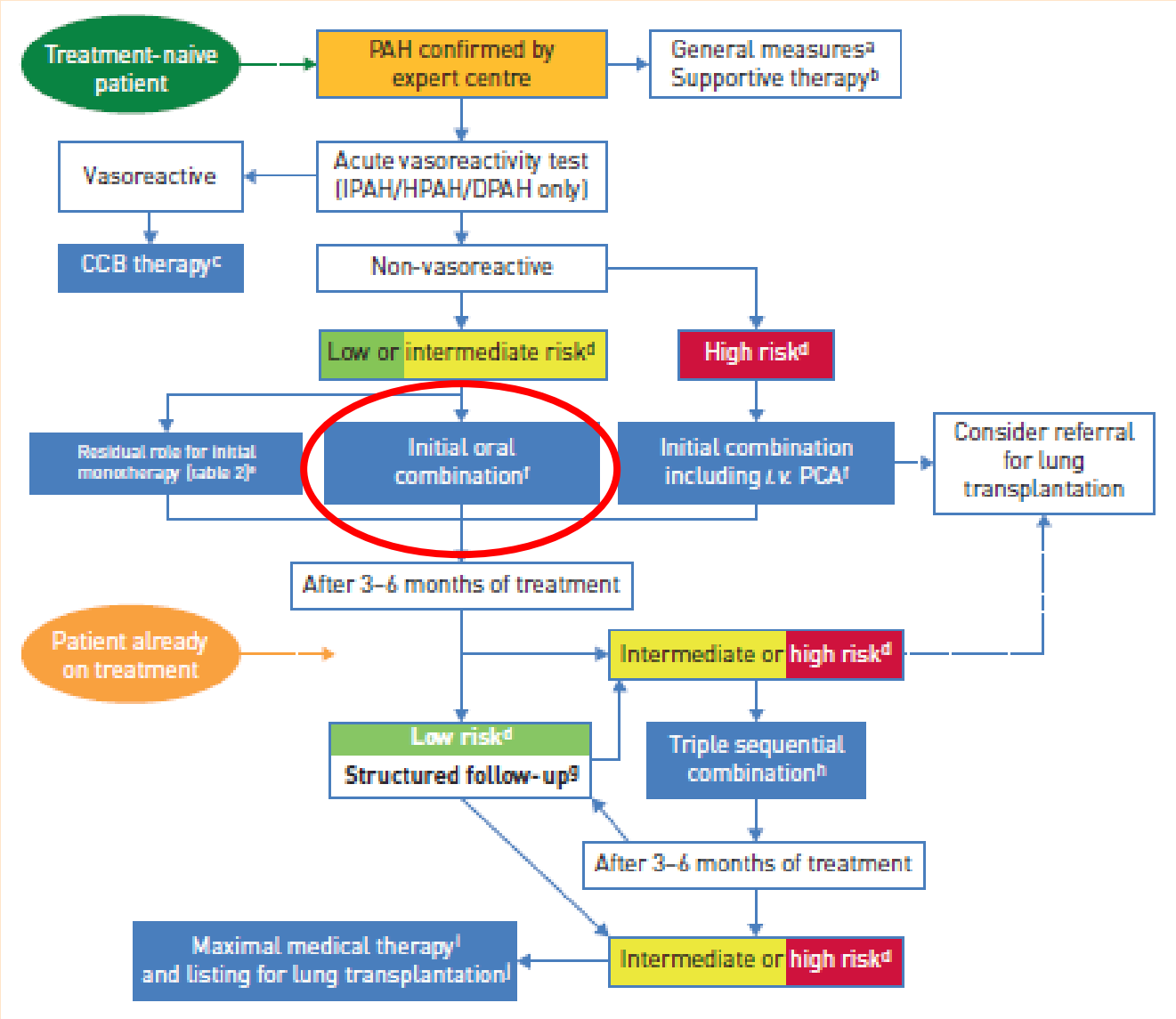
Η αρχική θεραπευτική προσέγγιση στη πλειοψηφία των ασθενών με πνευμονική αρτηριακή υπέρταση ειναι:

1. **Μονοθεραπεία με ERA**
2. **Μονοθεραπεία με PDE-5i/sGC stimulator**
3. **Συνδυαστική θεραπεία με ERA και PDE-5i/sGC stimulator**
4. **Συνδυαστική θεραπεία που περιλαμβάνει I.V. προστανοειδή**

Η αρχική θεραπευτική προσέγγιση στη πλειοψηφία των ασθενών με πνευμονική αρτηριακή υπέρταση ειναι:

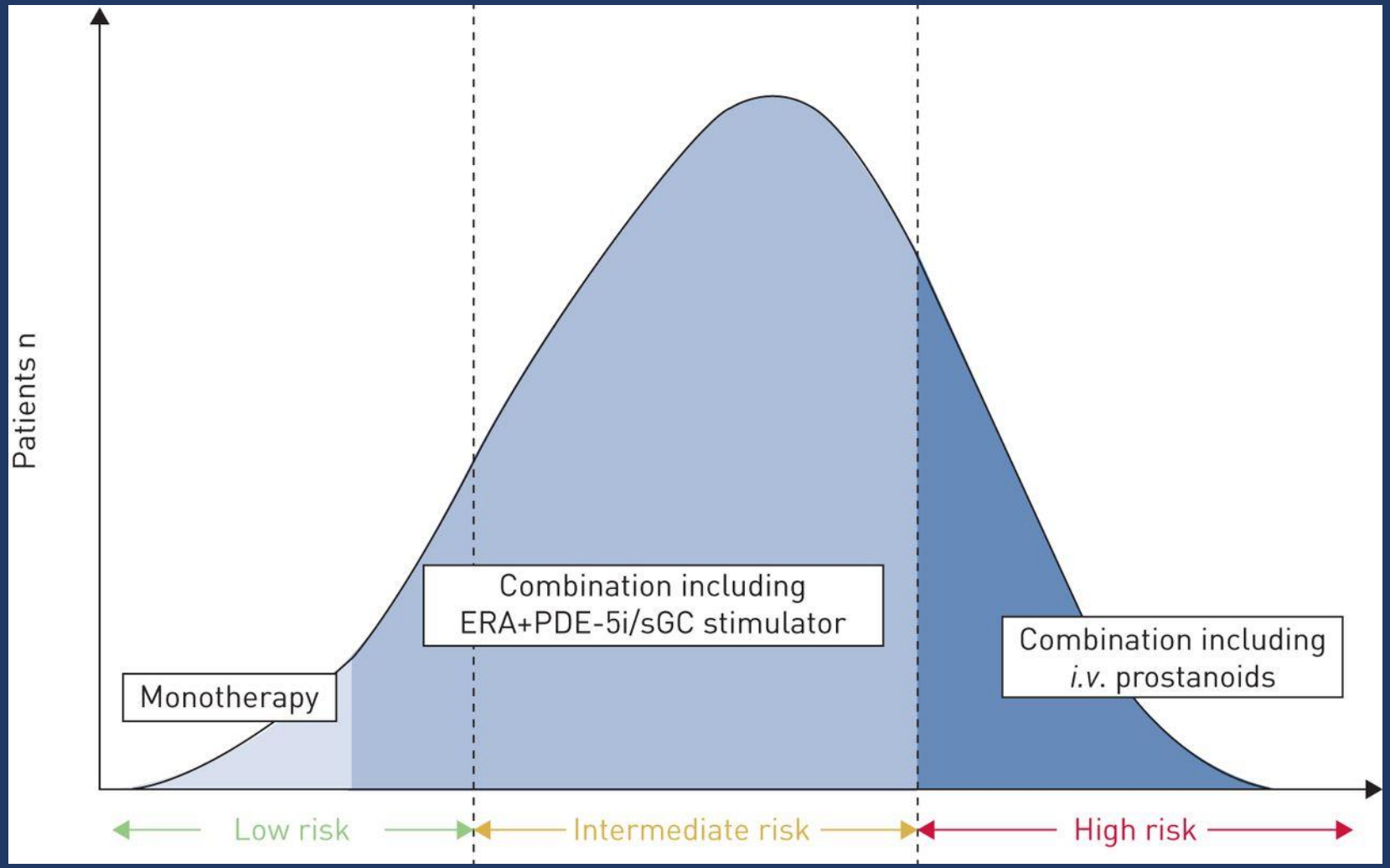
1. **Μονοθεραπεία με ERA**
2. **Μονοθεραπεία με PDE-5i/sGC stimulator**
3. **Συνδυαστική θεραπεία με ERA και PDE-5i/sGC stimulator**
4. **Συνδυαστική θεραπεία που περιλαμβάνει I.V. προστανοειδή**

Treatment algorithm for PAH patients



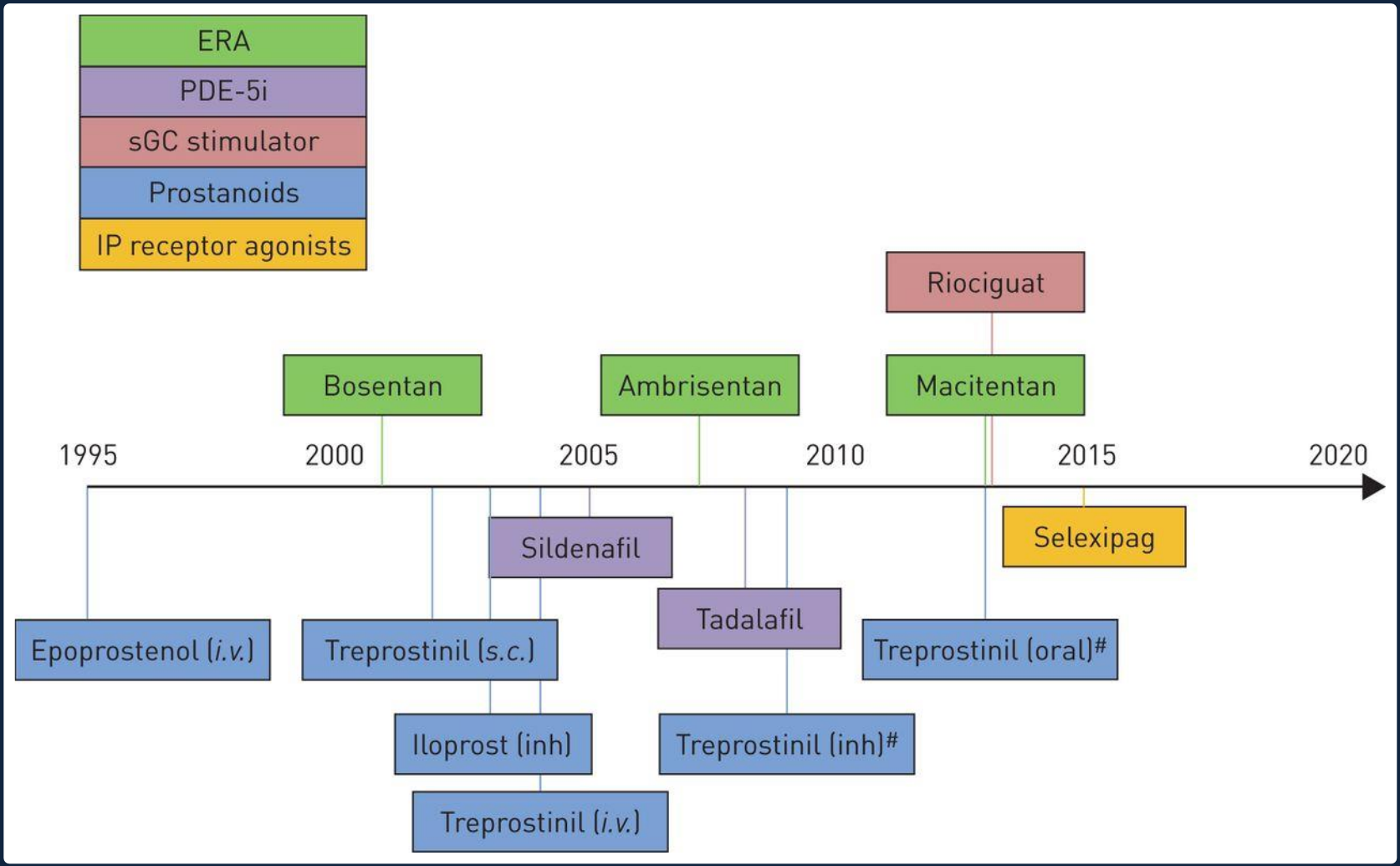
"Proceedings of the 6th World Symposium on PH" *Eur Respir J* 2018

Initial management of pulmonary arterial hypertension in the current era



Sean Gaine & Vallerie McLaughlin Eur Respir Rev 2017

Timeline of approval of therapies for pulmonary arterial hypertension



Sean Gaine & Vallerie McLaughlin Eur Respir Rev 2017

Evolution of treatment strategies