Upfront combination therapy or sequential step-wise therapy?

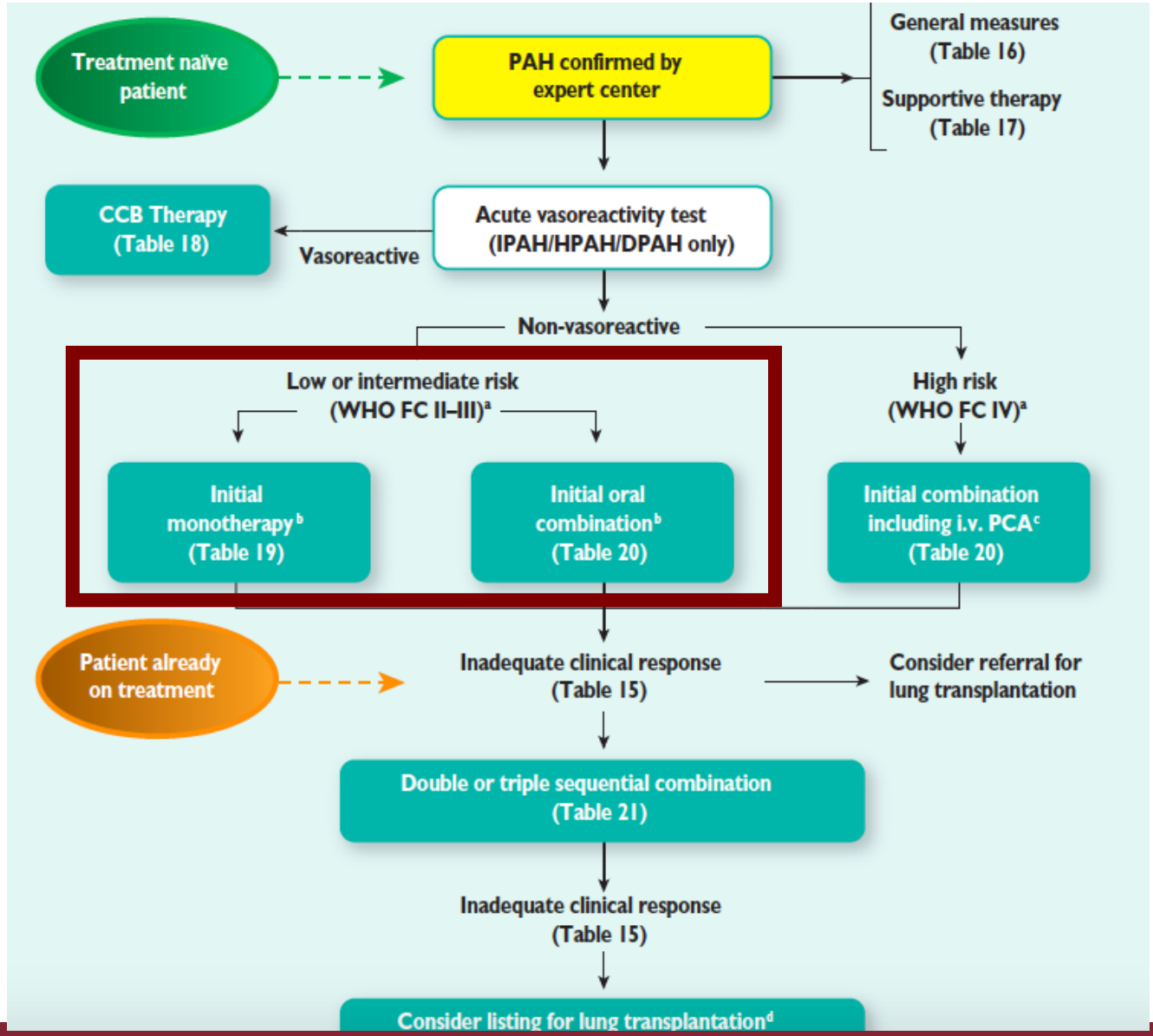
Carmine Dario Vizza
Pulmonary Hypertension Unit
“Sapienza” Universita’ di Roma
Dario.vizza@uniroma1.it

Disclosure

I have received fees for serving as a speaker, consultant and advisory board member from the following:

- Actelion
- Bayer
- Dompè
- GSK
- Italfarmaco
- Lilly
- Mochida
- Pfizer
- United Therapeutics
- Galenica

Treatment algorithm 2015



Therapeutic goal

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%

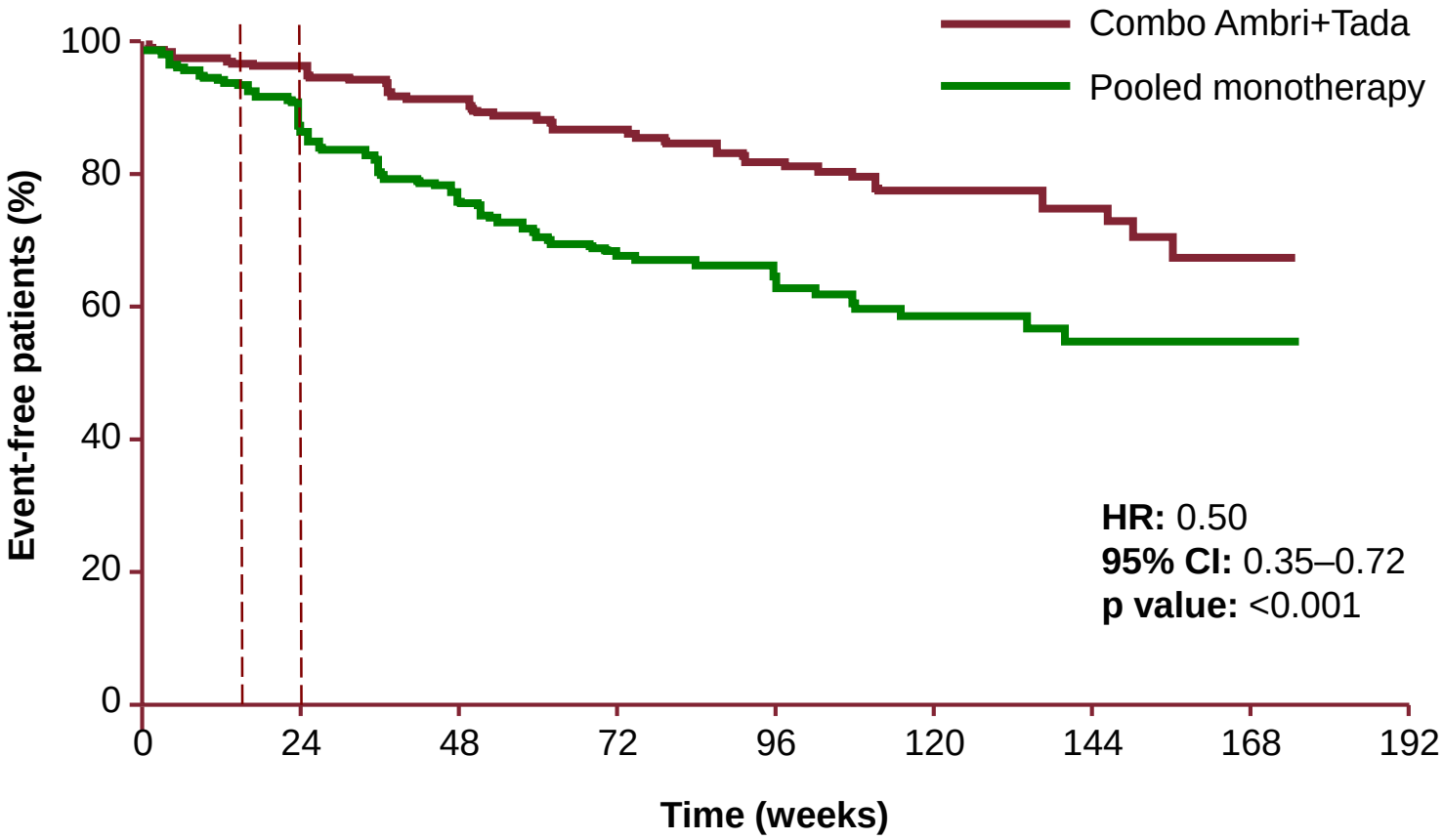
The big question in low-moderate risk naive PAH patients

- Sequential oral combination therapy ?

or

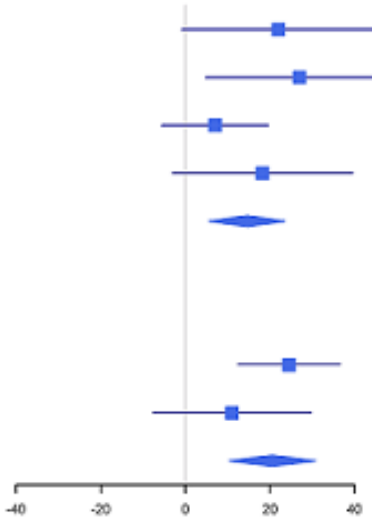
- Up-front oral combination therapy ?

Clinical worsening mono vs combo upfront



The impact of delayed treatment on 6-minute walk distance : a meta-analysis

Study	Active N	Active Mean	Active SD	Ex-Placebo N	Ex-Placebo Mean	Ex-Placebo SD	Mean Difference	95%-CI
Subset 1: Change in 6MWD								
BREATHE OLE	133	41.0	71.6	61	19.0	77.5	22.0	[-0.9; 44.9]
ARIES OLE	261	38.0	96.9	132	11.0	110.3	27.0	[4.8; 49.2]
PATENT-2	231	53.0	70.0	109	46.0	47.0	7.0	[-5.6; 19.6]
PHIRST-2	110	53.8	61.5	59	35.6	70.1	18.2	[-3.1; 39.5]
Fixed effect model	**735**			**361**			**14.6**	**[5.6; 23.5]**
Subset 2: Change in 6MWD								
FREEDOM OLE	348	34.8	77.2	221	10.3	67.8	24.5	[12.4; 36.6]
TRIUMPH OLE	74	37.4	55.9	77	26.4	61.3	11.0	[-7.7; 29.7]
Fixed effect model	**422**			**298**			**20.5**	**[10.4; 30.7]**



Vizza CD, Badagliacca R, et al Int J Cardiol. 2018;254:299-301.

The big question in PAH …

- Sequential oral combination therapy ?

or

- Up-front oral combination therapy ?

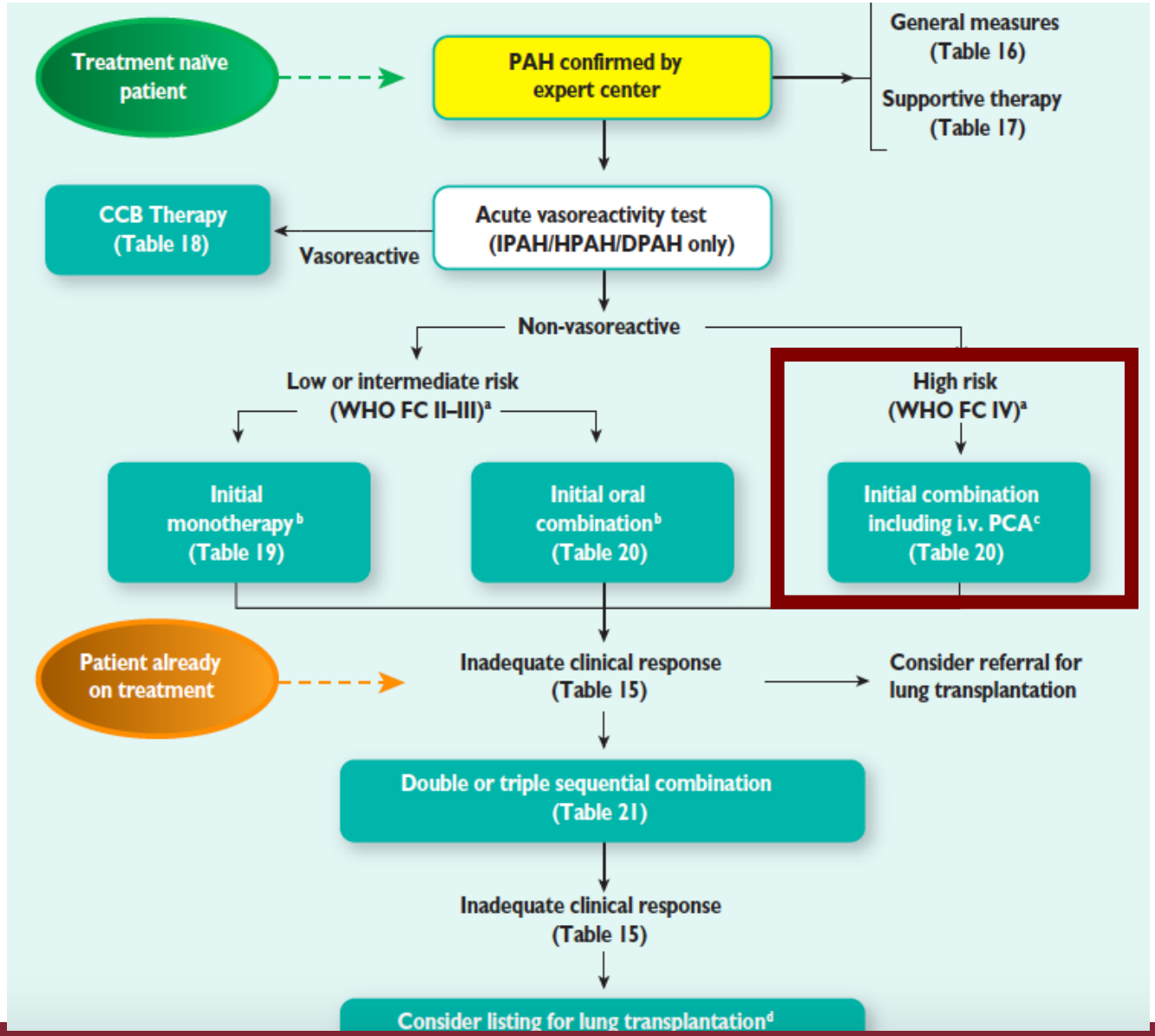
Oral up-front is better in the most of the patients!

Ambrisentan+Tadalafil is the only oral upfront with a dedicated study

Initial combination therapy: ESC/ERS Guidelines 2015

Measure/ treatment	Class[a]-Level[b]					
	WHO-FC I		WHO-FC III		WHO-FC IV	
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C

Treatment algorithm 2015



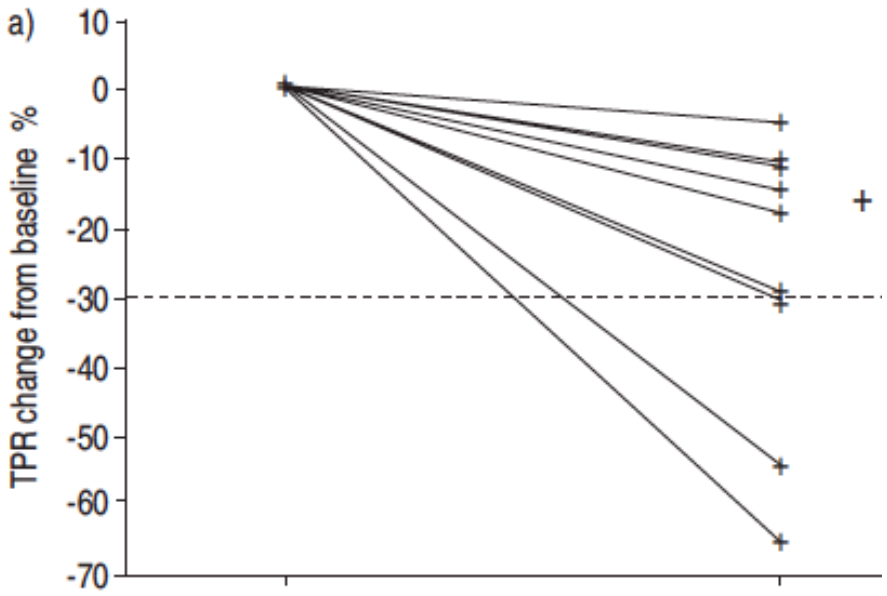
Upfront combination therapy: Bosentan + Epoprostenol

Characteristic	Placebo/epoprostenol	Bosentan/epoprostenol
Subjects n	11	22
M:F	5 (45):6 (55)	5 (23):17 (77)
Age yrs	47±19 (15–68)	45±17 (16–69)
Weight kg	78±16 (53–103)	70±21 (40–109)
Ethnic group		
Caucasian/White	10 (91)	18 (82)
Black	1 (9)	1 (5)
Asian		1 (5)
Other		2 (9)
Aetiology of PAH		
Primary	10 (91)	17 (77)
Scleroderma	1 (9)	4(18)
Systemic lupus erythematosus		1 (5)
Modified NYHA functional class		
III	8 (73)	17 (77)
IV	3 (27)	5 (23)
Clinical signs of heart failure	4 (36)	10 (45)
Concomitant PAH medications (only when >4 in at least one group)		
Antithrombotic agents	10 (91)	19 (86)
High-ceiling diuretics	10 (91)	19 (86)
Potassium sparing agents	5 (45)	14 (64)
Cardiac glycosides	2 (18)	7 (32)
Calcium channel blockers	3 (27)	6 (27)
Use of supplemental oxygen	4 (36)	6 (27)
Time since diagnosis months	15±21 (1–61)	13±30 (1–138)

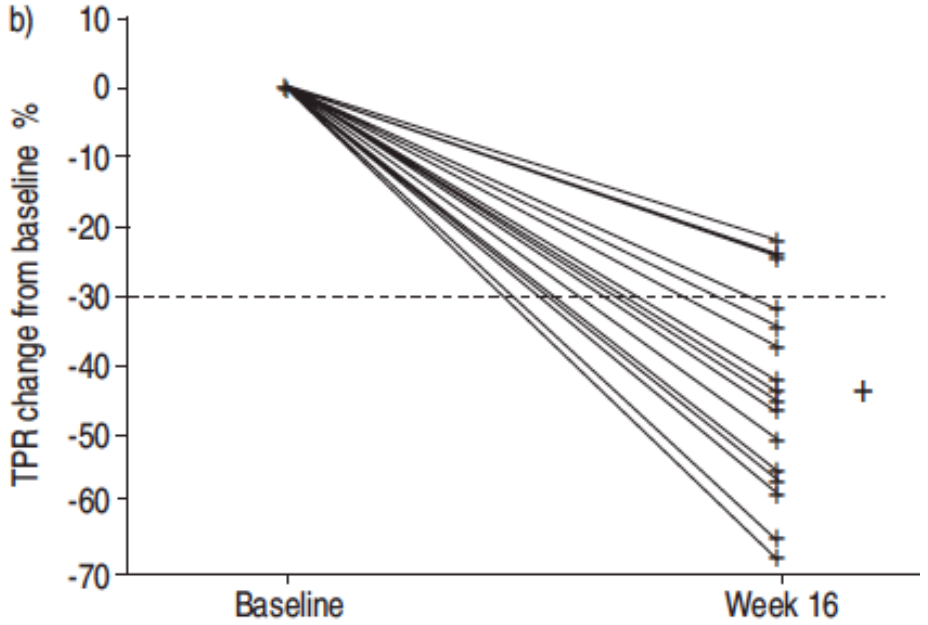
Humbert M. Eur Respir J 2004; 24: 353–359

Upfront combination therapy: Bosentan + Epoprostenol

Epoprostenol



Epoprostenol + Bosentan

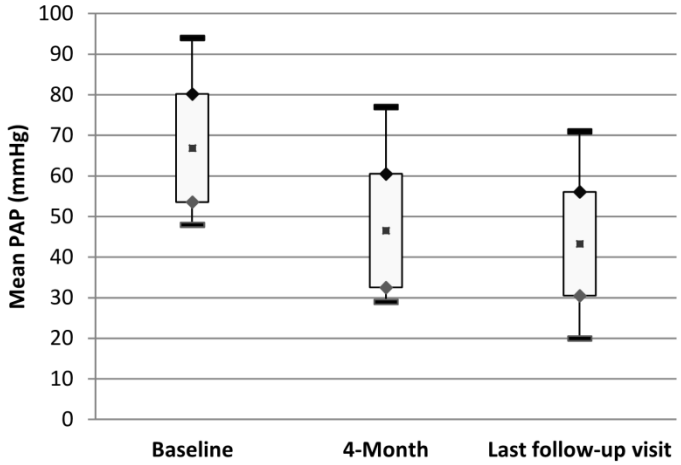


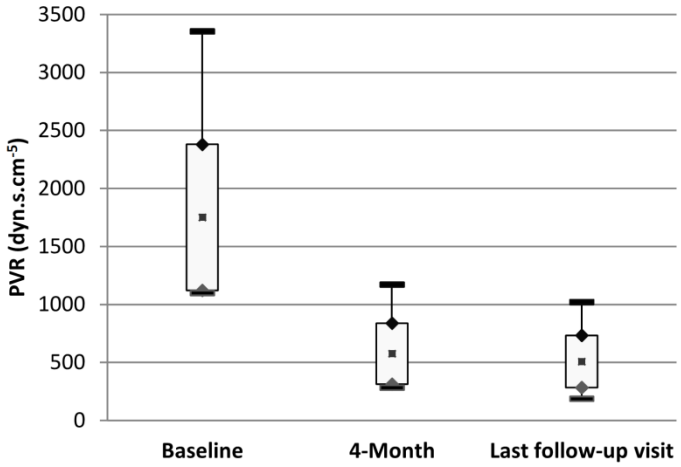
Eur Respir J 2004; 24: 353–359.

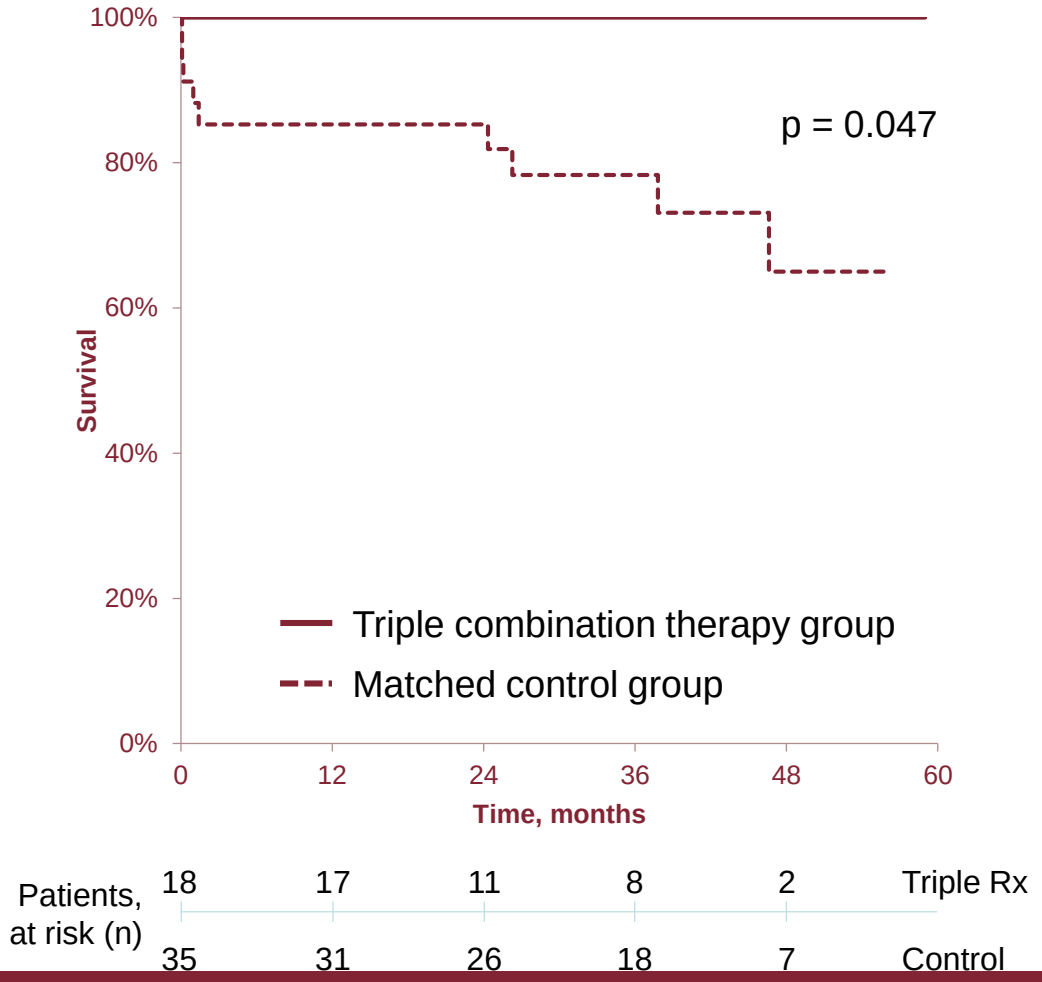
Upfront triple combination therapy: bosentan + epoprostenol + sildenafil

Subjects	19
Age years (range)	39.4±14.2 (18.1–63.1)
Females	17 (89)
Idiopathic/heritable/anorexigen-associated PAH	9/10/0
***BMPR2* mutation carrier n/n tested (%)**	10/13 (77)
NYHA functional class III/IV	8 (42)/11 (58)
6-min walk distance m	215±174
Haemodynamics	
Right atrial pressure mmHg	12.2±5.2
Mean pulmonary arterial pressure mmHg	67.7±15.8
Pulmonary capillary wedge pressure mmHg	8.3±3.4
Cardiac output $L \cdot min^{-1}$	2.83±0.77
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	1.64±0.34
Pulmonary vascular resistance $dyn \cdot s \cdot cm^{-5}$	1807±722
Mean blood pressure mmHg	91.7±12.2
Heart rate beats per min	92.3±10.7
Mixed venous oxygen saturation %	50.1±9.0

Upfront triple combination therapy in IPAH







Article in Press

Risk Reduction and Right Heart Reverse Remodeling by Upfront Triple Combination Therapy in Pulmonary Arterial Hypertension

Michele D'Alto, MD, PhD[a,*], Roberto Badagliacca, MD, PhD[b], Paola Argiento, MD, PhD[a], Emanuele Romeo, MD, PhD[a], Andrea Farro, MD[a], Silvia Papa, MD[b], Berardo Sarubbi, MD, PhD[a], Maria Giovanna Russo, MD[a], Carmine Dario Vizza, MD, PhD[b], Paolo Golino, MD, PhD[a], Robert Naeije, MD, PhD[c]

DOI: https://doi.org/10.1016/j.chest.2019.09.009

CHEST JOURNAL
OFFICIAL PUBLICATION OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

Impact of long-term triple upfront combination therapy on Hemodynamics an Right heart

	Baseline	Follow-up	Change (%)	*p*
RAP (mmHg)	13±3	5±2	-8 (-62)	<0.001
mPAP (mmHg)	60±9	42±5	-18 (-30)	<0.001
PAWP (mmHg)	8±2	9±3	1 (+12)	0.545
CI (L/min/m^2)	1.8±0.3	3.5±0.8	+1.7 (+94)	<0.001
PVR (WU)	16.4±4.4	5.5±1.3	-10.9 (-69)	<0.001
SvO_2 (%)	56±6	70±7	+14 (+25)	<0.001

	Baseline	Follow-up	Change (%)	*p*
Right atrial area (cm^2)	29±3	21±2	-8 (-28)	<0.001
RV end-diastolic area (cm^2)	28±2	20±3	-8 (-29)	<0.001
RV end-systolic area (cm^2)	21±2	12±2	-9 (-43)	<0.001
Fractional area change (%)	27±4	40±5	+13 (+63)	<0.001
LV eccentricity index	1.5±0.1	1.2±0.1	-0.3 (-20)	<0.001

D'Alto M. *et al.* CHEST in press

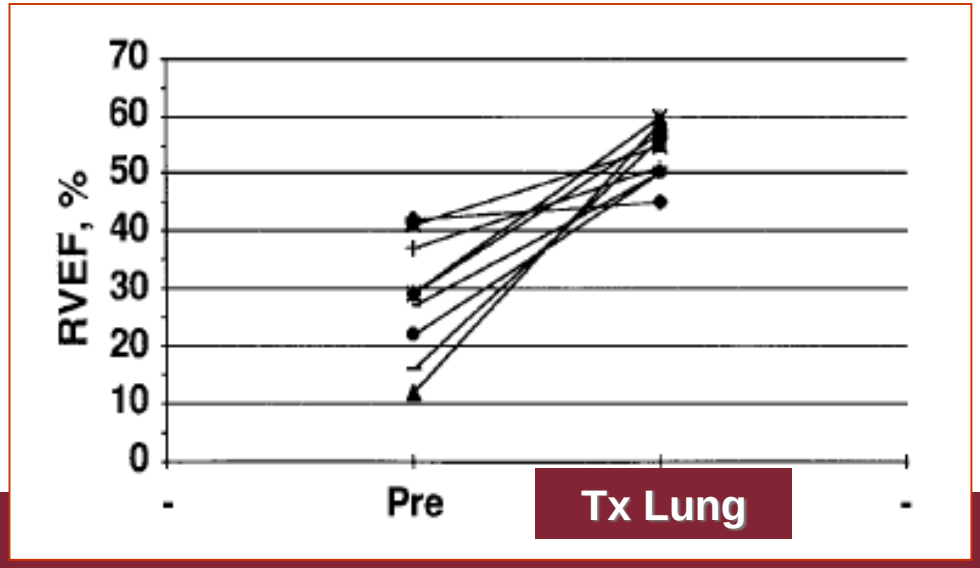
Probably we should change our minds and start to think to the core of the problem….

The right ventricle
The pulmonary vascular resistance
The pulmonary pressure

Pathophysiology of RV dysfunction in PH

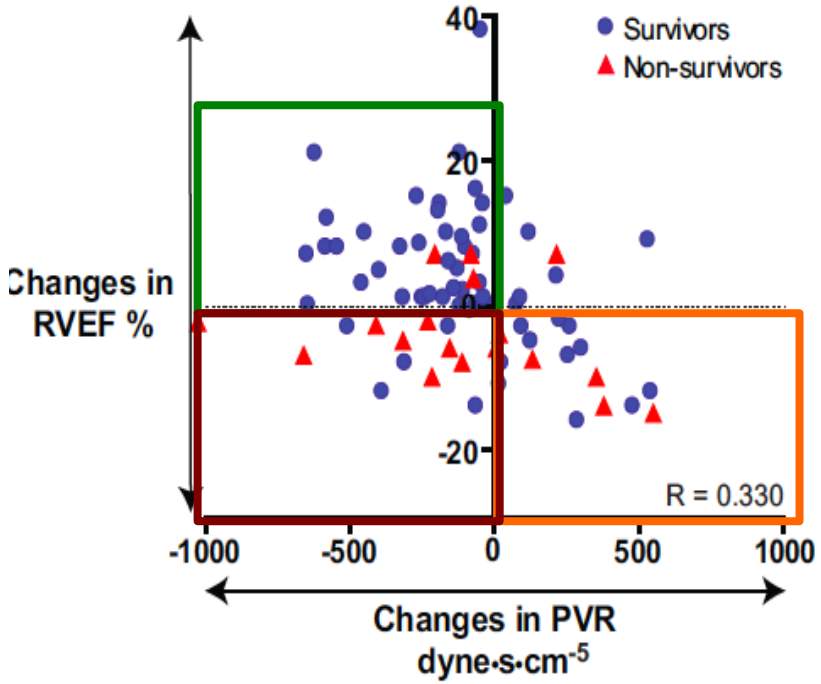
Afterload mismatch

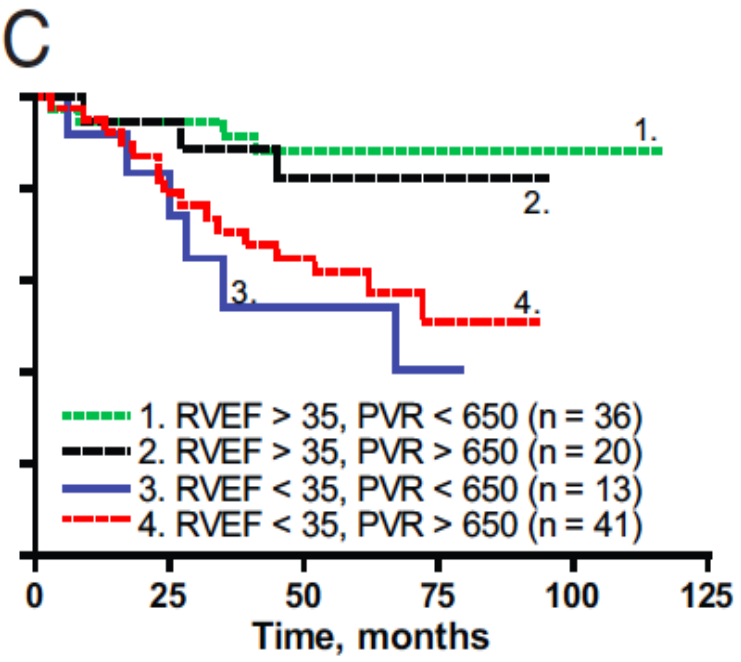
- RV contractility is increased, but not enough compared to the afterload
- PVR could be considered an approximation of RV afterload
- If you normalize the afterload, the RV should recover



Vizza, Chest 1998

Impact of RV EF and PVR changes after therapy





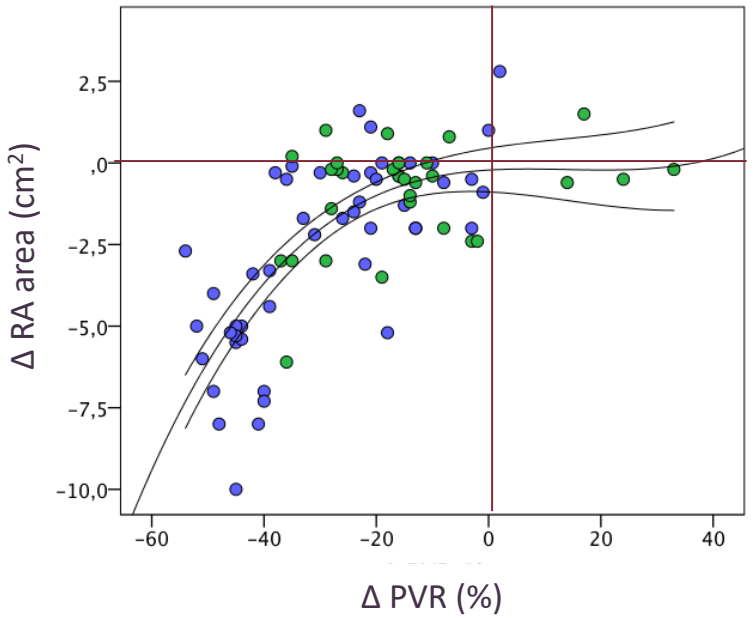
- Significant PVR reduction in order to obtain RVEF improvement
- In a subgroup RVEF drops despite PVR reduction (myocardial damage)

van de Veerdonk M. J Am Coll Cardiol 2011;58:2511–9

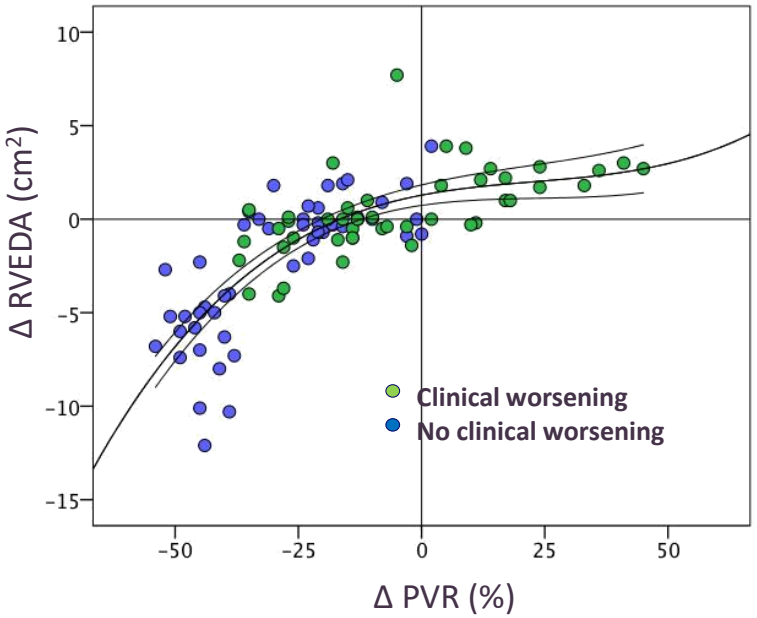
Reverse remodeling and RV afterload

- 102 IPAH treatment-naïve patients, evaluated by echo and hemodynamics at baseline and after 1 year of treatment

Relationship between changes in RA area and PVR at 1 year



Relationship between changes in RVEDA and PVR at 1 year



RVEDA, right ventricular end-diastolic area. RA area, right atrial area.

Badagliacca R ... Vizza CD. *J Heart Lung Transplant.* 2018;37:195–205.

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension

Roberto Badagliacca, MD, PhD,[a] Amresh Raina, MD,[b] Stefano Ghio, MD,[c] Michele D'Alto, MD,[d] Marco Confalonieri, MD,[e] Michele Correale, MD,[f] Marco Corda, MD,[g] Giuseppe Paciocco, MD,[h] Carlo Lombardi, MD,[i] Massimiliano Mulè, MD,[j] Roberto Poscia, MD,[a] Laura Scelsi, MD,[c] Paola Argiento, MD,[d] Susanna Sciomer, MD,[a] Raymond L. Benza, MD,[b] and Carmine Dario Vizza, MD[a]

Strategies and treatment response

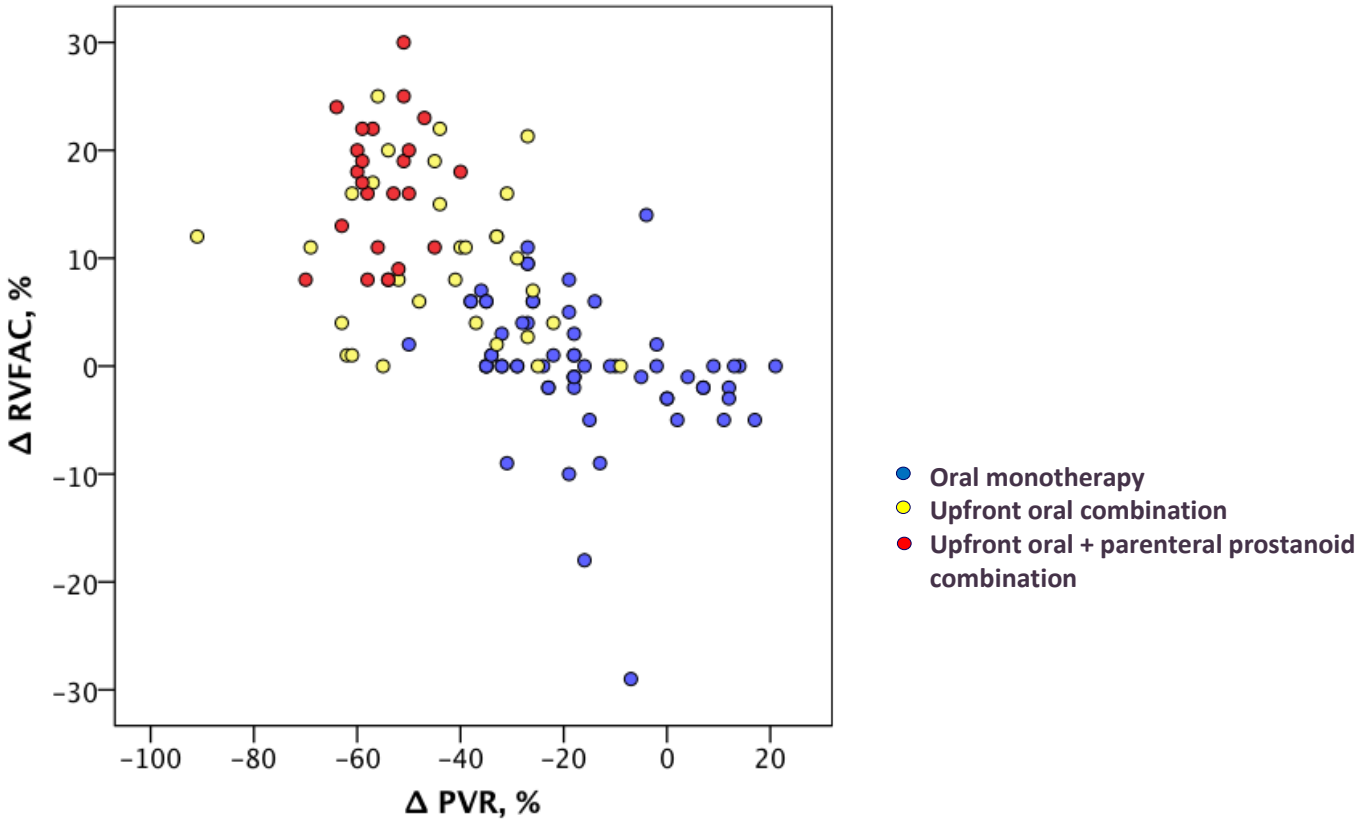
naive IPAH: 4 matched groups

Trieste, Pavia, Brescia, Monza, Roma, Cagliari, Napoli, Foggia, Catania … and Pittsburgh

enrolled between 2011 and 2015

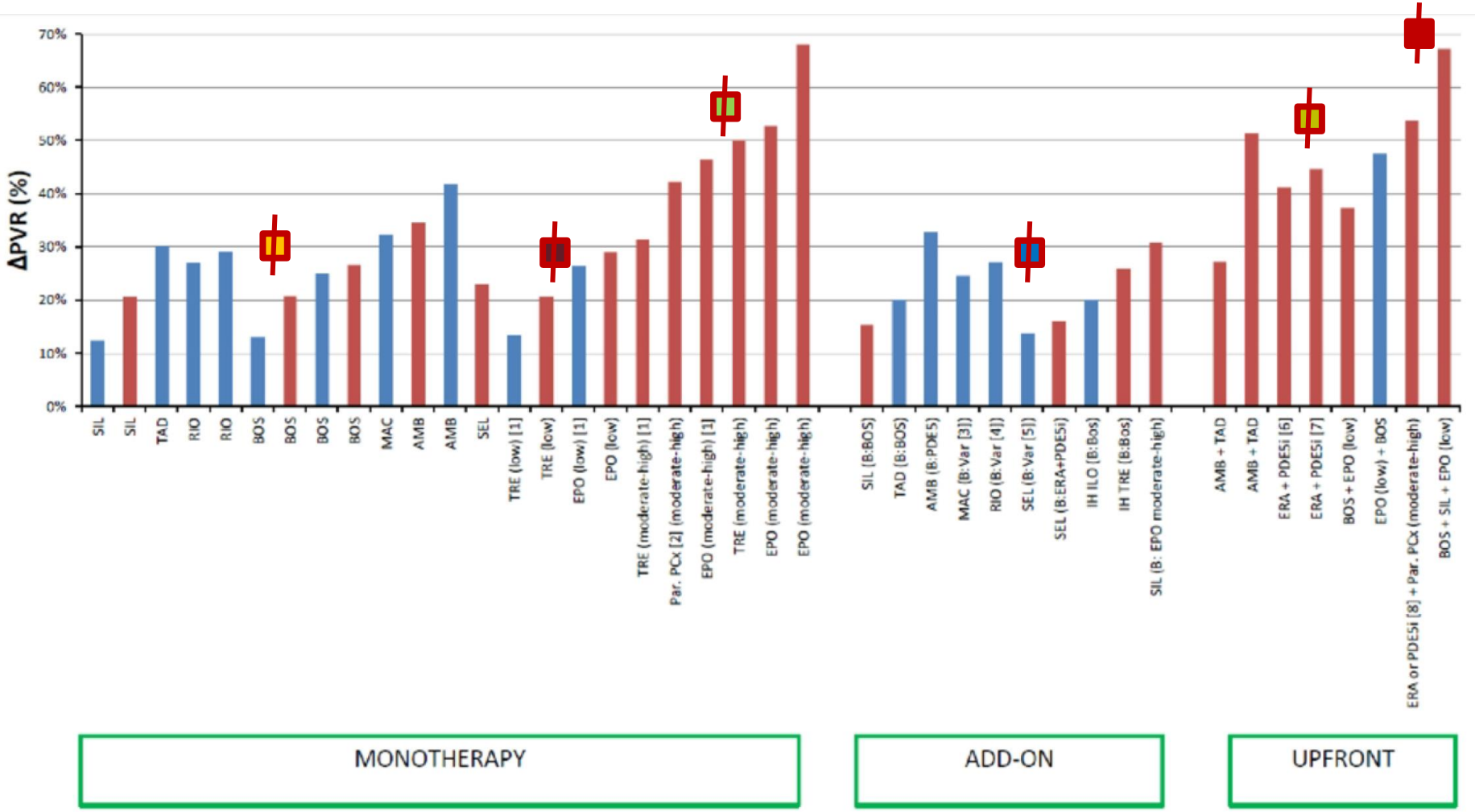
	Upfront therapy		Monotherapy		
	Prosta+oral Group 1 ($n = 27$)	Double oral Group 2 ($n = 42$)	Mono oral Group 3 ($n = 69$)	Mono prosta Group 4 ($n = 27$)	p
Age (years)	53 ± 18	55 ± 14	54 ± 13	54 ± 15	NS
Gender (F:M)	18:9	26:16	42:27	16:11	NS
Height (cm)	163 ± 9	164 ± 11	165 ± 10	166 ± 9	NS
Weight (kg)	68 ± 14	72 ± 15	71 ± 18	68 ± 13	NS
Time symptoms—diagnosis[a]	8.1 ± 4.9	8.0 ± 7.5	10.1 ± 7.4	9.4 ± 3.4	NS
WHO	3.2 ± 0.4	3.1 ± 0.4	3.0 ± 0.6	3.2 ± 0.4	NS
6MWT (m)	306 ± 88	314 ± 104	321 ± 103	322 ± 78	NS
Hemodynamics					
RAP (mm Hg)	10.4 ± 2.2	9.4 ± 4.7	9.1 ± 4.5	9.7 ± 3.6	NS
mPAP (mm Hg)	54.4 ± 11	52.5 ± 9.6	54 ± 13.3	55.4 ± 11.7	NS
CI (l/min/m^2)	2.1 ± 0.5	2.2 ± 0.6	2.2 ± 0.5	2.2 ± 0.5	NS
PVR (WU)	13.4 ± 4.2	12.4 ± 5.9	12.0 ± 5.5	12.8 ± 4.1	NS
Echocardiography					
RVEDA (cm^2	26.6 ± 3.7	27.8 ± 4.4	29.2 ± 6.6	28.6 ± 4.2	NS
RVESA (cm^2	19.0 ± 2.6	20.0 ± 3.6	20.4 ± 5.8	19.9 ± 3.9	NS
RVFAC (%)	28.0 ± 6.8	27.6 ± 7.8	30.3 ± 9.6	30.3 ± 9.2	NS
TAPSE (mm)	15.6 ± 2.4	15.8 ± 4.1	16.4 ± 4.0	16.1 ± 3.5	NS
RA area (cm^2)	27.9 ± 4.5	24.8 ± 7.1	27.6 ± 10	24.9 ± 8.4	NS

Impact of different therapeutic strategies on PVR changes and RVFAC



Badagliacca R, iPHNET, J Heart Lung Transplant. 2018;37:365-375

Effect of various therapeutic strategies on PVR



Badagliacca R, … Vizza CD Int J Cardiol. In press

Is it possibile to normalize the mPAP ?

Up to now we do not have information if :

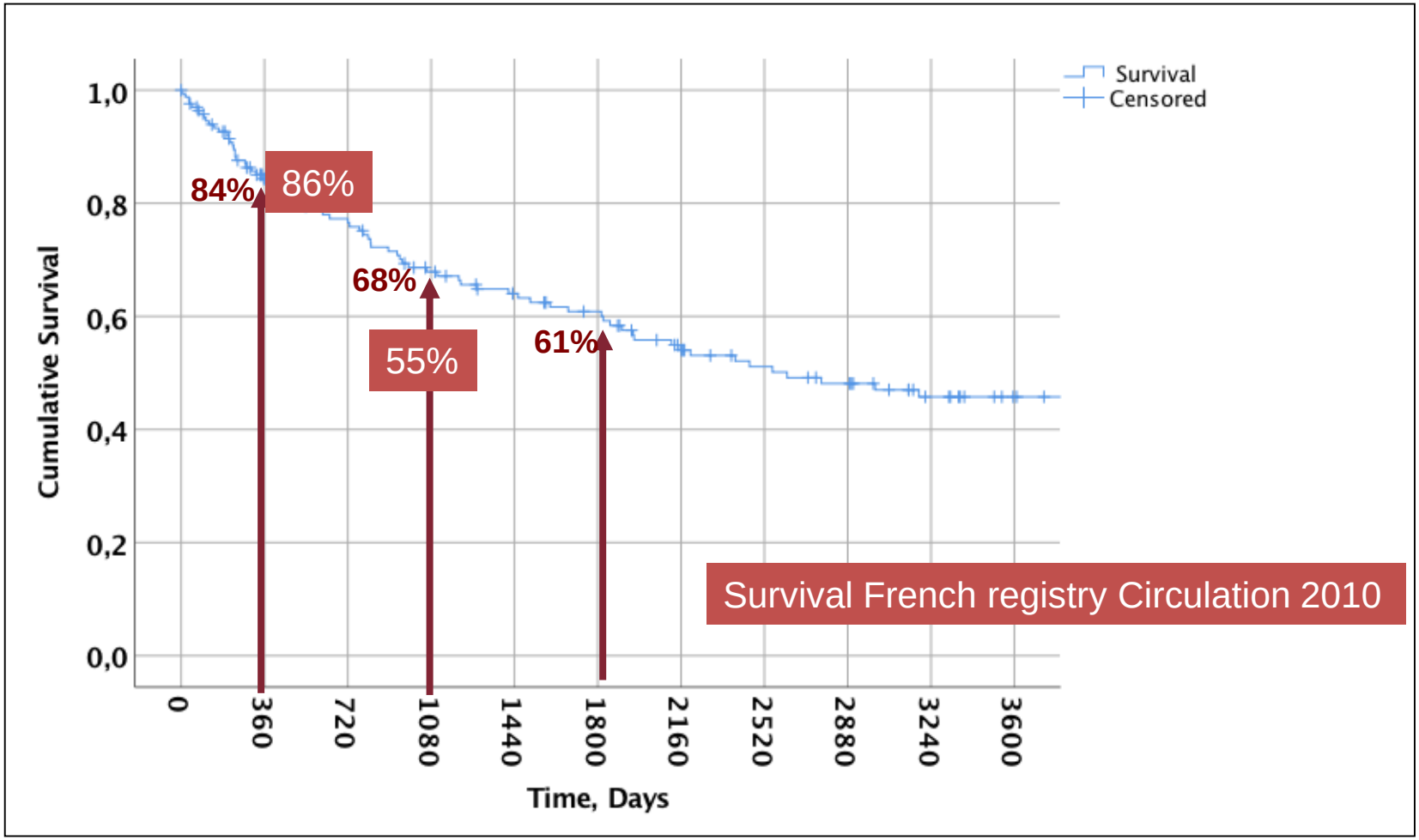
-It is possible to obtain a PAPm near-normalization (<30 mmHg) after treatment

-Which is the prognostic impact

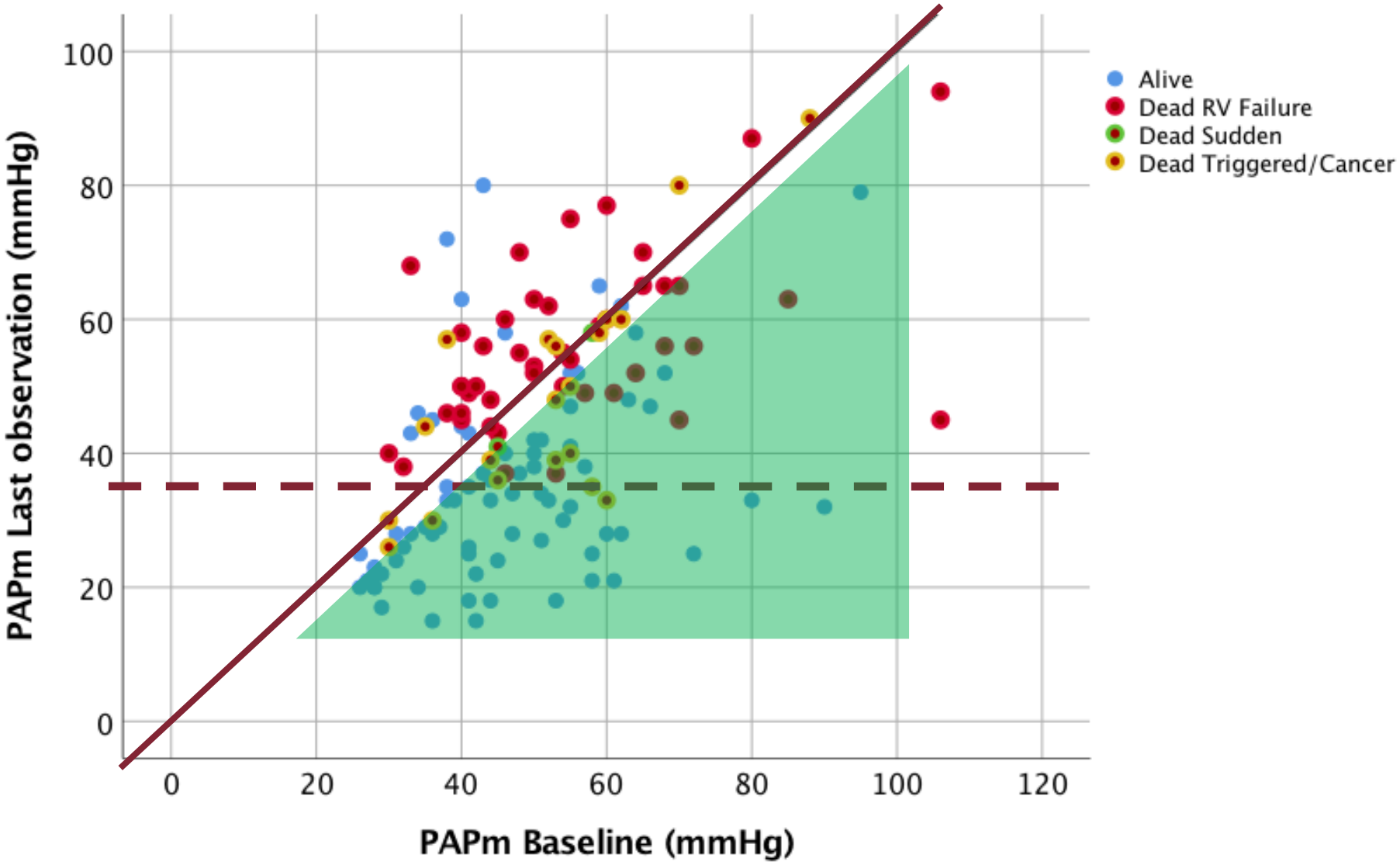
Population

Patients, n	153
Age, years	54±21
Gender F:M	101:52
Weight, Kg	70±17
Height, cm	164±25
PAH I/F/A	147/3/3
WHO FC Class	
II	66 (43)
III	81 (53%)
IV	6 (4%)
6MWT, m	403±101
Hemodynamics	
RAP, mmHg	8.5± 4.7
mPAP, mmHg	49.5±15
PWP, mmHg	10± 5
CI, l/min/m2	2.3±0.8
PVR, WU	11±6.5

Overall survival



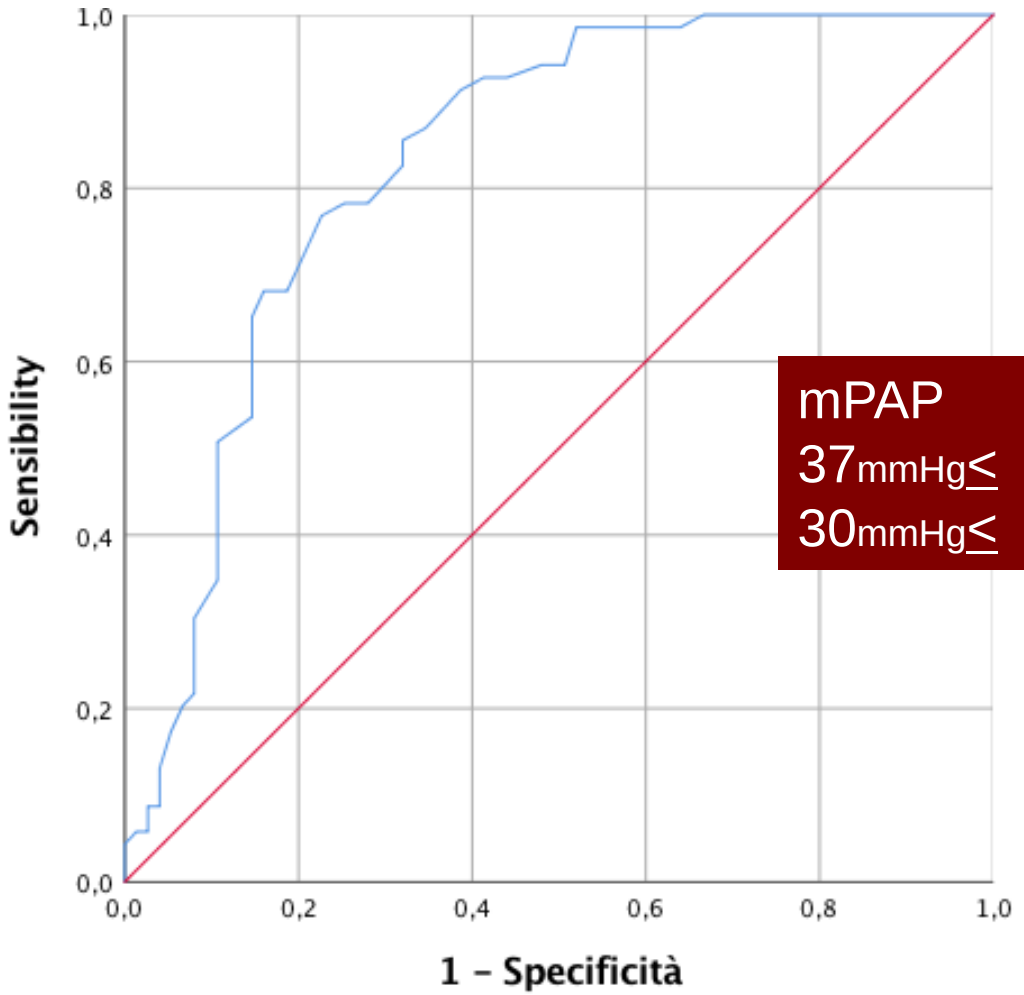
Relationship between mPAP at baseline and last observation and survival status



Derteminants of PAPm normalization

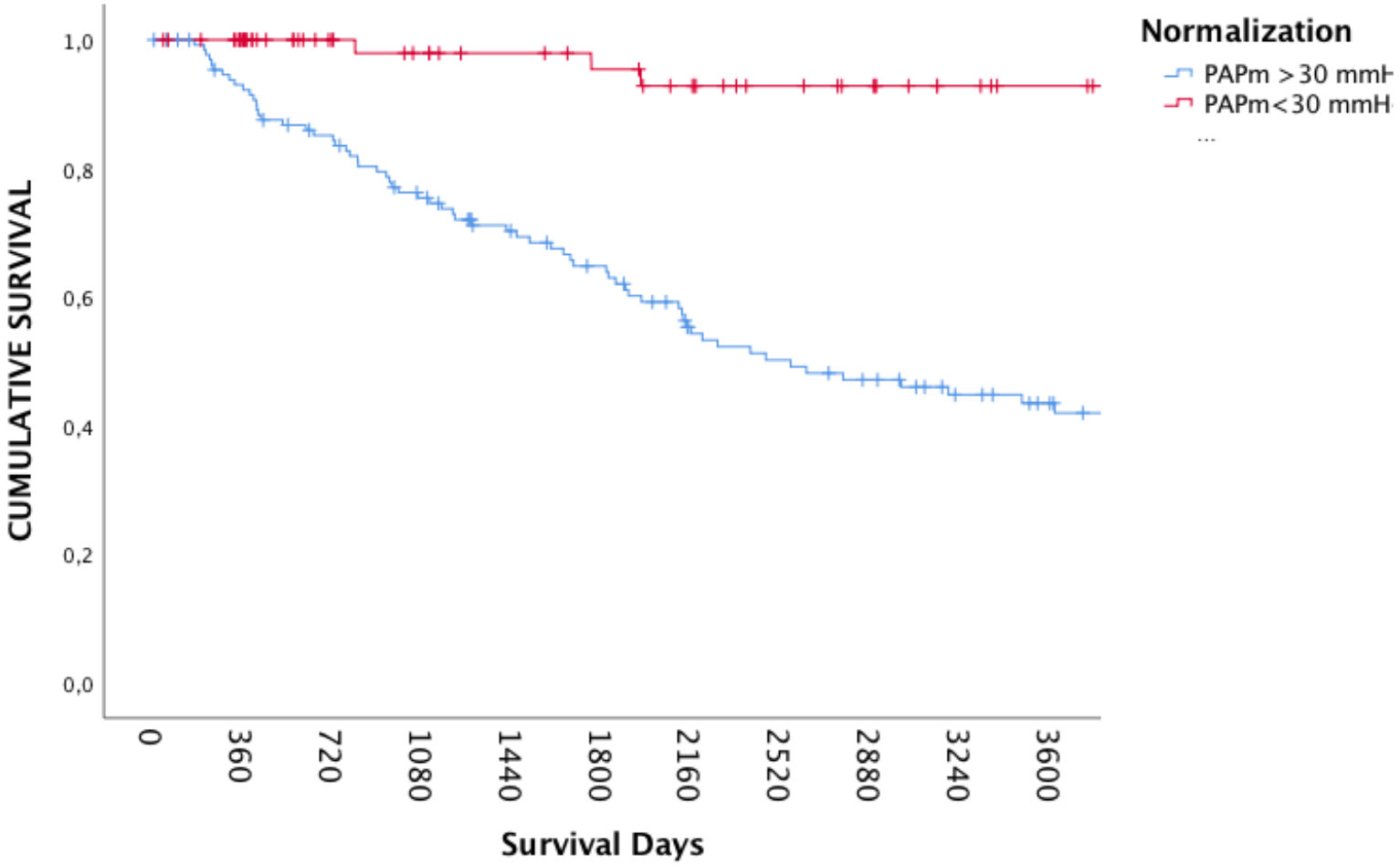
	B	S.E.	Wald	p	Exp(B)	95% C.I.	
						Inferior	Superior
PAPm	-,069	,014	24,3	,000	,933	,91	,96
Therapy			21,2	,000			
Combo oral	,610	,457	1,78	,182	1,841	,75	4,5
Prosta Mono	-,880	,806	1,19	,275	,415	,085	2,013
Prosta+Oral	2,079	,642	10,4	,001	7,996	2,270	28,160
Triple	2,495	,735	11,5	,001	12,128	2,873	51,189

mPAP cut-off value at last observation in predicting survival



mPAP	Sens	Spec
37mmHg≤	87%	65%
30mmHg≤	98%	44%

Survival stratified by near-normalization mPAP



Key points

- Up-front combination therapy should be the preferred treatment in most of the patients

- Oral combo should be considered in stable intermediate risk patients

- Oral+parenteral prostanoid should be considered in more advanced patients

Food for thoughts

- Should we adapt our therapeutic approach on the basis of RV changes ?

- Should we treat our patients with the goal of almost normalization of the mPAP ?