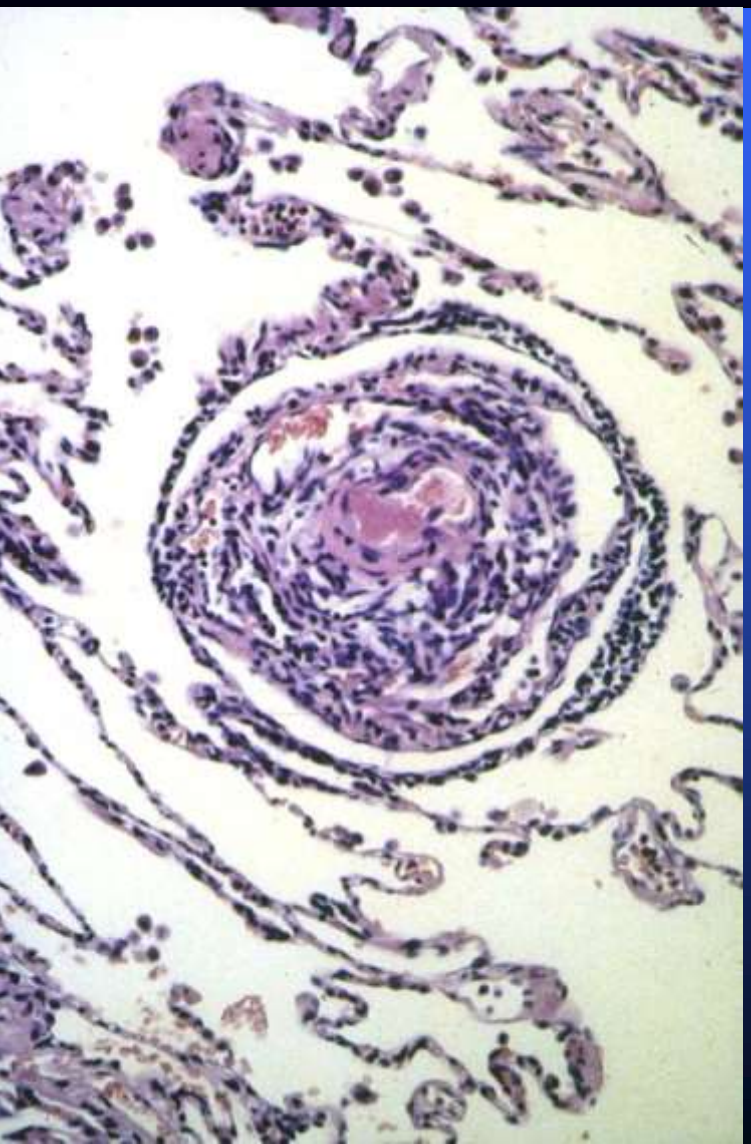
Ipertensione Polmonare: Novità Classificative e Terapeutiche



PneumoTrieste 2014

Trieste Aprile 2014

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Definitions and diagnosis of PH

A new hemodynamic definition of PAH

- **PAH is defined as the presence of pre-capillary PH including an end-expiratory PAWP ≤ 15 mmHg and a PVR > 3 Wood units**
- **Patients with mPAP values between 21 and 24 mmHg should be carefully followed, particularly if they are at risk of developing PAH (e.g. CTD patients or family members of IPAH/HPAH patients)**
  - **The term "borderline PH" should not be used**
- **PVR should be included in the hemodynamic characterization of patients with PAH as follows: patients with PAH are characterized by pre-capillary PH (i.e., mPAP ≥ 25 mmHg, PAWP ≤ 15 mm Hg and elevated PVR [> 3 Wood units])**

Hoeper MM, *et al. J Am Coll Cardiol* 2013; 62:D42-50.

Updated clinical classification of PH

Updated classification of PH

Table 1 Updated Classification of Pulmonary Hypertension*

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Updated classification is now the same for adult and pediatric patients

New gene mutations added

PPHN moved from Group 1 (PAH) as has more differences than similarities to other PAH subgroups

Added for consistency with pediatric classification

Chronic hemolytic anemia moved from Group 1 (PAH) given the differences to PAH in pathological findings, hemodynamics and response to therapy

* Main modifications to the previous WSPH proceedings (Dana point) are indicated by green boxes

Simonneau G, *et al. J Am Coll Cardiol* 2013; 62:D34-41.

Updated classification for drug- and toxin-induced PAH

New addition (included as a risk factor in ESC/ERS Guidelines)

Moved from 'possible' to 'definite' risk factor

New addition

New additions

Table 2 Updated Classification for Drug- and Toxin-Induced PAH*

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Interferon α and β
SSRIs†	Amphetamine-like drugs
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-Tryptophan	Estrogen
Methamphetamines	Cigarette smoking
Dasatinib	

* Main modifications to the previous WSPH proceedings (Dana point) are indicated by green boxes

Simonneau G, *et al. J Am Coll Cardiol* 2013; 62:D34-41.

The wording for the classification of PAH-CHD has been modified

Table 3 Updated Clinical Classification of Pulmonary Arterial Hypertension Associated With Congenital Heart Disease*

1. Eisenmenger syndrome
   Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.
2. Left-to-right shunts#
   - Correctable†
   - Noncorrectable

   Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.
3. Pulmonary arterial hypertension (PAH) with coincidental congenital heart disease
   Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects in contraindicated.
4. Post-operative PAH
   Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

New addition

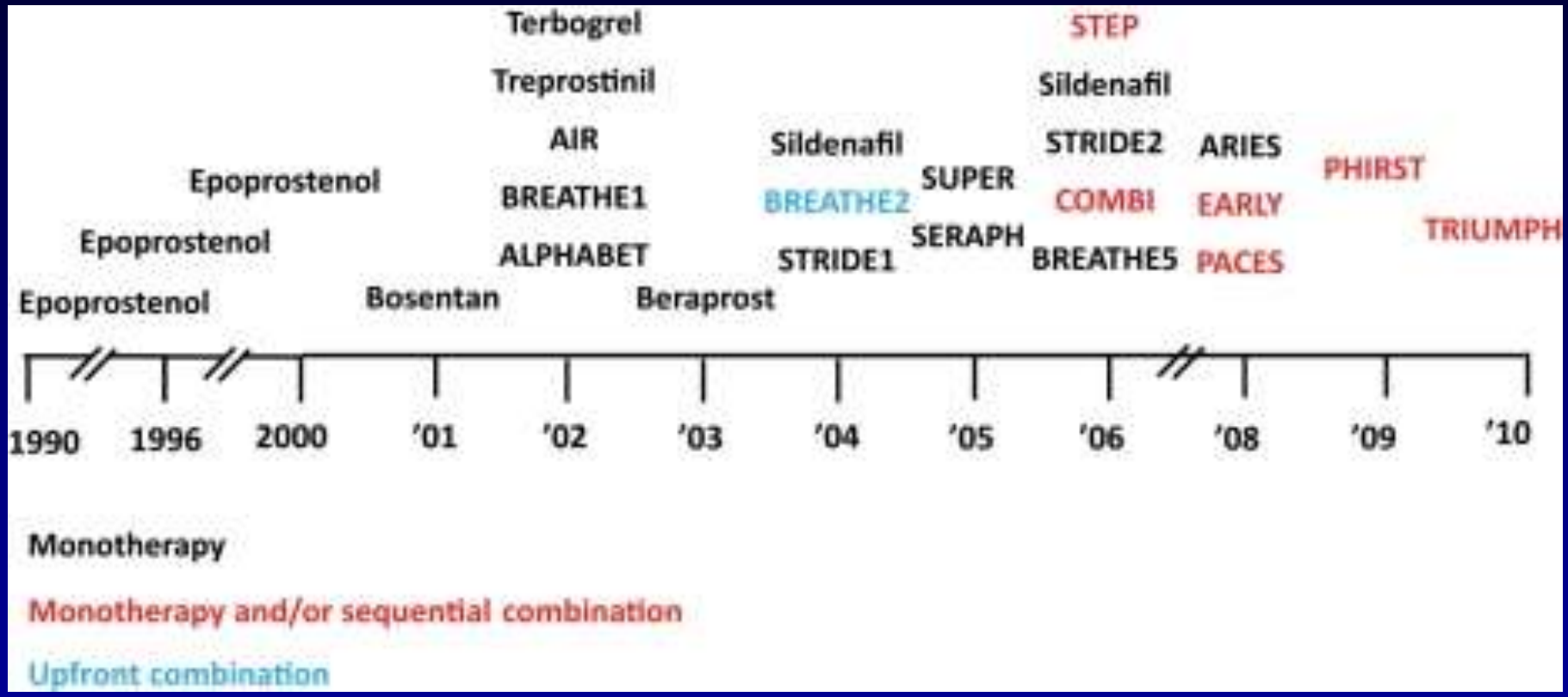
- The clinical subclassification of PAH-CHD is now aligned with the Nice Pediatric classification, as PAH-CHD is a life-long disease

* Main modifications to the previous WSPH proceedings (Dana point) are indicated by green boxes; changes in wording are underlined in green
† Correctable with surgery or intravascular nonsurgical procedure
# Proposed criteria for left-to-right shunt closure are listed in an additional table

Simonneau G, *et al. J Am Coll Cardiol* 2013; 62:D34-41.

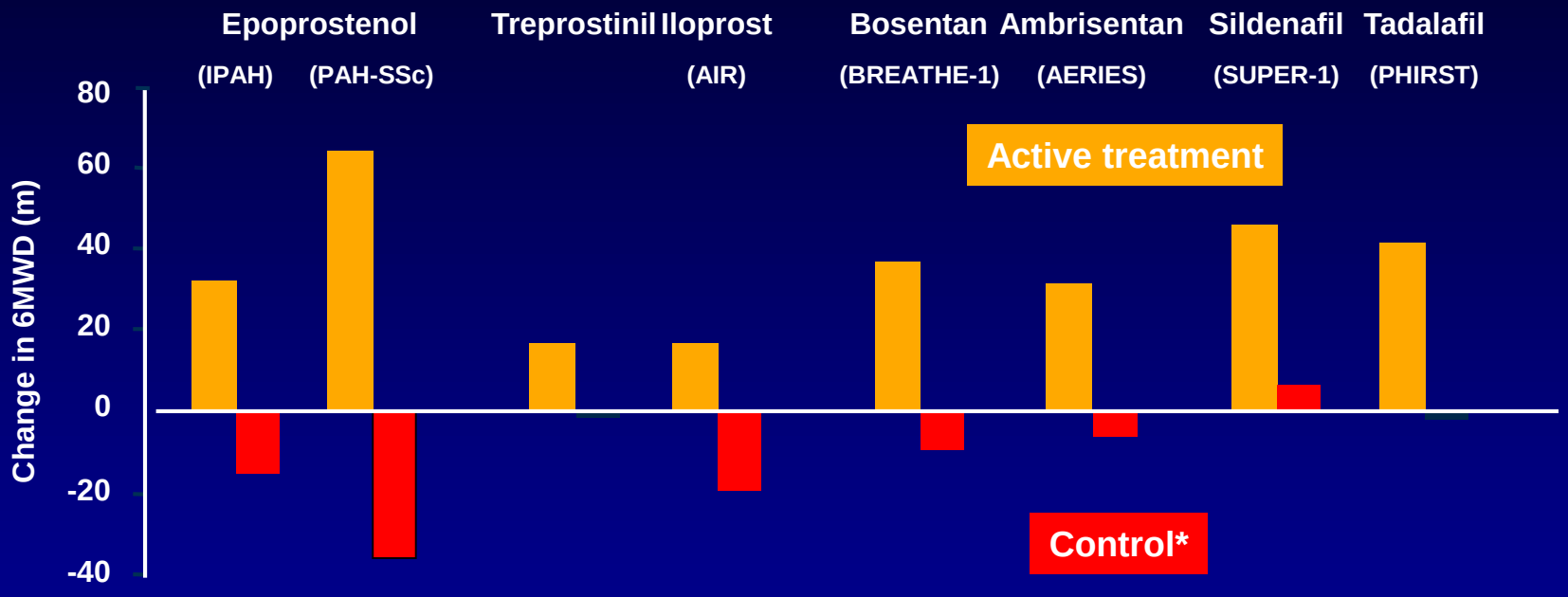
Therapy: what is new ?

RCTs in PAH


Terbogrel
Treprostinil
AIR
BREATHE1
ALPHABET
STEP
Sildenafil
STRIDE2
COMBI
BREATHE5
ARIES
EARLY
PACES
PHIRST
TRIUMPH
Epoprostenol
Epoprostenol
Epoprostenol
Bosentan
Sildenafil
BREATHE2
STRIDE1
SUPER
SERAPH
Beraprost
1990
1996
2000
'01
'02
'03
'04
'05
'06
'08
'09
'10
Monotherapy
Monotherapy and/or sequential combination
Upfront combination

RCTs with monotherapy in PAH

Improvement in exercise capacity (3-4 months)



Treatment effect	+ 47 m	+ 108 m*	+ 18 m	+ 36 m	+ 44 m	+ 44 m	+ 42 m	+ 44 m#
p	< 0.003	< 0.001	0.005	0.004	0.0002	< 0.001	< 0.001	< 0.001

* Control = placebo except for epoprostenol trials ('Conventional therapy')

#: monotherapy only

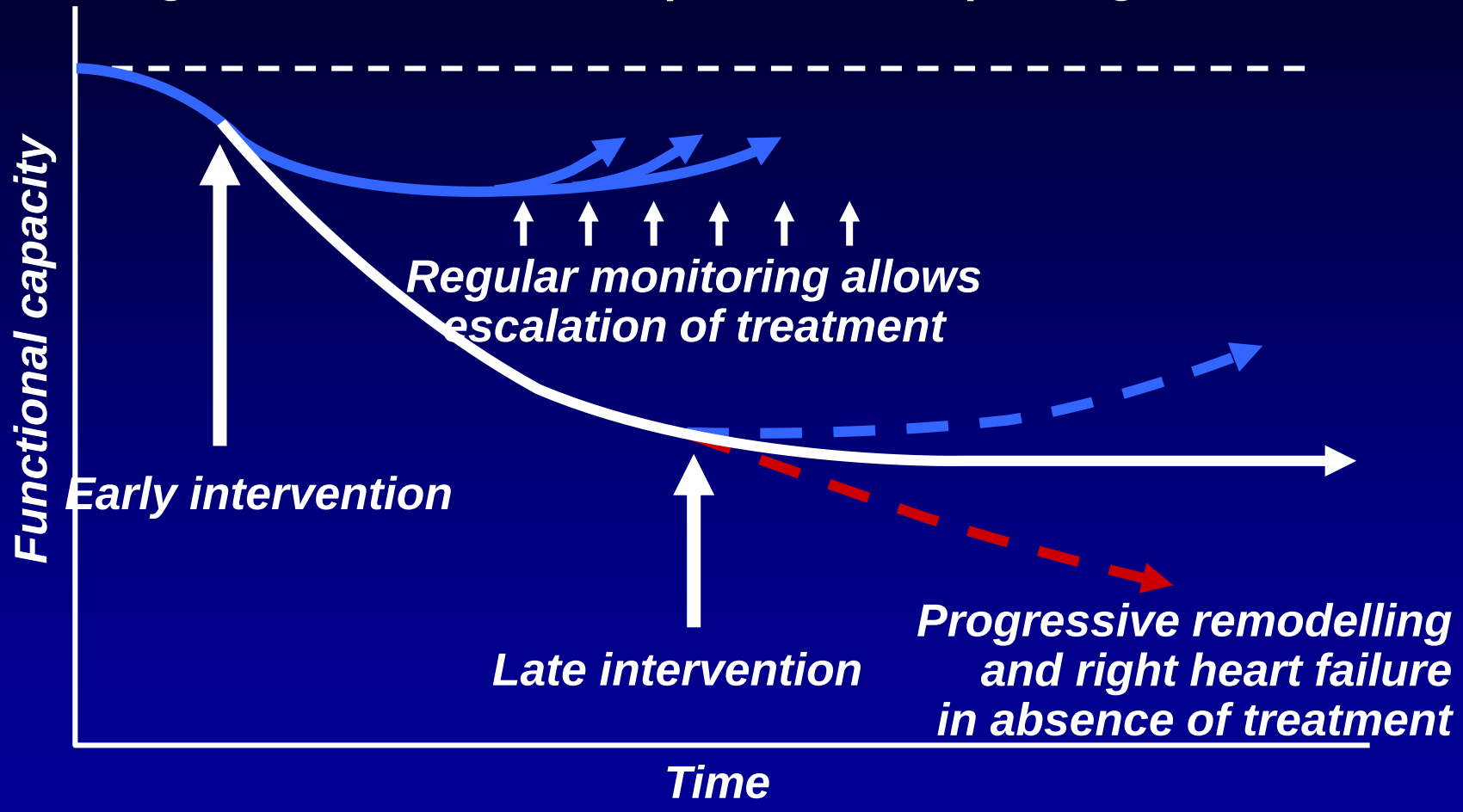
Barst, NEJM 1996.
Badesch, Ann Int Med 2000.
Simonneau, AJRCCM 2002.
Olschewski, NEJM 2002.
Rubin, NEJM 2002.
Galiè, Circulation 2008.
Galiè, NEJM 2005.
Galiè, Circulation 2009.

How to do better?

- Do better with what we have
  - Detect and treat “early”
  - Treat-to-target and sequential combo therapy
  - Changing strategy: Upfront combo therapy
- Develop new drugs
  - Targeting the current pathways (macitentan, riociguat, selexipag…)
  - Targeting novel pathways (TKIs…)

How to assess responsiveness to therapy?

Ultimate goals: No functional impairment and prolongation of life



Sitbon O. *Eur Respir Rev* 2010.

Diagnosis of PAH is typically delayed

- Low prevalence[1,2]
- Low suspicion[3]
- Asymptomatic in early stages[4]
- Non-specific symptoms[3]

DIAGNOSIS IS TYPICALLY DELAYED BY ≥ 2 YEARS[3]

1. Taichman DB, *et al. Clin Chest Med* 2007; 28:1-22.
2. Peacock AJ, *et al. Eur Resp J* 2007; 30: 104-9.
3. Gibbs JSR. *Eur Respir Rev* 2007; 16:8-12.
4. Barst R, *et al*. *JACC* 2004; 43: 40S-47S.

Recommendations on screening of high-risk populations for PAH

- **Significant progress has been made in the diagnosis of SSc patients, for whom the DETECT study has provided important data on screening for PAH**
- **Screening of patients with the SSc spectrum of diseases without clinical signs and symptoms of PH should include a 2-step approach:**
  1) **Clinical assessment for the presence of telangiectasia, anti-centromere antibodies, PFT and DLCO measurements, electrocardiogram and biomarkers (NT-proBNP and uric acid)**
  2) **Electrocardiography and consideration of RHC in patients with abnormal findings, although there is a lack of data with DLCO > 60%**

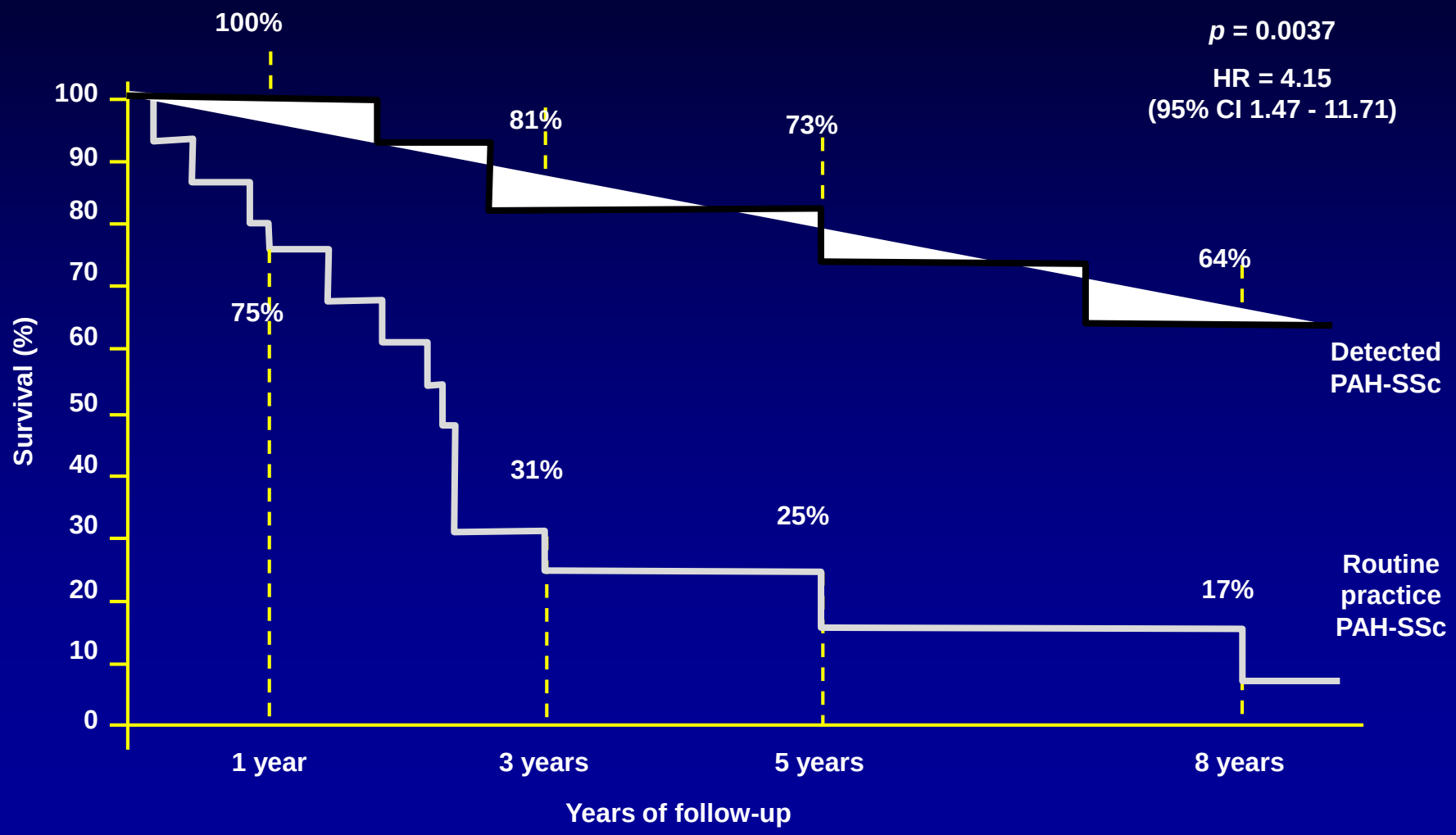
Hoeper MM, *et al. J Am Coll Cardiol* 2013; 62:D42-50.

Detection of milder disease with screening

	Systemic Sclerosis[1]		HIV infection[2]	
	Previously known PAH (n=29)	Newly diagnosed PAH (n=18)	Previously known PAH (n=30)	Newly diagnosed PAH (n=5)
mPAP (mmHg)	49 ± 17	30 ± 9	46 ± 13	30 ± 9
CI (L/min/m^2)	2.8 ± 0.7	3.2 ± 1.0	3.0 ± 0.8	3.6 ± 0.8
PVR (d.s.cm^{-5})	1007 ± 615	524 ± 382	800 ± 320	320 ± 240

1. Hachulla E, et al. *Arthritis Rheum* 2005;52:3792-800.
2. Sitbon O, *et al*. *Am J Respir Crit Care Med* 2008;177:108-13.

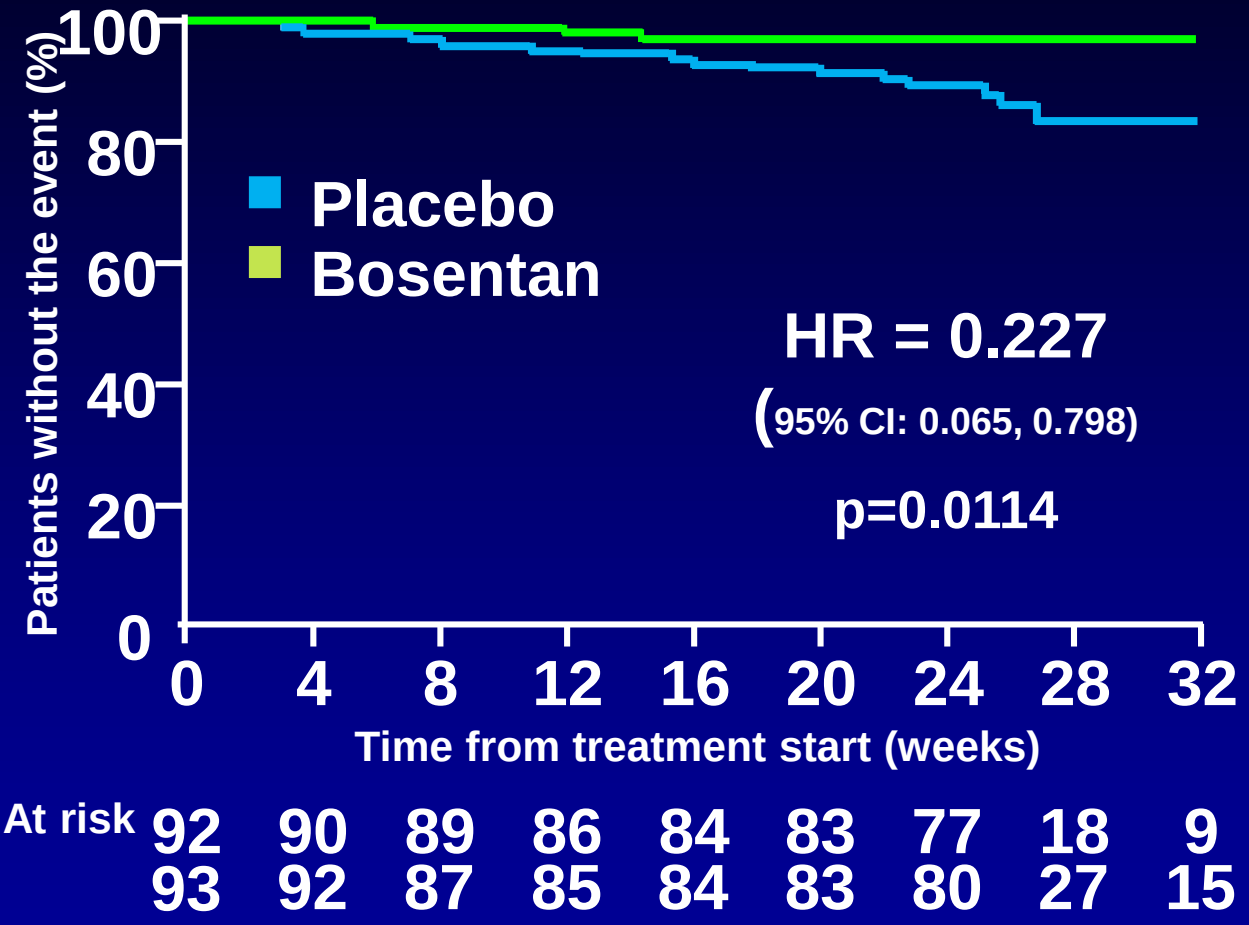
Prognosis of “routine practice” and “detected” PAH-SSc patients



Humbert M, *et al. Arthritis Rheum* 2011; Epub ahead of print.

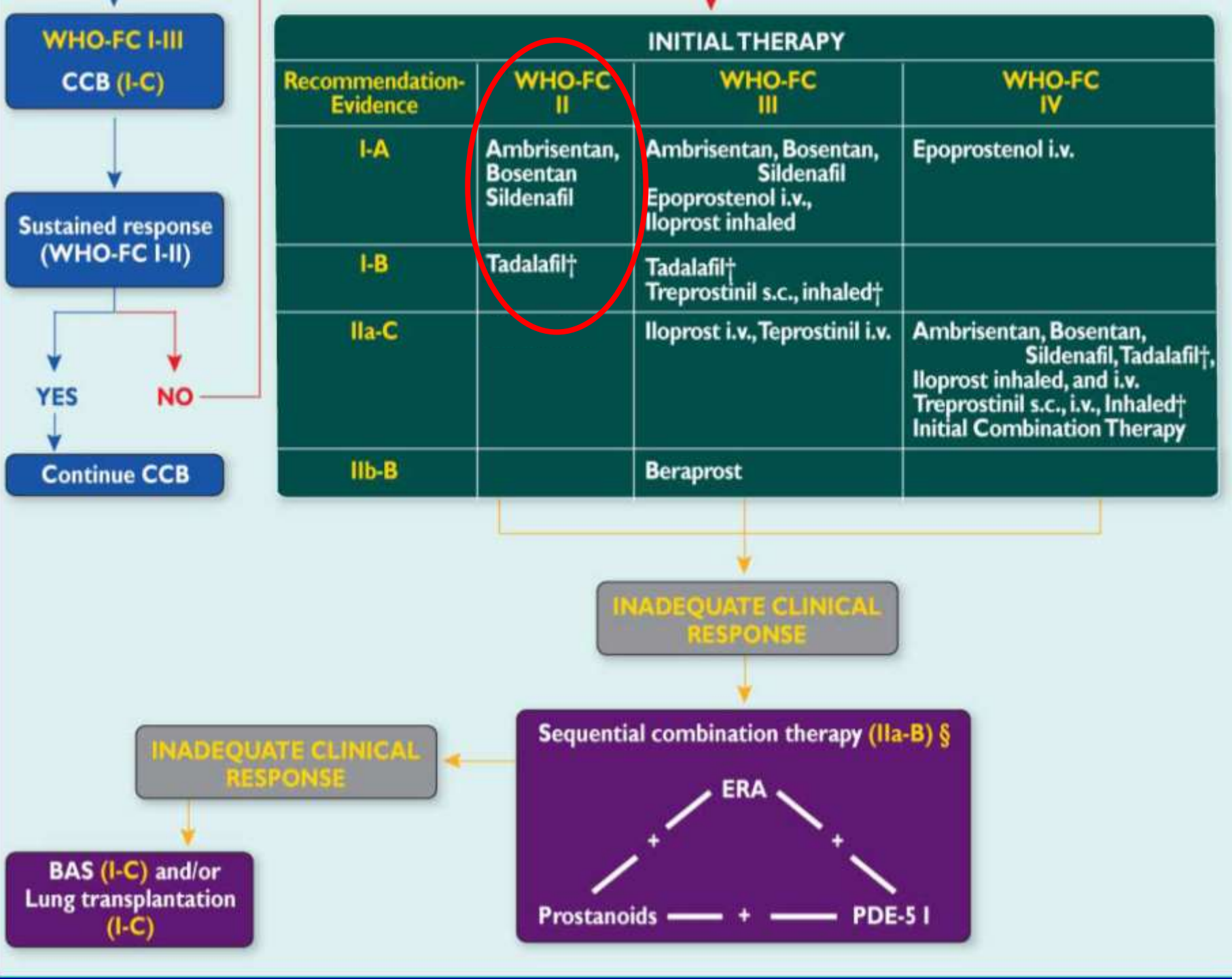
Time to clinical worsening in class II PAH patients

EARLY: effect of bosentan on TTCW in class II PAH patients

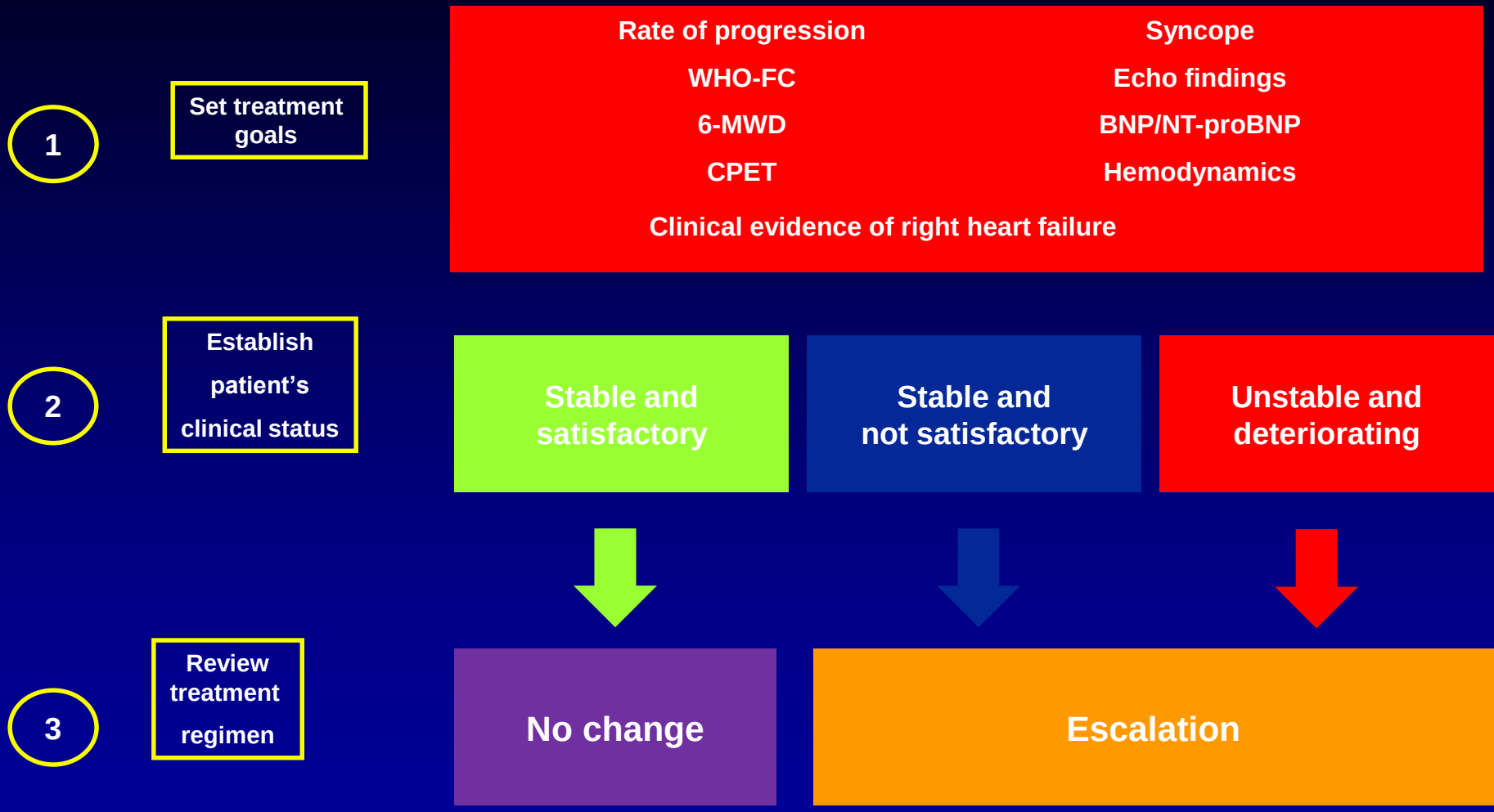


	Placebo	Bosentan
6-MWD (m)	431 ± 91	438 ± 86
PVR (dyn.sec.cm^{-5})	805 ± 369	839 ± 531

Galiè N, *et al*. *Lancet* 2008; 371:2093-100.


WHO-FC I-III
CCB (I-C)
Sustained response (WHO-FC I-II)
YES
NO
Continue CCB
INITIAL THERAPY
Recommendation-Evidence
WHO-FC II
WHO-FC III
WHO-FC IV
I-A
Ambrisentan, Bosentan Sildenafil
Ambrisentan, Bosentan, Sildenafil Epoprostenol i.v., Iloprost inhaled
Epoprostenol i.v.
I-B
Tadalafil†
Tadalafil† Treprostinil s.c., inhaled†
IIa-C
Iloprost i.v., Teprostinil i.v.
Ambrisentan, Bosentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., Inhaled† Initial Combination Therapy
IIb-B
Beraprost
INADEQUATE CLINICAL RESPONSE
Sequential combination therapy (IIa-B) §
ERA
+
+
Prostanoids
+
PDE-5 I
INADEQUATE CLINICAL RESPONSE
BAS (I-C) and/or Lung transplantation (I-C)

Treat-to-target approach for PAH



Adapted from Galiè N, *et al. Eur Heart J* 2009; 30:2493-537.

L’ottimizzazione della gestione del paziente PAH

Prognosi migliore
No
Lenta
No
I/II
Lunga distanza >500 metri
Consumo di O_2 al picco >15 ml/min/Kg
Normali o lievemente aumentati
≥ 18 mm
Segni di versamento pericardico assenti
RAP < 8 mmHg e CI ≥2.5 L/min/m^2

Uscire dalla zona grigia

per puntare a questi goals di trattamento

Galiè et al., Eur Heart J 2009; 30 2493-2537

L'ottimizzazione della gestione del paziente PAH

Prognosi migliore	Fattori prognostici	Progno
No	Segni di scompenso ventricolare destro	
Lenta	Progressione dei sintomi	Rapida
No	Sincope	Si
I/II	Classe funzionale	IV
Lunga distanza >500 metri	6-MWT	Breve distanza <300 metri
Consumo di O_2 al picco >15 ml/min/Kg	Test esercizio cardiopolmonare (CPET)	Consumo di O_2 al picco <12 ml/min/Kg
Normali o lievemente aumentati	Livelli plasmatici di NT-proBNP	Nettamente aumentati
≥ 18 mm	**TAPSE** ***(Tricuspid anular plane systolic excursion)***	≤ 18 mm
Segni di versamento pericardico assenti	Reperti ecocardiografici	Presenti segni di versamento pericardico
RAP < 8 mmHg e CI ≥2.5 L/min/m^2	Valori emodinamici	RAP >15 mmHg e CI ≤ 2.0 L/min/m^2

Clinica

L'ottimizzazione della gestione del paziente PAH

Prognosi migliore	Fattori prognostici	Prognosi peggiore
No	Segni di scompenso ventricolare destro	Si
Lenta	Progressione dei sintomi	Rapida
No	Sincope	Si
I/II	Classe funzionale	IV
Lunga distanza >500 metri	6-MWT	Brev <3
Consumo di O_2 al picco >15 ml/min/Kg	Test esercizio cardiopolmonare (CPET)	Consum <12
Normali o lievemente aumentati	Livelli plasmatici di NT-proBNP	Nettamente aumentati
≥ 18 mm	**TAPSE** ***(Tricuspid anular plane systolic excursion)***	≤ 18 mm
Segni di versamento pericardico assenti	Reperti ecocardiografici	Presenti segni di versamento pericardico
RAP < 8 mmHg e CI ≥2.5 L/min/m^2	Valori emodinamici	RAP >15 mmHg e CI ≤ 2.0 L/min/m^2

Capacità di esercizio
Markers

L'ottimizzazione della gestione del paziente PAH

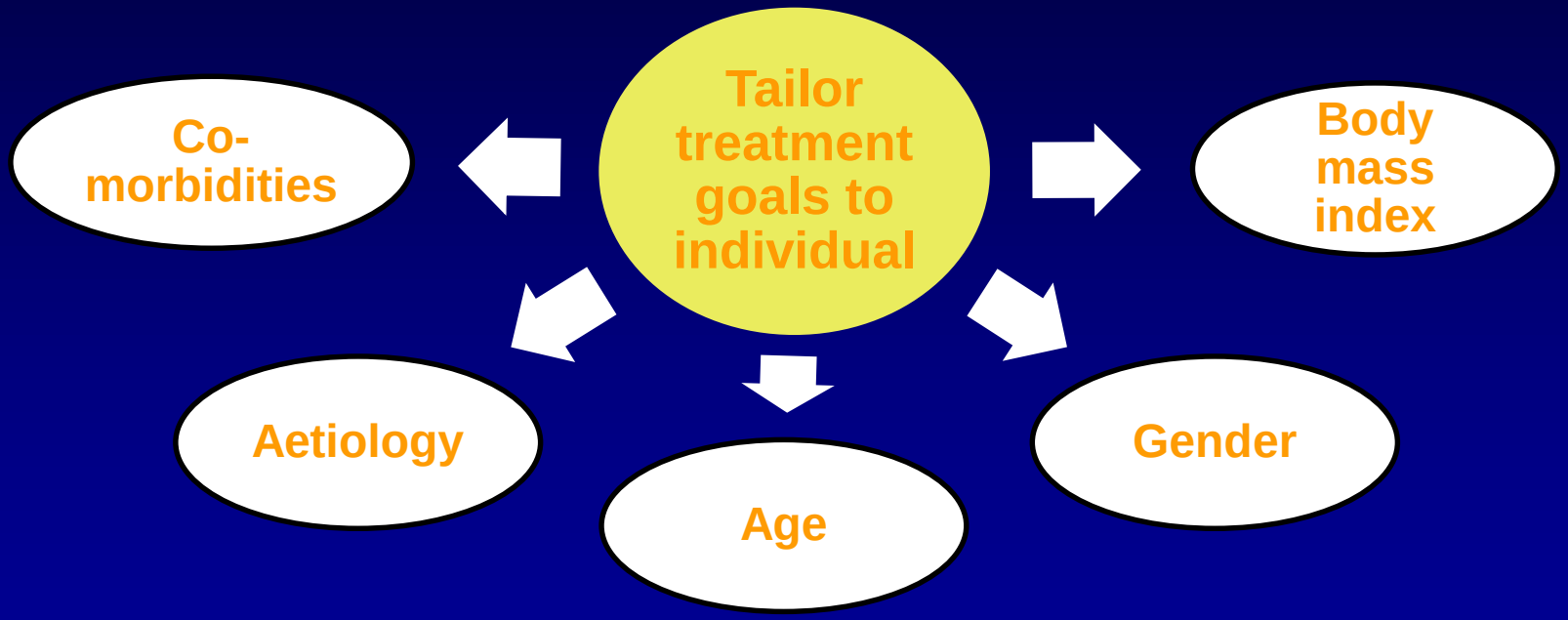
Prognosi migliore	Fattori prognostici	Prognosi peggiore
No	Segni di scompenso ventricolare destro	Si
Lenta	Progressione dei sintomi	Rapida
No	Sincope	Si
I/II	Classe funzionale	IV
Lunga distanza >500 metri	6-MWT	Breve distanza <300 metri
Consumo di O_2 al picco >15 ml/min/Kg	Test esercizio cardiopolmonare (CPET)	Consumo di O_2 al picco <12 ml/min/Kg
Normali o lievemente aumentati	Livelli plasmatici di NT-proBNP	Nettamente aumentati
≥ 18 mm	**TAPSE** ***(Tricuspid anular plane systolic excursion)***	≤ 18 mm
Segni di versamento pericardico assenti	Reperti ecocardiografici	versa
RAP < 8 mmHg e CI ≥2.5 L/min/m^2	Valori emodinamici	RAP >15 L/min/m^2

Dati strumentali Emodinamica

Implementation of treat-to-target strategy in PAH

	Nov 10	Mar 11	Aug 11	Jan 12
Treatment	None	Bosentan	bosentan + sildenafil	Bos. + Sil. + epoprostenol
NYHA FC	III	III	III	II
6MWD, *m (% theor.)*	519 (79%)	525 (80%)	441 (67%)	601 (91%)
Borg score	6	3	4	3
RAP, *mmHg*	7	8	8	3
mPAP, *mmHg*	55	60	65	47
CI, *L/min/m²*	2.01	2.50	2.09	3.35
PVR, *dyn.s.cm^{-5}*	1248	1066	1368	649
BNP, *pg/ml*	-	217	360	62
Status		Stable and unsatisfactory	Deteriorating	Stable and satisfactory
Action	Start first-line bosentan	Add sildenafil	Add epoprostenol	No change

Treatment goals in PAH:
They should be adapted to the individual patient



Monitoring patients with PAH:
When and how to assess?

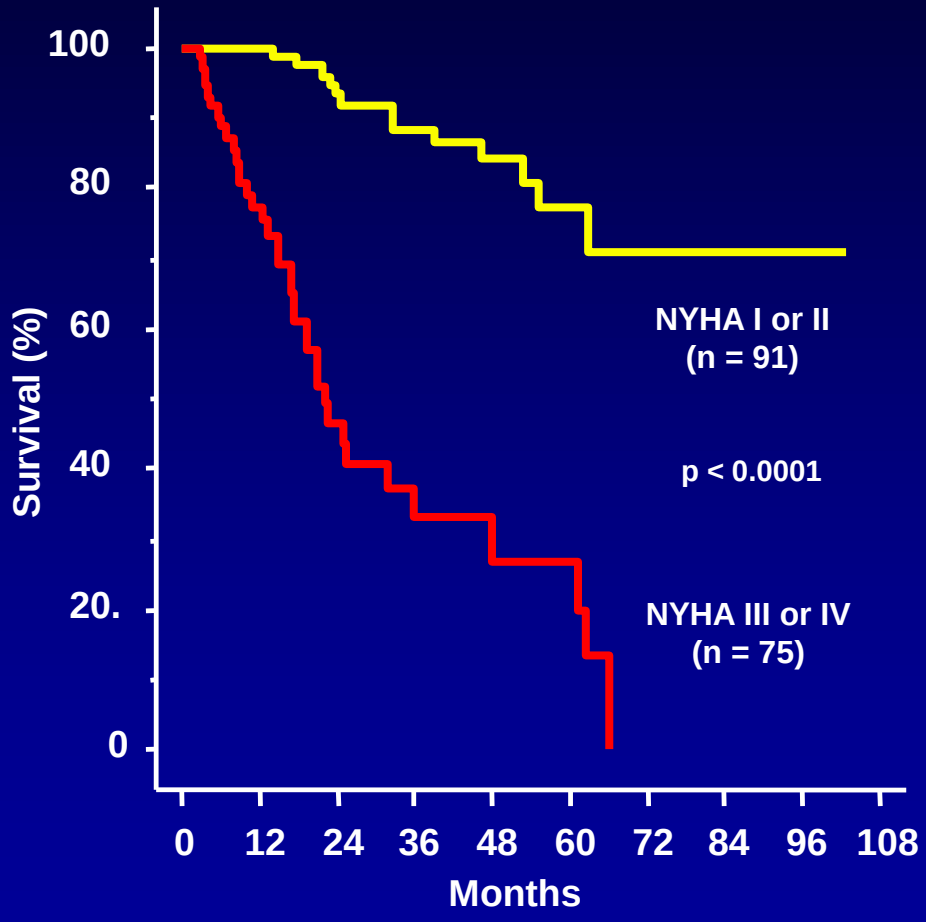
	At baseline (prior to therapy)	Every 3-6 months	3-4 months after initiation or changes in therapy	In case of clinical worsening
Clinical assessment NYHA/WHO-FC ECG	✓	✓	✓	✓
6-MWD	✓	✓	✓	✓
Cardio-pulmonary exercise testing	✓		✓	✓
BNP/NT-proBNP	✓	✓	✓	✓
Echocardiography	✓		✓	✓
RHC	✓		✓	✓

Eur Heart J 2009; 30:2493-537.

Prognostic impact of follow-up assessment

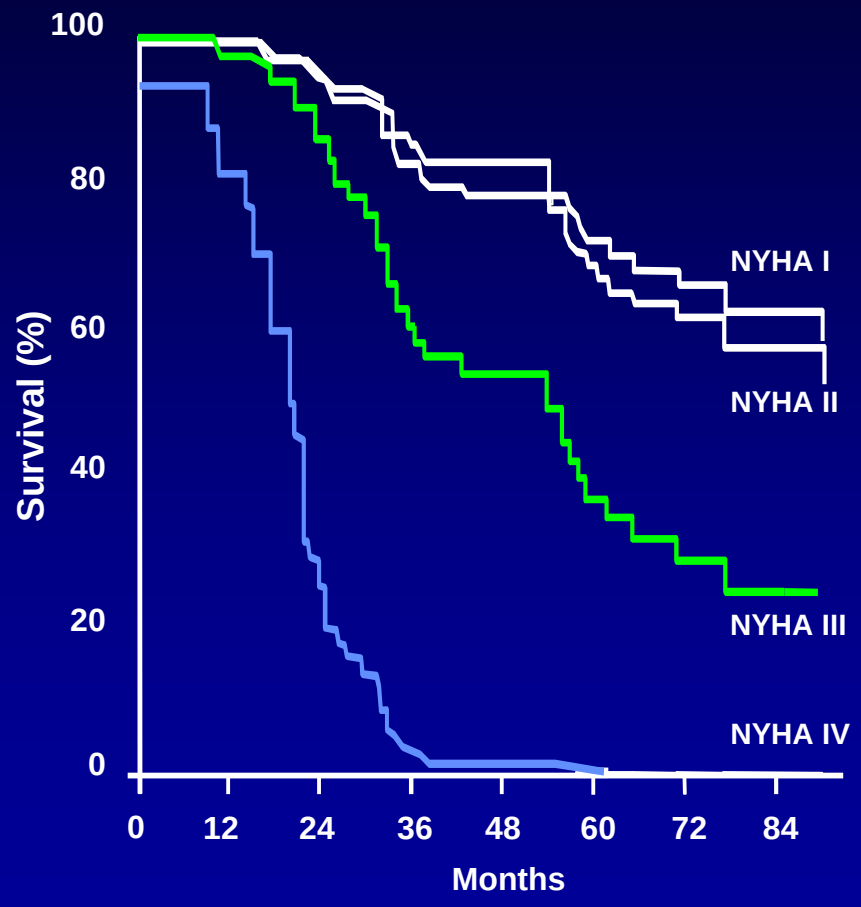
NYHA FC at follow up is the strongest prognostic factor in PAH…

After 3-month epoprostenol



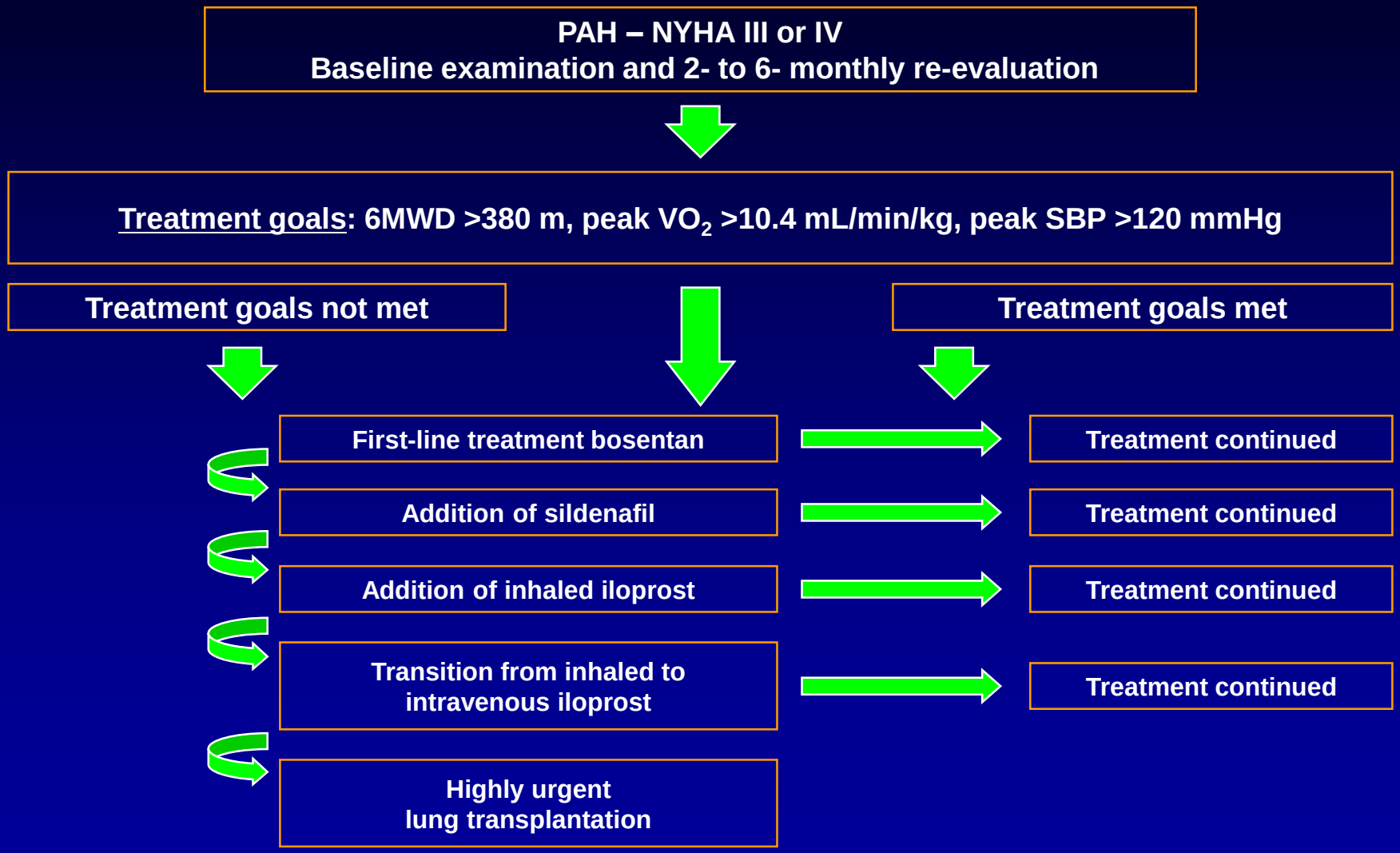
Sitbon O, et al. J Am Coll Cardiol 2002;40:780-8.

After 17 ±15 months on epoprostenol



McLaughlin VV, et al. Circulation 2002;106:1477-82.

Goal-orientated strategy and combination therapy for PAH



Hoeper MM, *et al. Eur Respir J* 2005; 26:858–63.

Sequential combination therapy in PAH

What is the evidence?

	Current therapy	Added therapy	Patients (n)	Study duration	Primary endpoint	Primary EP met	Secondary EP met
STEP[1]	Bosentan	Iloprost	67	12 weeks	6MWD	No	TTCW
PACES[2]	Epoprostenol	Sildenafil	267	16 weeks	6MWD	Yes	TTCW
PHIRST[3]	Naïve or bosentan	Tadalafil	405 (206)	16 weeks	6MWD	Yes (No)	TTCW, (No)
TRIUMPH-1[4]	Bosentan or sildenafil	Treprostinil (inhaled)	235	12 weeks	6MWD	Yes	No
FREEDOM-C[5]	Bosentan and/or sildenafil	Treprostinil (oral)	354	16 weeks	6MWD	No	No

1. McLaughlin VV, *et al. Am J Respir Crit Care Med* 2006;174:1257–63.
2. Simonneau G, *et al. Ann Intern Med* 2008;149:521–30.
3. Galiè *N et al. Circulation* 2009;119:2894–903.
4. McLaughlin V, *J Am Coll Cardiol* 2010;55:1915–22.
5. www.clinicaltrials.gov identifier NCT00325442

Sequential combination therapy in PAH

What is the evidence?

- Exercise capacity (6MWD): primary endpoint in all studies on sequential combination therapy
- Only 2 out of 5 reached statistical significance
- Effect on TTCW has been variable (2 out of 5 positive)
- Only PACES (sildenafil on background epoprostenol) reached statistical significance in both EP

Is there something wrong ?

Population – aetiologies, duration of disease…
Endpoint – need for “harder” endpoints
Strategy – upfront combination ?

Combination therapy in PAH

The next regimen?

Current dogma

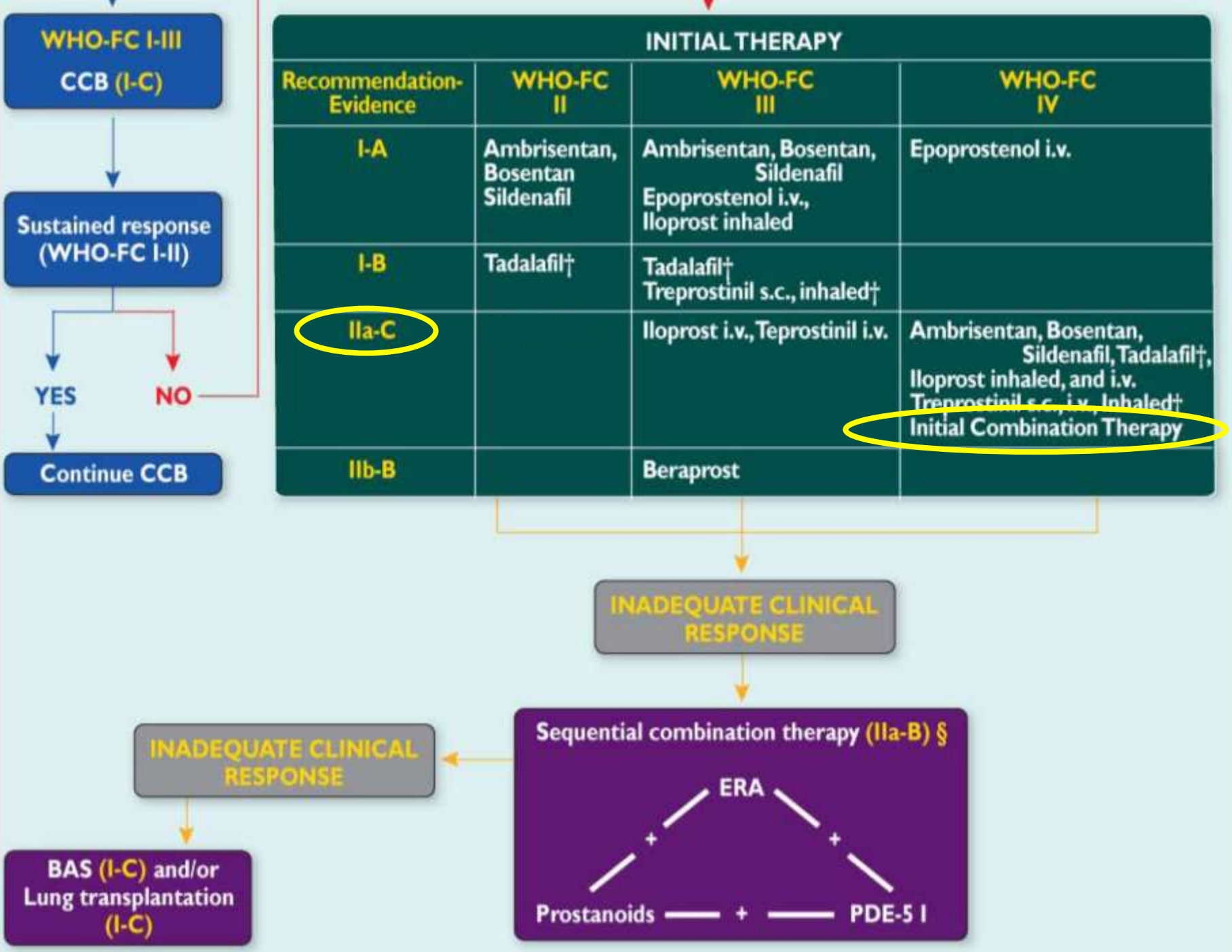
- 2 drugs regimen
- Sequential approach

----> Approval trials

Alternative approaches

- Upfront combination
- “Induction” trial combining 3 targets

----> Strategy trials
(improve management)


WHO-FC I-III
CCB (I-C)
Sustained response (WHO-FC I-II)
YES
NO
Continue CCB
INITIAL THERAPY
Recommendation-Evidence
WHO-FC II
WHO-FC III
WHO-FC IV
I-A
Ambrisentan, Bosentan Sildenafil
Ambrisentan, Bosentan, Sildenafil Epoprostenol i.v., Iloprost inhaled
Epoprostenol i.v.
I-B
Tadalafil†
Tadalafil† Treprostinil s.c., inhaled†
IIa-C
Iloprost i.v., Teprostinil i.v.
Ambrisentan, Bosentan, Sildenafil, Tadalafil†, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., Inhaled†
Initial Combination Therapy
IIb-B
Beraprost
INADEQUATE CLINICAL RESPONSE
Sequential combination therapy (IIa-B) §
ERA
+
+
Prostanoids
+
PDE-5 I
INADEQUATE CLINICAL RESPONSE
BAS (I-C) and/or Lung transplantation (I-C)

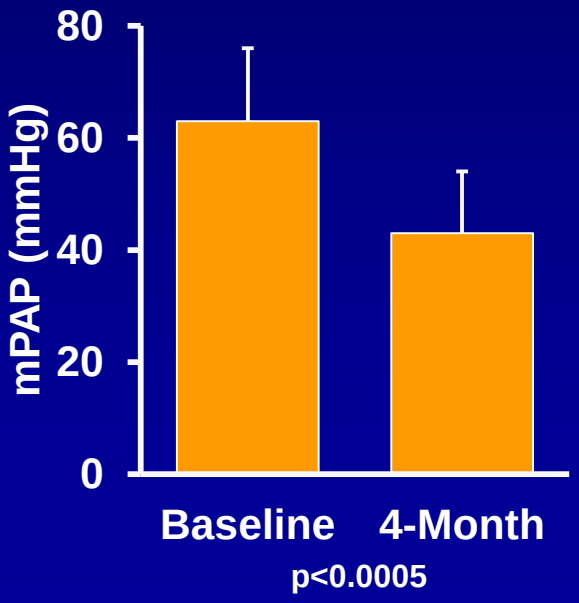
Up-front triple combination therapy in PAH

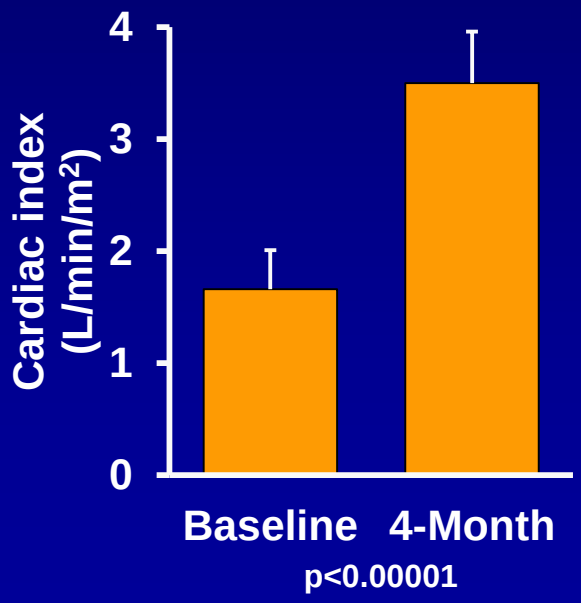
- Experience from the French Reference Centre
- Up-front triple combination therapy with i.v. epoprostenol + bosentan + sildenafil
- 12 newly diagnosed Idiopathic/Heritable PAH patients
- Mean age 41 ± 14 years (20 – 63)
- NYHA III (6) or IV (6) / 6MWD = 254 ± 170 m

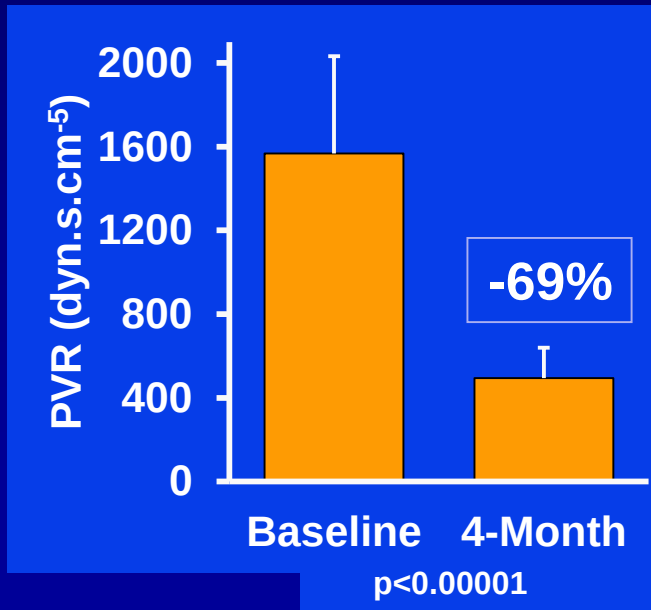
RAP, *mmHg*	13 ± 5
mPAP, *mmHg*	67 ± 17
PCWP, *mmHg*	9 ± 3
CI, $L.min^{-1}.m^{-2}$	1.6 ± 0.3
PVR, $dyn.s.cm^{-5}$	1734 ± 675
SvO_2, *%*	49 ± 10

Up-front triple combination therapy in PAH

- After 4-month triple combination therapy
  - The most severe patient failed and underwent urgent HLT before reassessment
  - Dramatic improvement in 11 / 12 patients
    - All in NYHA class II (p<0.001)
    - 6MWD 469 ± 73 m (*vs* 277 ± 157 m, p<0.0003)







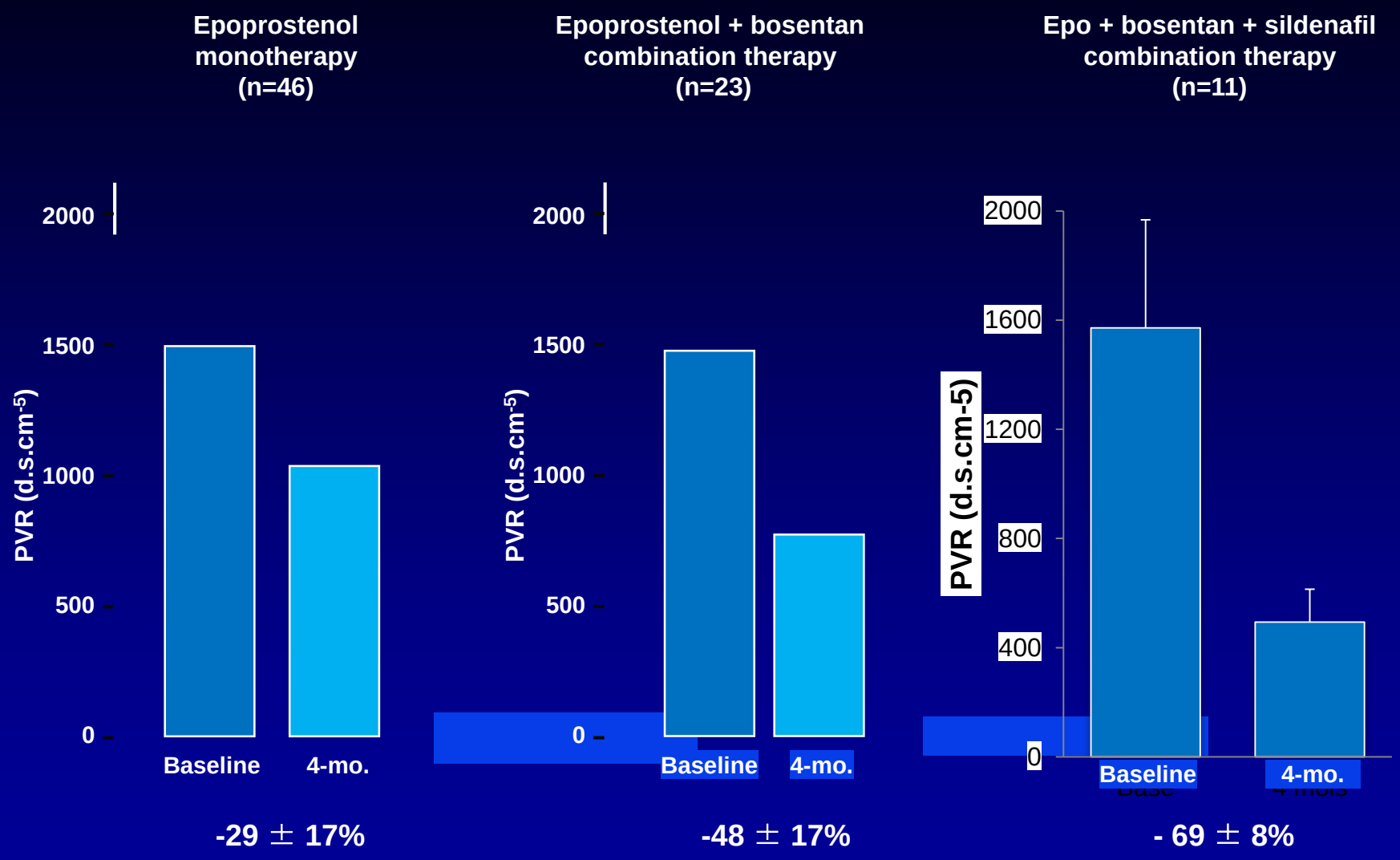
Up-front triple combination therapy in PAH

- Median follow-up = 22 months (range: 7 - 42 months)
- All patients alive, in NYHA class I-II
- 7 patients reassessed after 14 - 38 months

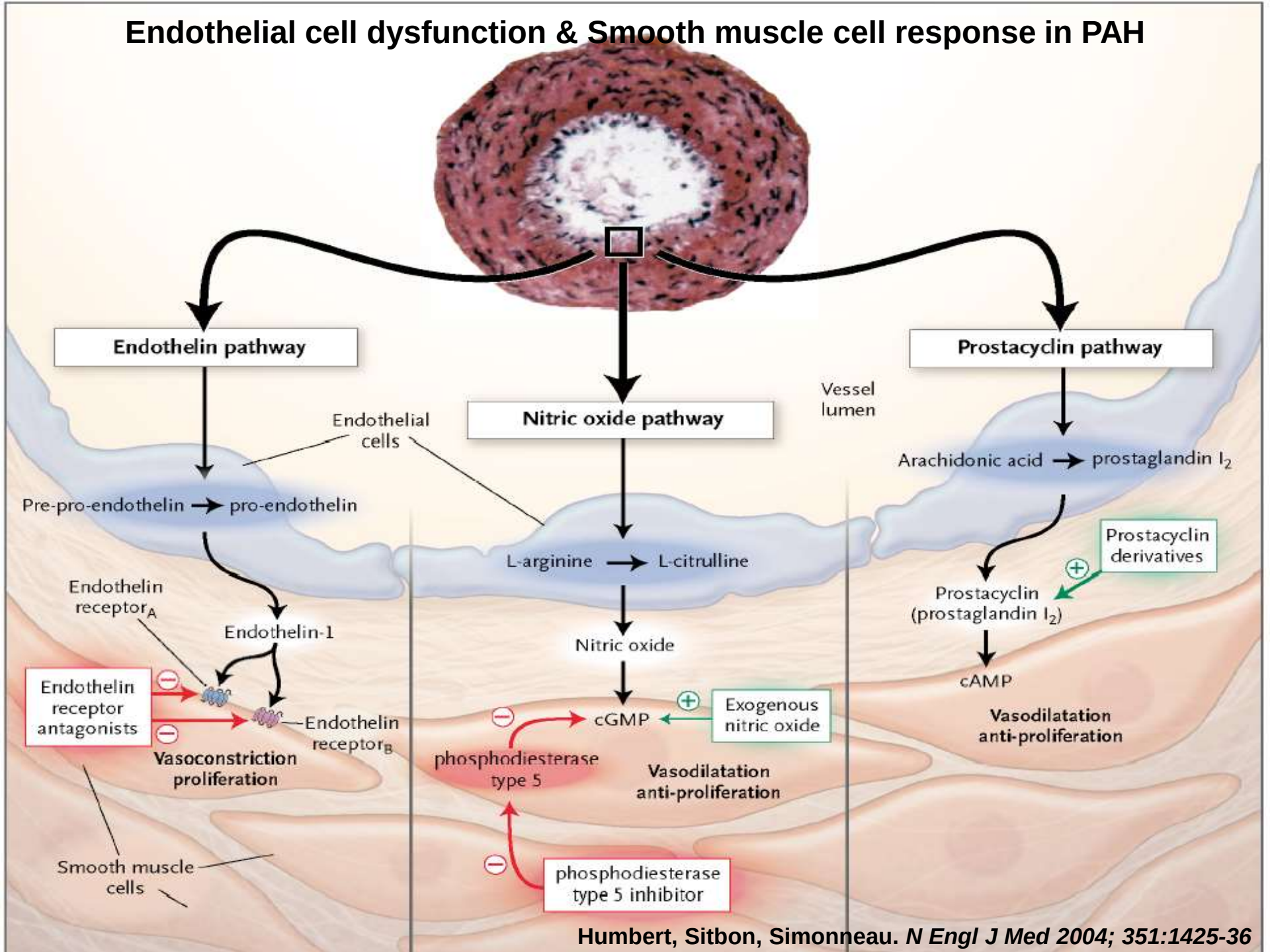
N = 7	Baseline	4-month visit	Last visit (14-38 mo.)	P value
NYHA I:II:III:IV, *n*	0:0:2:5	0:7:0:0	2:5:0:0	<0.001
6MWD, *m*	217 ± 169	454 ± 67	497 ± 52	<0.01
mPAP, *mmHg*	61 ± 13	43 ± 13	46 ± 11	<0.05
CI, *L/min/m²*	1.6 ± 0.4	3.5 ± 0.5	3.3 ± 0.5	<0.01
PVR, *dyn.s.cm⁻⁵*	1554 ± 342	461 ± 123	557 ± 203	<0.01
Mean BP, *mmHg*	90 ± 17	78 ± 10	83 ± 19	NS
Epoprostenol dose, *ng/kg/min*	0	17 ± 1 (16-18)	19 ± 5 (16-30)	-

* Chi-2 or Friedman test, as appropriate

Up-front triple combination therapy in PAH

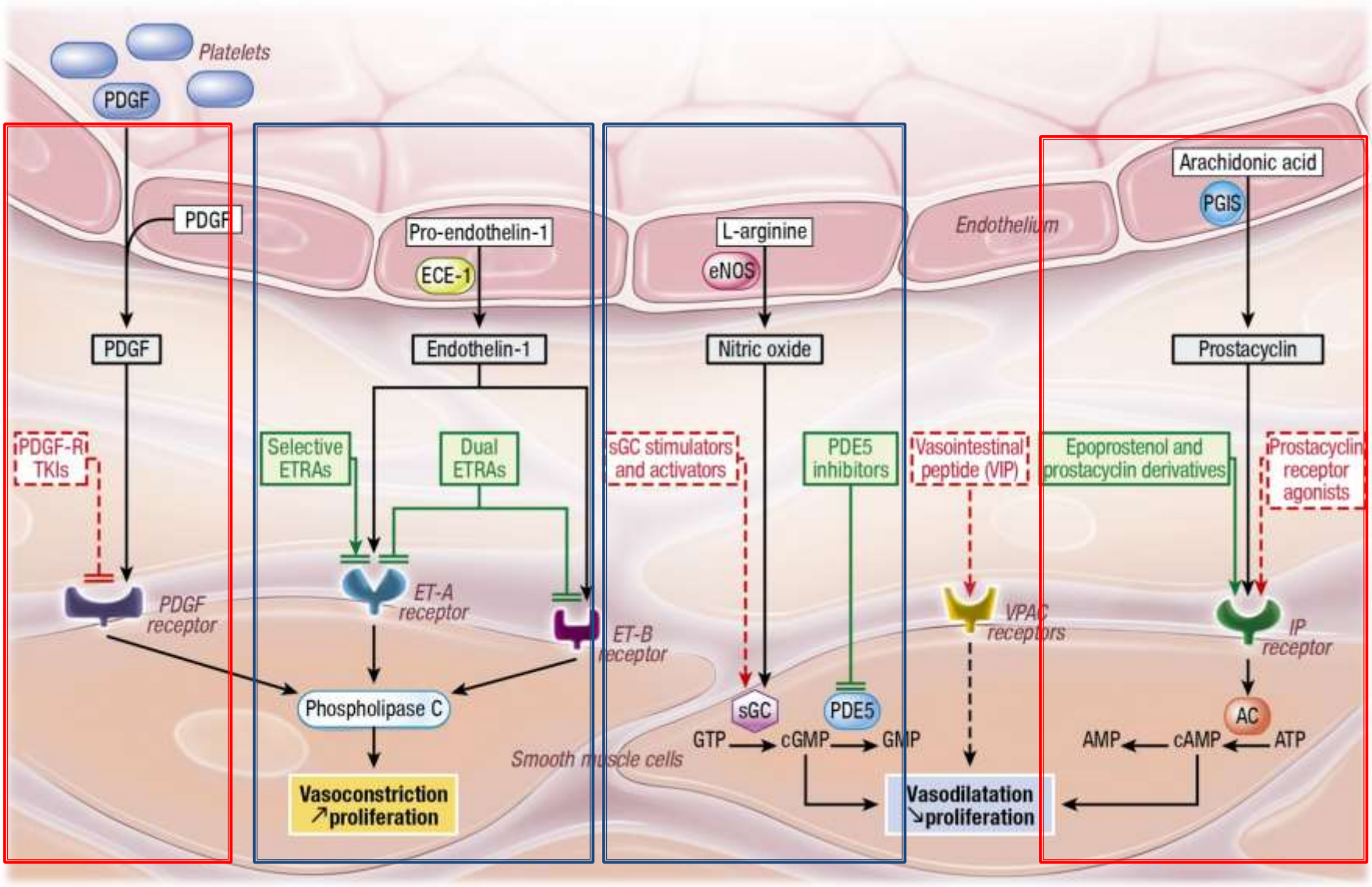


Endothelial cell dysfunction & Smooth muscle cell response in PAH



Humbert, Sitbon, Simonneau. *N Engl J Med 2004; 351:1425-36*

Current and Emerging Targets and Therapies in PAH



O'Callaghan DS, Savale L, Montani D, Jaïs X, Sitbon O, Simonneau G & Humbert M. Nat Clin Practice Cardiol 2011; 19:526-538

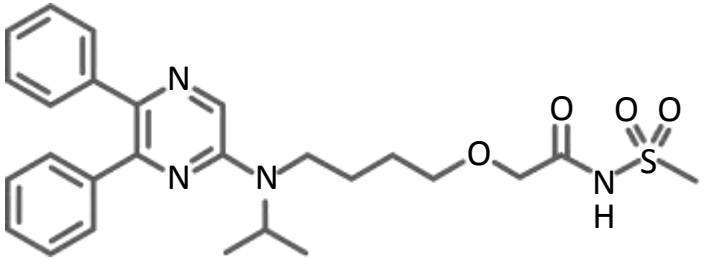
New drugs targeting established pathways in PAH

Drug	Company	Mode of action	Phase of development
Selexipag	Actelion	Oral selecive prostacyclin (IP) receptor agonist	III ongoing
Treprostinil oral	United Therapeutics	Prostacyclin analogue	III, results available (3 trials)
Riociguat	Bayer	Oral sGC stimulator that targets the NO-sGC-cGMP vpathway	III, results available
Macitentan	Actelion	Dual ERA with sustained binding and tissue penetration properties	III, results available

www.clinicaltrials.gov

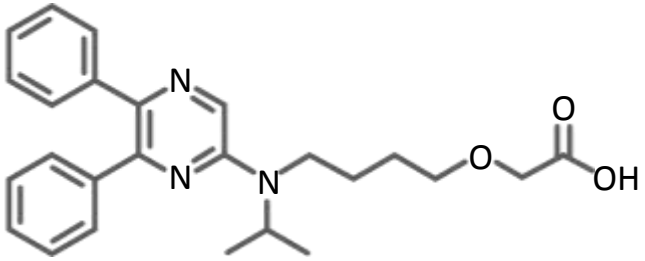
Selexipag: oral, selective IP receptor agonist

Selexipag (parent molecule)



Hydrolysis

T-333679 (major metabolite)

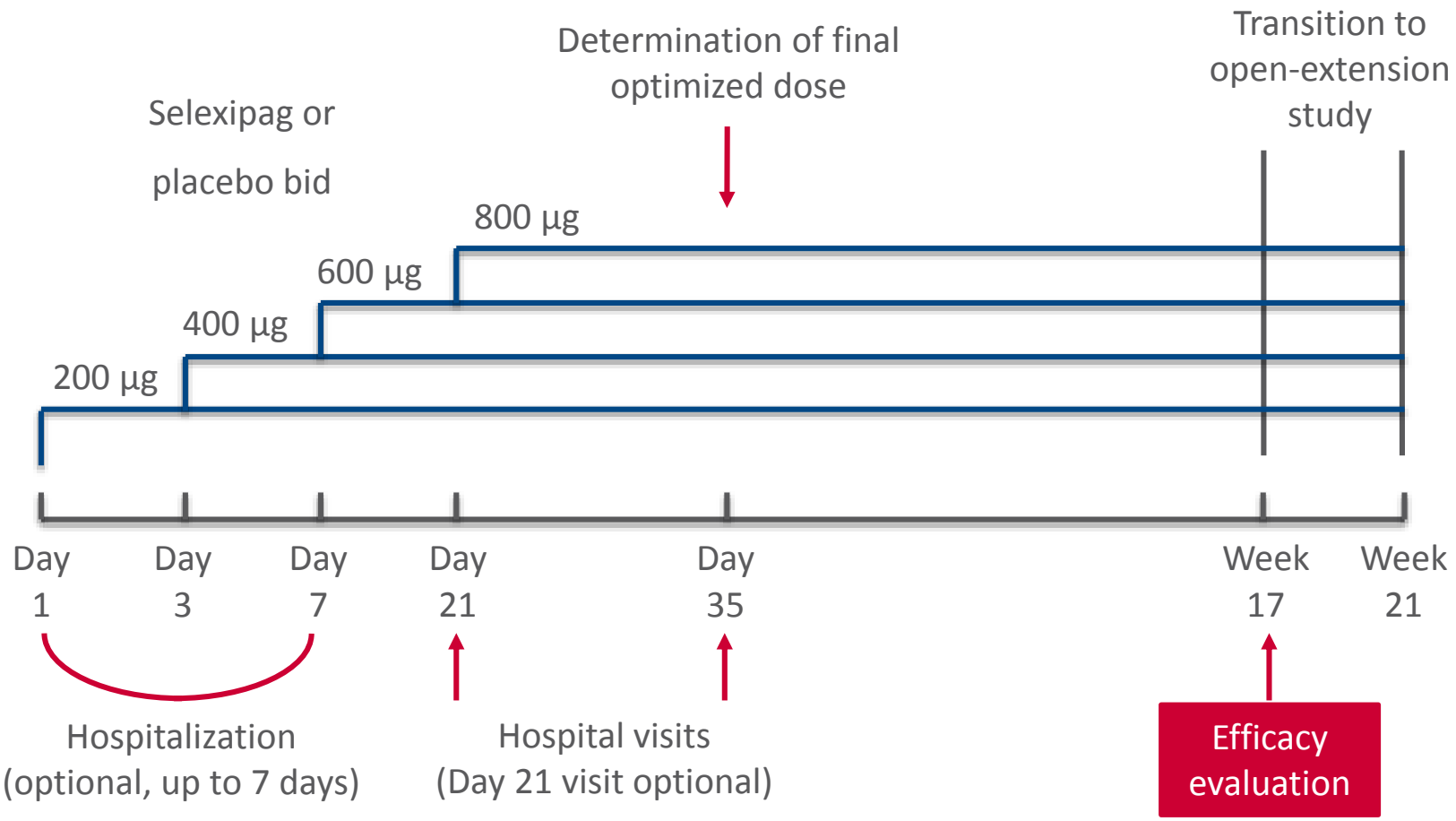


- Orally available diphenyl-pyrazine derivative
- Chemically distinct from prostacyclin and prostacyclin analogs
- Short half-life: ~1–2 h in humans

- Potent and highly selective IP receptor agonist
- >130-fold more selective for IP receptor over other prostanoid receptors
- Prolonged half-life: >8 h in humans

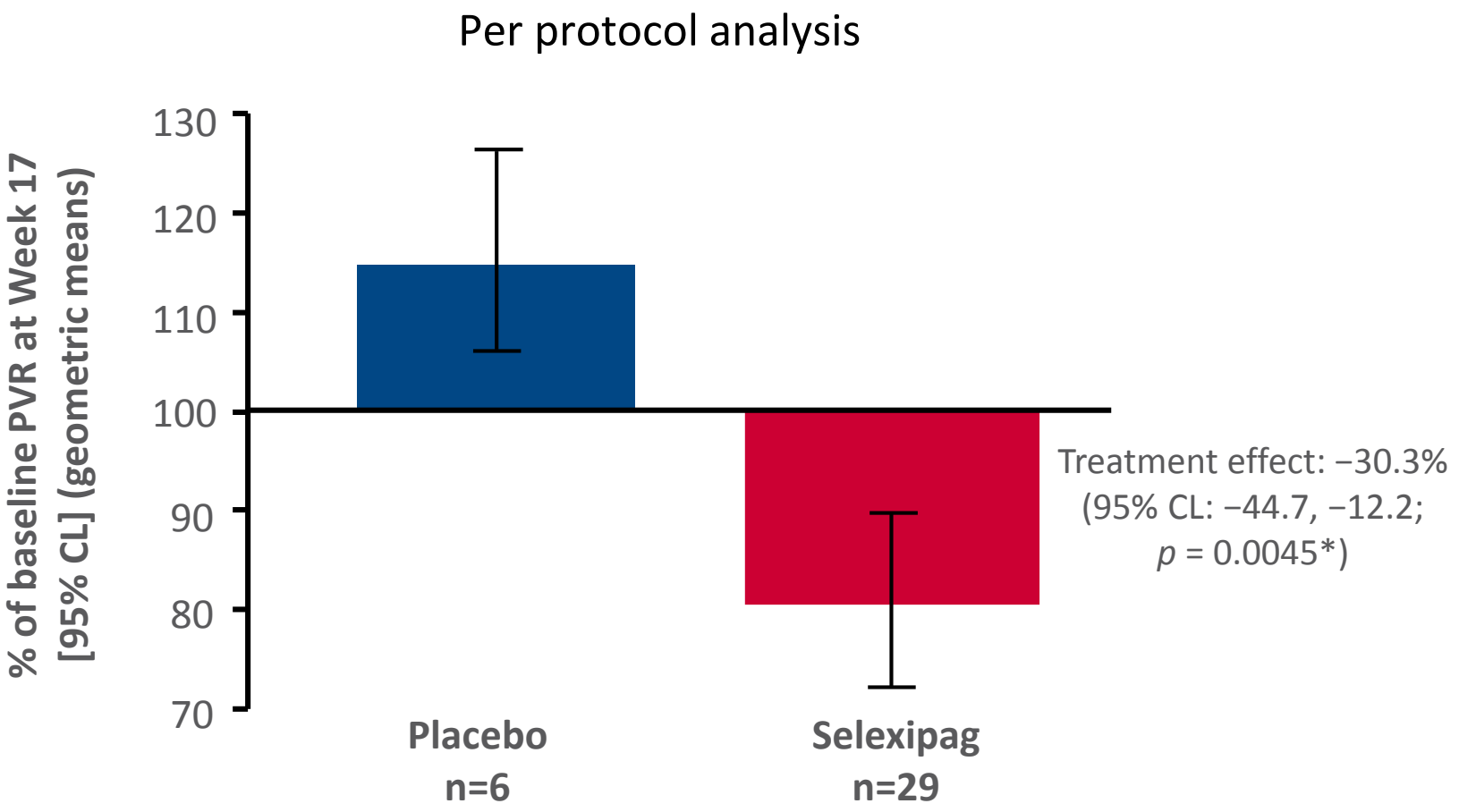
Kuwano K, *et al*. *J Pharmacol Exp Ther* 2007

Selexipag Phase II in PAH: study design



Simonneau G, et al. *Eur Resp J 2012*

Selexipag Phase 2a in PAH: selexipag significantly reduced PVR at Week 17



*Wilcoxon rank sum test

ITT analysis: Treatment effect: −33.0% (95% CL: −47.0, −15.2; $p = 0.0022$*)

Simonneau G, et al. *Eur Resp J 2012*

GRIPHON study(phase III)

Prosta**G**landin I_2 **R**eceptor agonist

In **P**ulmonary arterial **H**ypertensi**ON**

- Multicenter, double-blind,Long-term, placebo-controlled
- PAH adult patients
- background treatment with ERA and/or PDE-5i allowed
- Primary endpoint: time to clinical worsening
- Estimated ample size: N=1100
- Results pending

GRIPHON

Prostacyclin (PGI_2) Receptor agonist In Pulmonary arterial HypertensiON

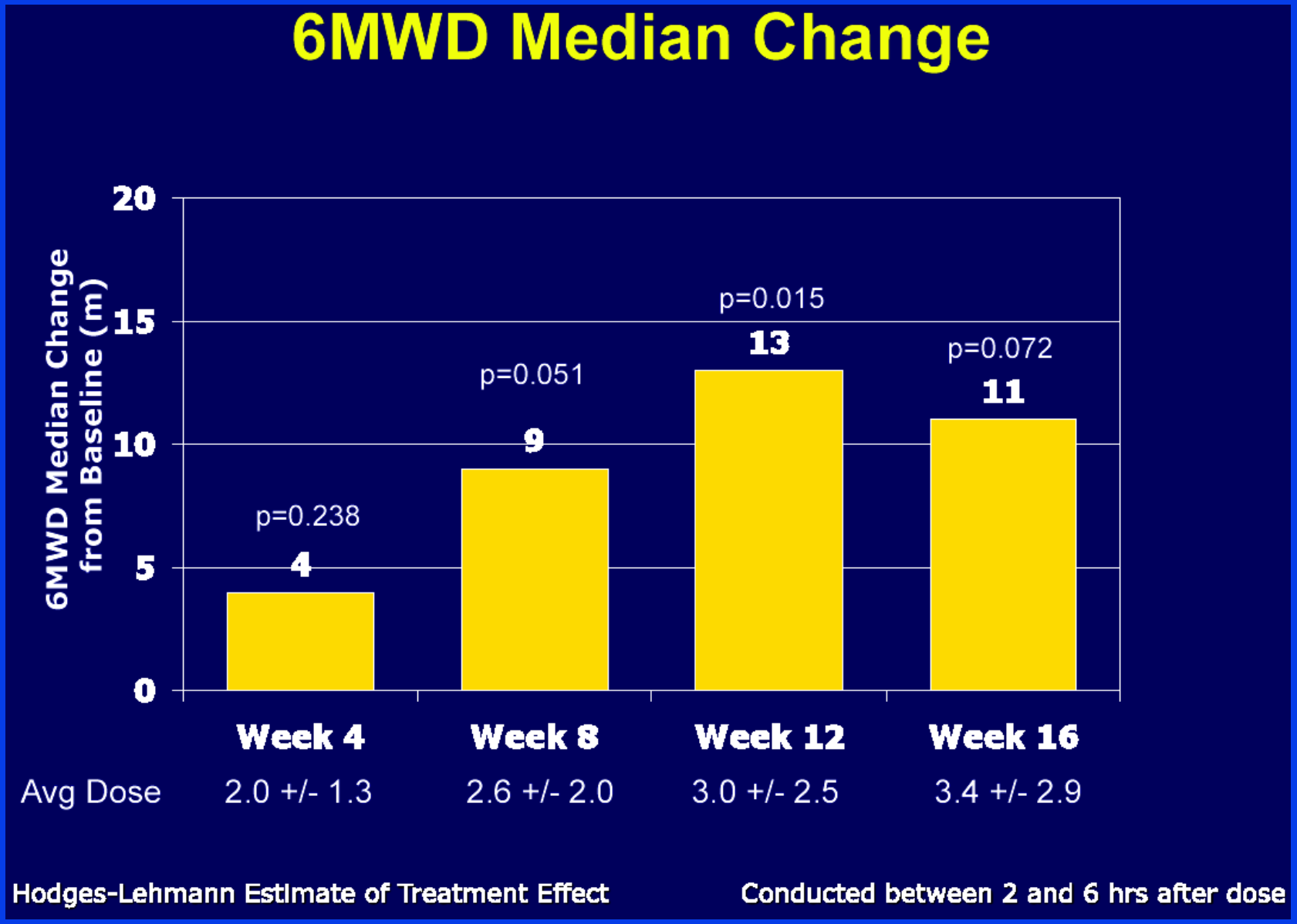
NCT01106014: *www.clinicaltrials.gov* [accessed 06 Feb 2011]

Freedom studies with oral treprostinil

Author	Acronym	Study drug	Patients	N	Duration (wks)	1 EP	Efficacy	
							1EP	TtCW
Tapson V CHEST 2012	**FREEDOM C**	UT 15 C	PAH	354	16	**6MWD**	-	-
Tapson V ATS 2012	**Freedom M**	UT 15 C	PAH	300	16	**6MWD**	+	-
Tapson V ATS 2012	**FREEDOM C [2]**	UT 15 C	PAH	310	16	**6MWD**	-	-

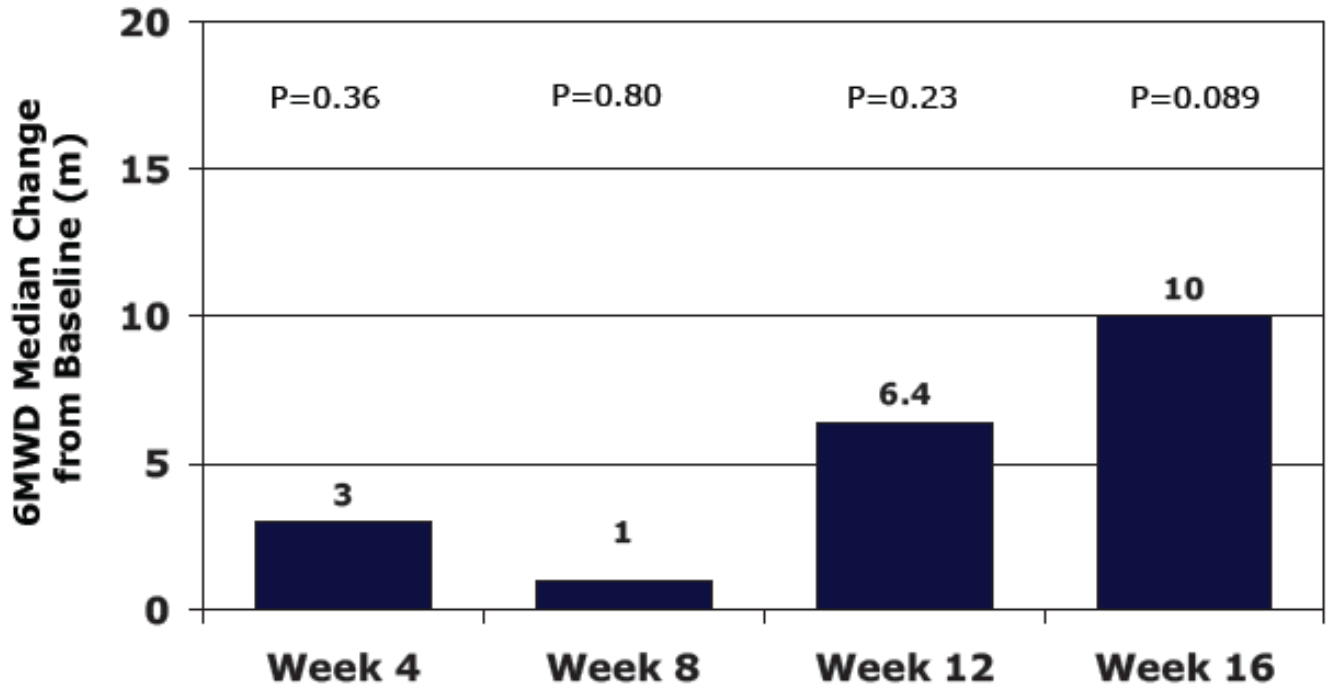
Unpublished data.
6mwt, 6-minute walk test; CHD, congenital heart disease; CTD, connective-tissue disease; I EP, initial endpoint; IPAH, idiopathic PAH; ND, no significant difference; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TPR, total pulmonary resistance; TtCW, time to clinical worsening.

FREEDOM-C1


6MWD Median Change
6MWD Median Change from Baseline (m)
20
15
10
5
0
p=0.238
4
p=0.051
9
p=0.015
13
p=0.072
11
Week 4
Week 8
Week 12
Week 16
Avg Dose
2.0 +/- 1.3
2.6 +/- 2.0
3.0 +/- 2.5
3.4 +/- 2.9
Hodges-Lehmann Estimate of Treatment Effect
Conducted between 2 and 6 hrs after dose

FREEDOM-C2

Primary Endpoint: Placebo-Corrected 6MWD Median Change



Hodges-Lehmann Estimate of Treatment Effect

Conducted between 3 and 6 hrs after dose

Preliminary Analysis—Final Results May Vary

United Therapeutics CORPORATION

FREEDOM-M: Efficacy and Safety of Oral Treprostinil Diethanolamine as Monotherapy in Patients With Pulmonary Arterial Hypertension

Lewis Rubin, MD; Keyur Parikh, MD; Tomas Pulido, MD; Carlos Jerjes-Sanchez, MD; Roblee Allen, MD; James White, MD; Adam Torbicki, MD; Kaifeng Xu, MD; David Yehle, BS; Kevin Laliberte, PharmD; Carl Arneson, MS; Zhi-Cheng Jing, MD

METHODS: Double-blind, randomized (2:1), placebo-controlled, parallel-group study comparing the twice daily (BID) administration of oral TRE to placebo (PBO) over 12 weeks in PAH patients not receiving approved PAH therapy. The primary endpoint was change in 6MWD (compared to PBO) from baseline to Week 12 in the patients with access to 0.25 mg tablets at randomization. Secondary efficacy included changes in 6MWD at Weeks 4, 8, 11 (trough), WHO functional class, Borg Dyspnea Score, dyspnea-fatigue index, signs and symptoms of PAH, and clinical worsening.

RESULTS: 349 patients were enrolled at 52 centers, with 228 patients in the primary analysis population.. Median 6MWD (peak) at Week 12 improved 23 m (Hodges-Lehmann; p=0.0125) compared to PBO (25 m for TRE and -5 m for PBO), while 6MWD at Weeks 4 and 8 improved 12 (p=0.05) and 17 meters (p=0.03). Other secondary efficacy measures did not differ significantly between oral treprostinil and placebo (p>0.05). Analysis of all 349 enrolled patients resulted in similar findings. Safety data is currently being analyzed.

CONCLUSIONS: First-line monotherapy with oral TRE significantly improves exercise capacity in PAH.

RIOCIGUAT :
A SOLUBLE GUANYLATE CYCLASE STIMULATOR

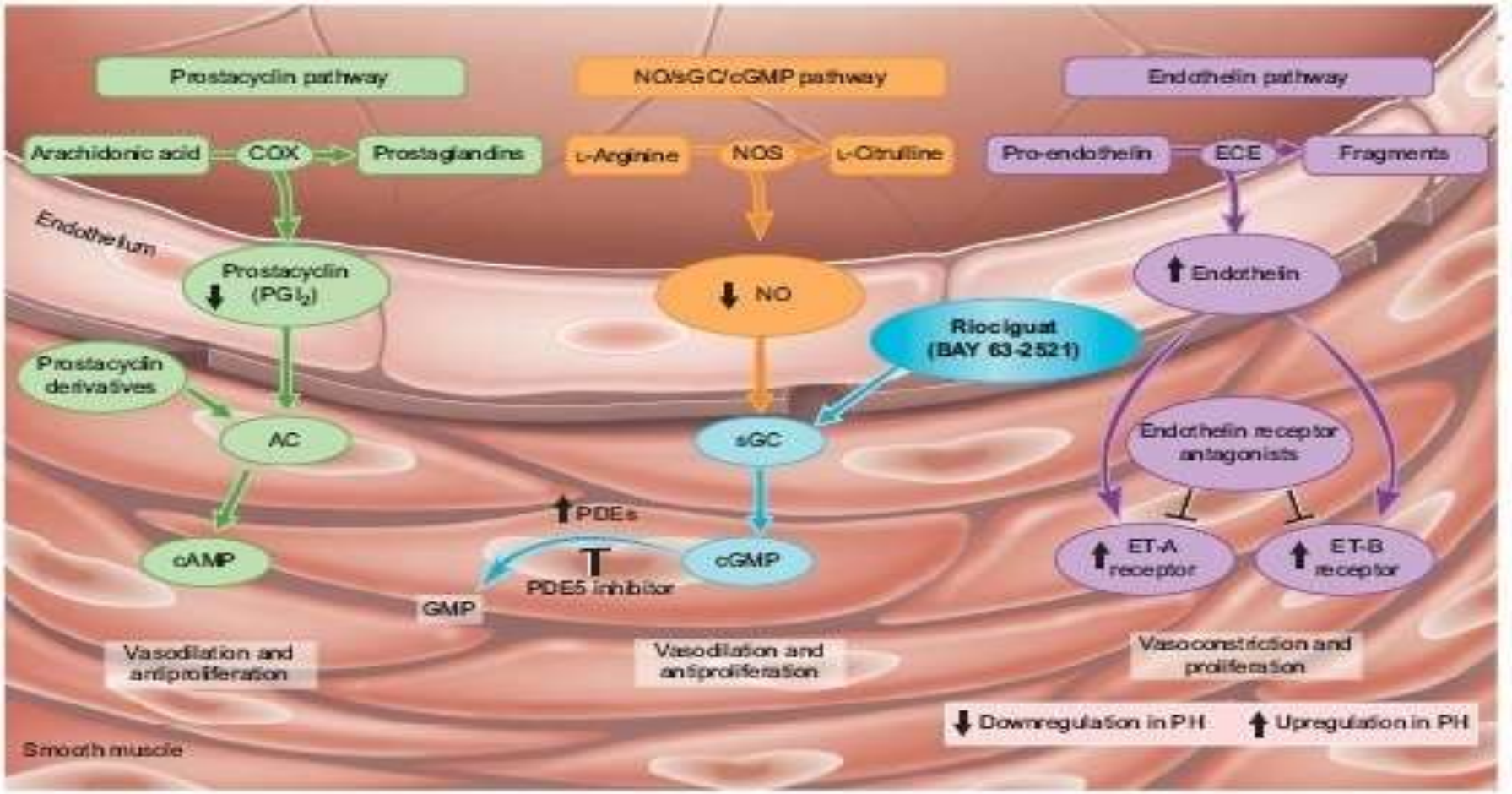


FIGURE 2. Mode of action of riociguat. Riociguat acts directly on the nitric oxide (NO) receptor soluble guanylate cyclase (sGC), and is able to stimulate the enzyme independently and in synergy with NO. AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; COX: cyclo-oxygenase; ECE: endothelin converting enzyme; ET: endothelin; GMP: guanosine monophosphate; NOS: NO synthase; PDE: phosphodiesterase; PH: pulmonary hypertension. Reproduced from [43] with permission from the publisher.

Ghofrani & Grimminger. Eur Resp Rev 2009

The NEW ENGLAND JOURNAL of MEDICINE

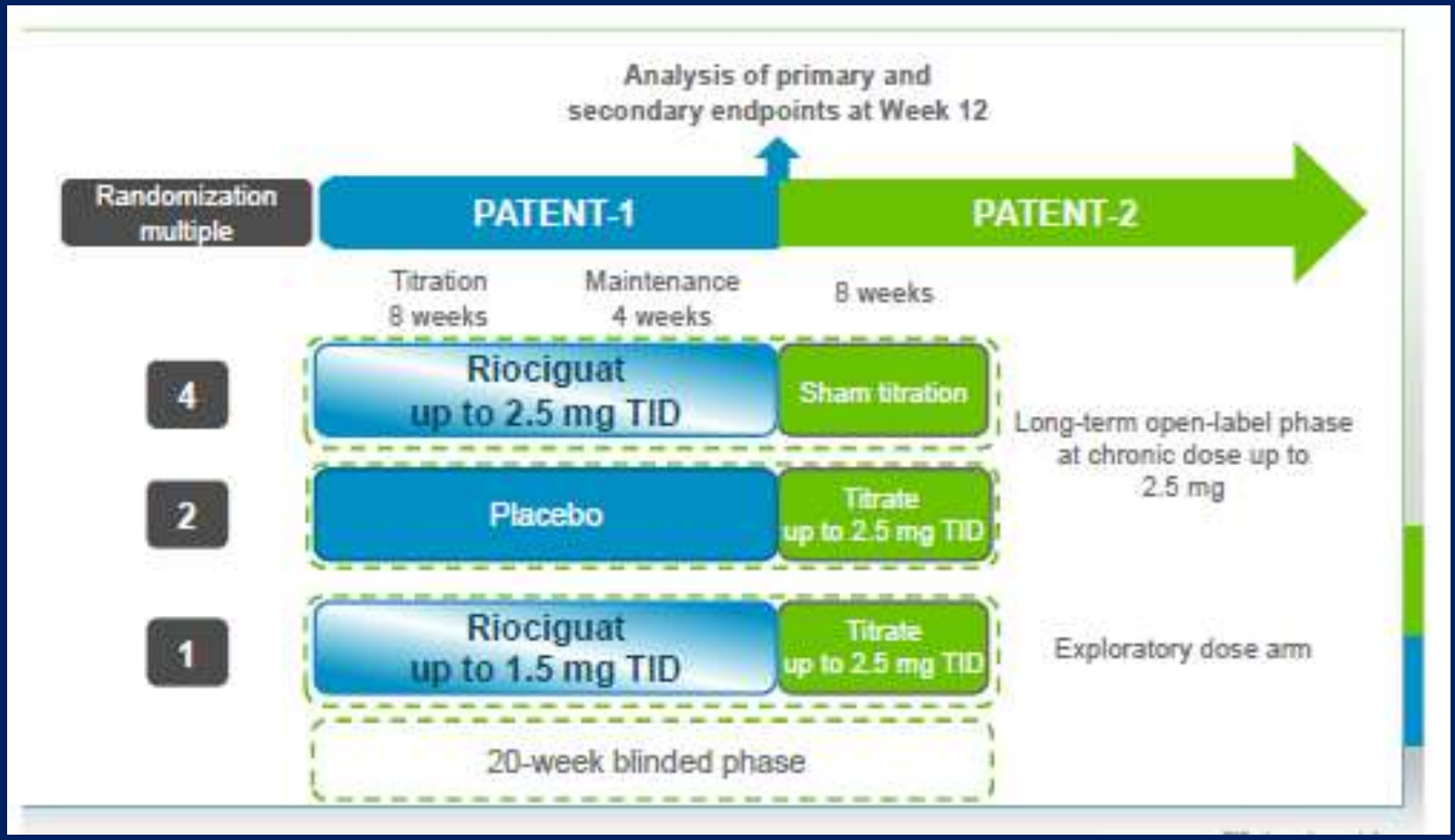
ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

Hossein-Ardeschir Ghofrani, M.D., Nazzareno Galiè, M.D., Friedrich Grimminger, M.D., Ekkehard Grünig, M.D., Marc Humbert, M.D., Zhi-Cheng Jing, M.D., Anne M. Keogh, M.D., David Langleben, M.D., Michael Ochan Kilama, M.D., Arno Fritsch, Ph.D., Dieter Neuser, M.D., and Lewis J. Rubin, M.D., for the PATENT-1 Study Group*

NEJM 2013; 369: 4

Patent study desin



A Ghofrani et al NEJM 2013

Riociguat for the treatment of Pulmonary arterial hypertension

- Riociguat, a soluble guanylate cyclase stimulator, has been shown in a phase 2 trial to be beneficial in the treatment of pulmonary arterial hypertension
- This phase 3, double-blind study, randomly assigned 443 patients with symptomatic pulmonary arterial hypertension to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily, or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily
- Patients who were receiving no other treatment for pulmonary arterial hypertension and patients who were receiving endothelin-receptor antagonists or (nonintravenous) prostanoids were eligible
- The primary end point was the change from baseline to the end of week 12 in the distance walked in 6 minutes
- Secondary end points included the change in pulmonary vascular resistance, N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, World Health Organization (WHO) functional class, time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables, and safety

Riociguat for the treatment of Pulmonary arterial hypertension

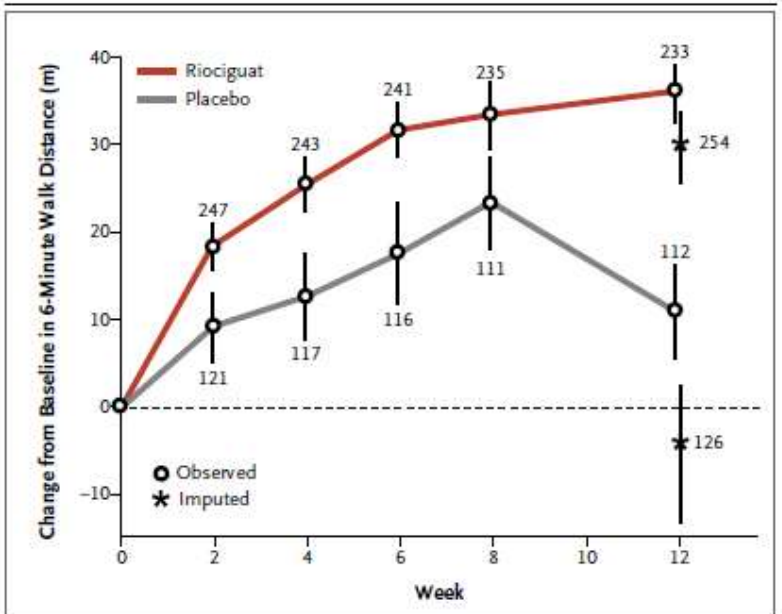


Figure 2. Mean Change from Baseline in the 6-Minute Walk Distance.

Mean (±SE) changes from baseline in the distance walked in 6 minutes during the 12-week PATENT-1 study period are shown in the group that received riociguat at a dose up to 2.5 mg three times daily as compared with the placebo group. The data were analyzed in the modified intention-to-treat population without imputation of missing values; imputed values are provided at week 12. The number at each data point indicates the number of patients included in the assessment at that time point. The least-squares mean difference in the 6-minute walk distance at week 12 was 36 m (95% CI, 20 to 52; P<0.001). The last observed value (not including follow-up) was carried forward for patients who completed the study or withdrew; the worst value (0 m) was imputed in the case of death or clinical worsening without a termination visit or without a measurement at the termination visit.

CONCLUSIONS

Riociguat significantly improved exercise capacity and secondary efficacy end points in patients with pulmonary arterial hypertension

This benefit was consistent in patients who were receiving endothelin-receptor antagonists or prostanoids and in those who were receiving no other treatment for the disease

EDITORIAL
Riociguat for Pulmonary Hypertension
A Glass Half Full

- The major limitation of PATENT-1 is the modest effect size achieved. Only 21% of treated patients had functional improvement at 12 weeks (as compared with 14% in the placebo group). The increase in 6-minute walk distance is similar to that observed in randomized, controlled trials of other oral therapies for Group 1 pulmonary hypertension.
- Another caveat is the relationship to the sponsoring company
- However, I view the glass as half full, because riociguat appears to be safe and is a promising addition to the pharmacopeia for Group 1 pulmonary hypertension

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

A multicenter, double-blind,randomized, placebo-controlled, event driven, phase 3 trial.

742 Patients randomized in three arms

Primary end point: time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension.

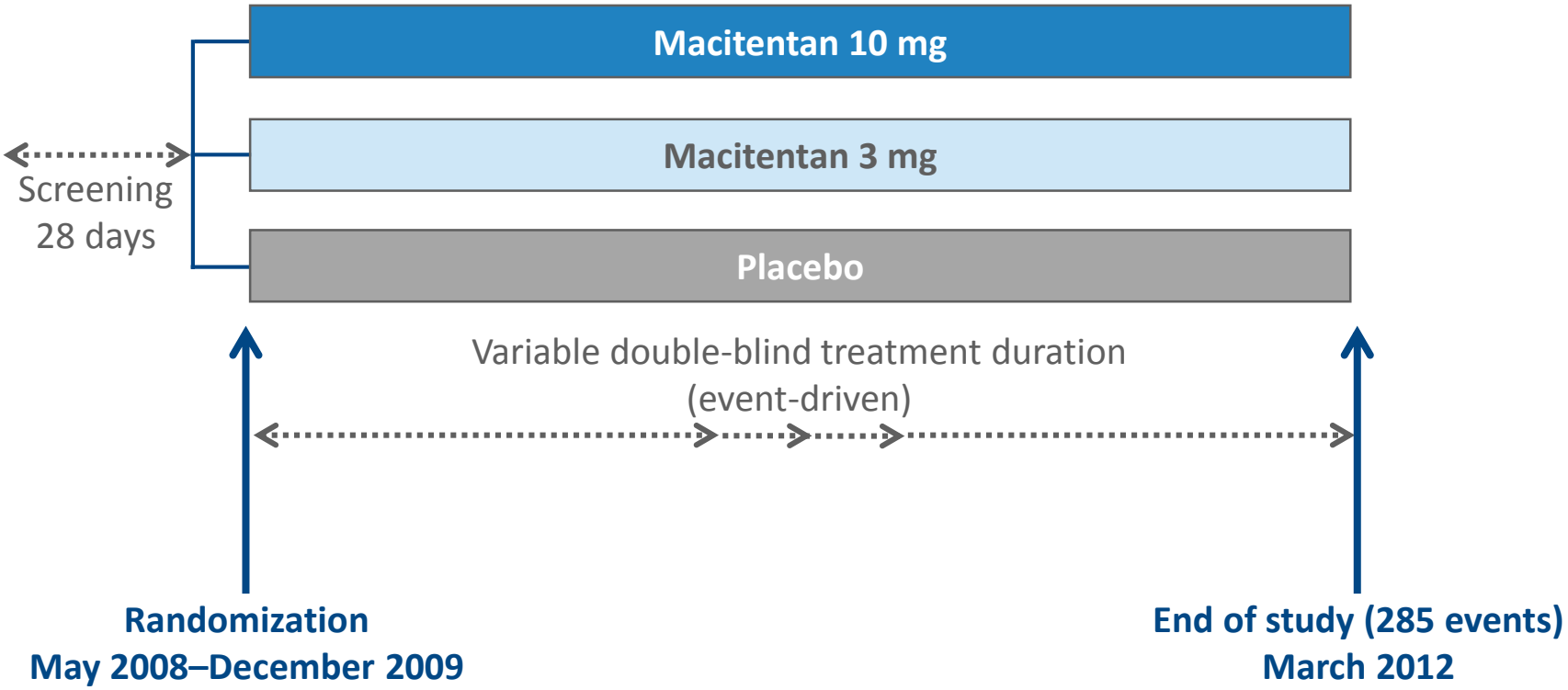
Pulido T et al, NEJM 2013

SERAPHIN study

- Objective: to study long-term efficacy and safety of macitentan in PAH using an event-driven trial design
- Primary endpoint
  - Time to the first morbidity or mortality event up to end of double-blind treatment
- Secondary endpoints
  - 6-minute walk distance (6MWD) at Month 6
  - WHO functional class (FC) at Month 6
  - Time to death due to PAH or hospitalization for PAH
  - All-cause mortality
  - Safety and tolerability

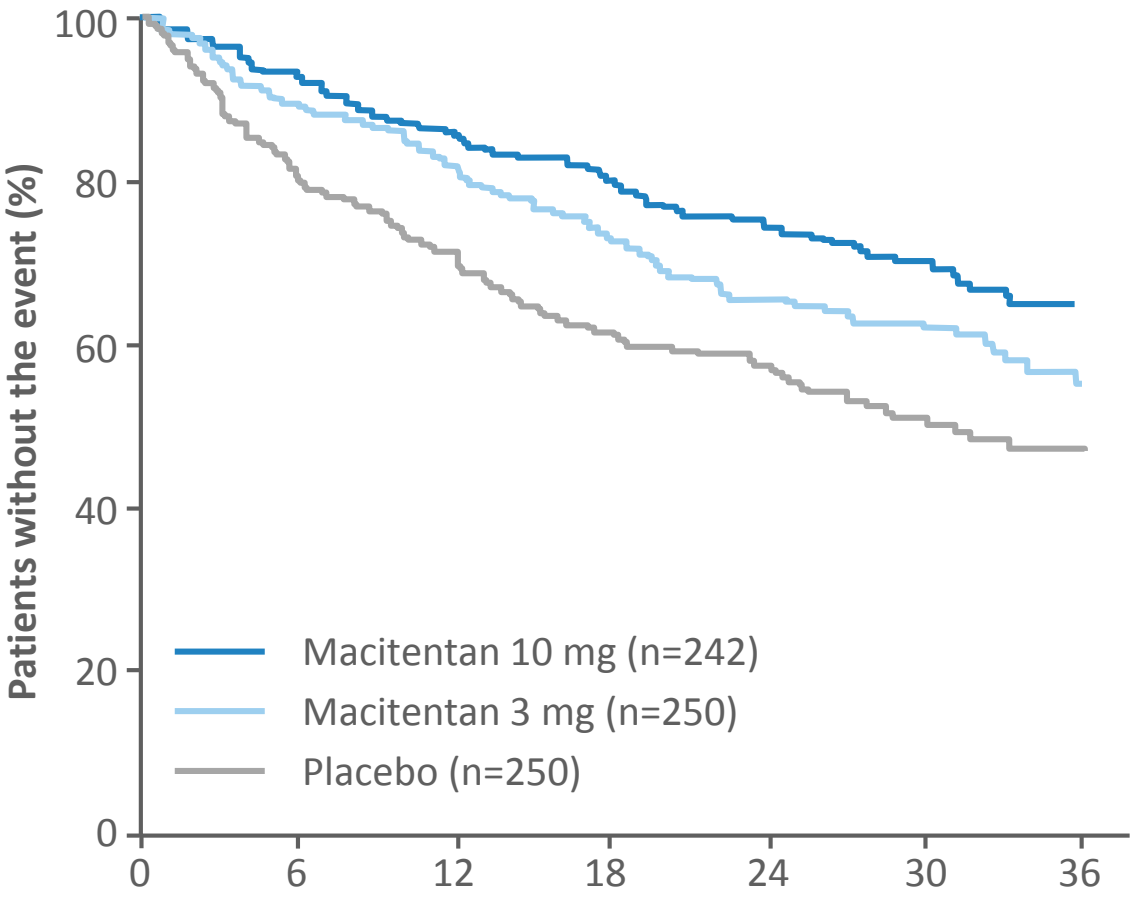
NCT identifier: 00660179

- Multicenter, double-blind, randomized, placebo-controlled, parallel-group, event-driven, phase III clinical trial



Patients were censored at end of double-blind treatment

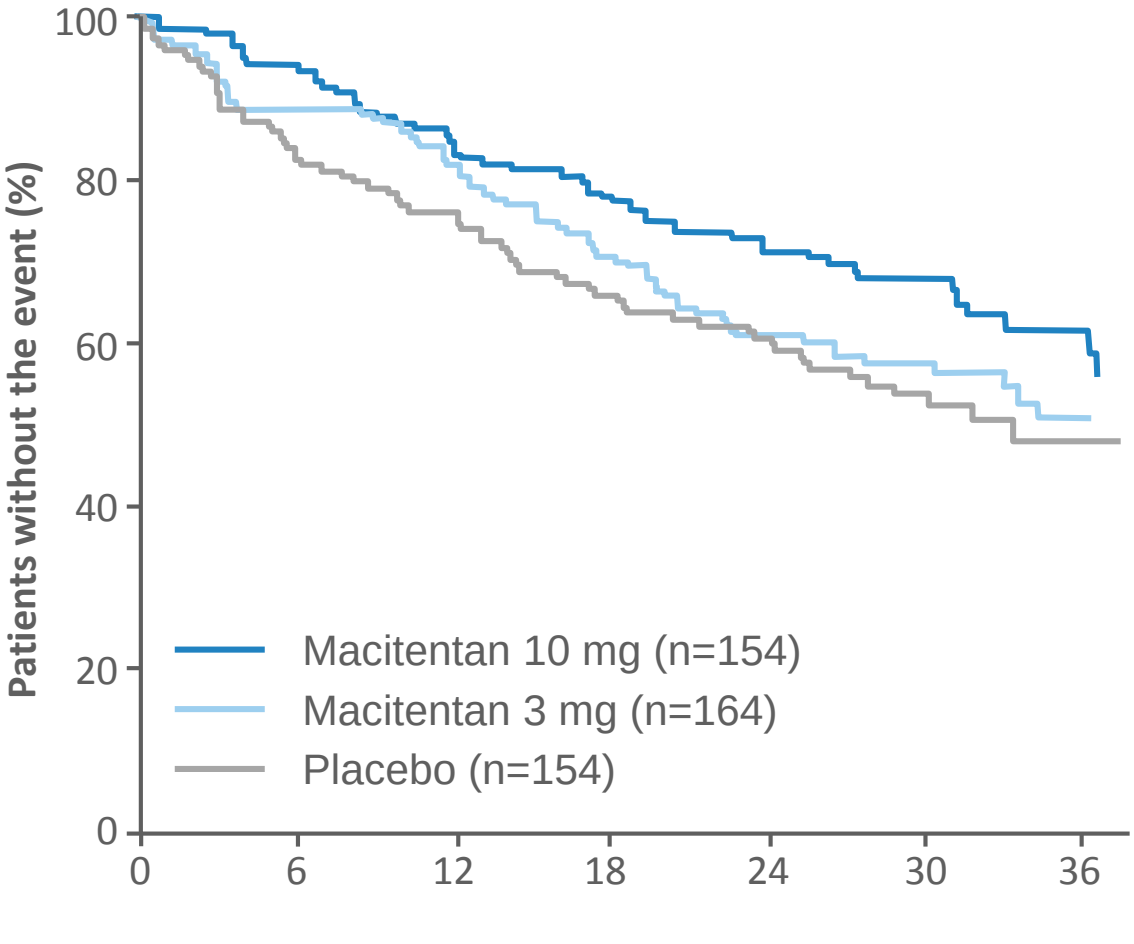
Primary endpoint: Morbidity and mortality



Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 45%
Macitentan 3 mg: 30%

Macitentan 10 mg: Hazard ratio=0.55; log-rank p<0.0001
Macitentan 3 mg: Hazard ratio=0.70; log-rank p=0.0108

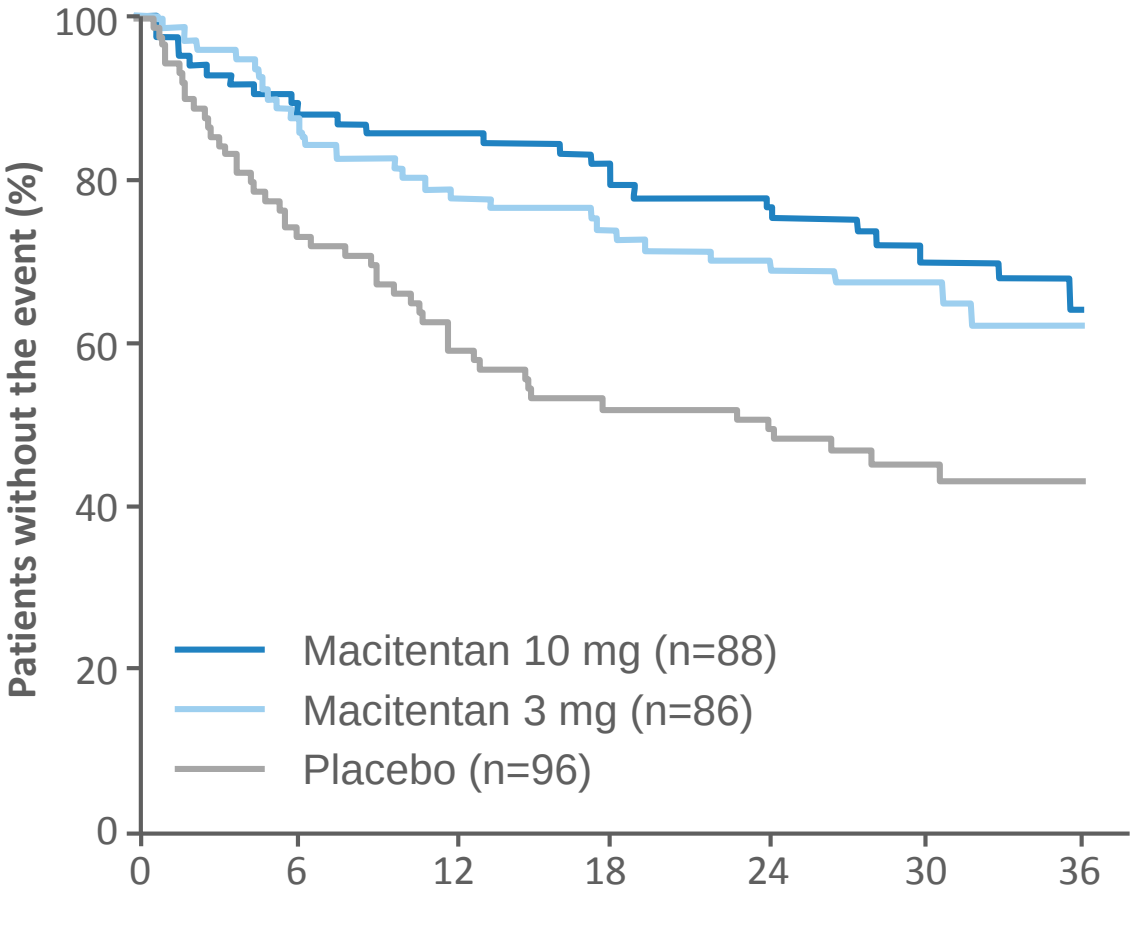
Morbidity and mortality in patients on background PAH therapy



Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 38%
Macitentan 3 mg: 17%

Macitentan 10 mg: Hazard ratio=0.62; log-rank p=0.0094
Macitentan 3 mg: Hazard ratio=0.83; log-rank p=0.2672

Morbidity and mortality in patients not on background PAH therapy



Risk reduction of primary endpoint event vs placebo
Macitentan 10 mg: 55%
Macitentan 3 mg: 47%

Macitentan 10 mg: Hazard ratio = 0.45; log-rank p = 0.0007
Macitentan 3 mg: Hazard ratio = 0.53; log-rank p = 0.0067

Drugs targeting novel pathways : PAH therapies currently under development

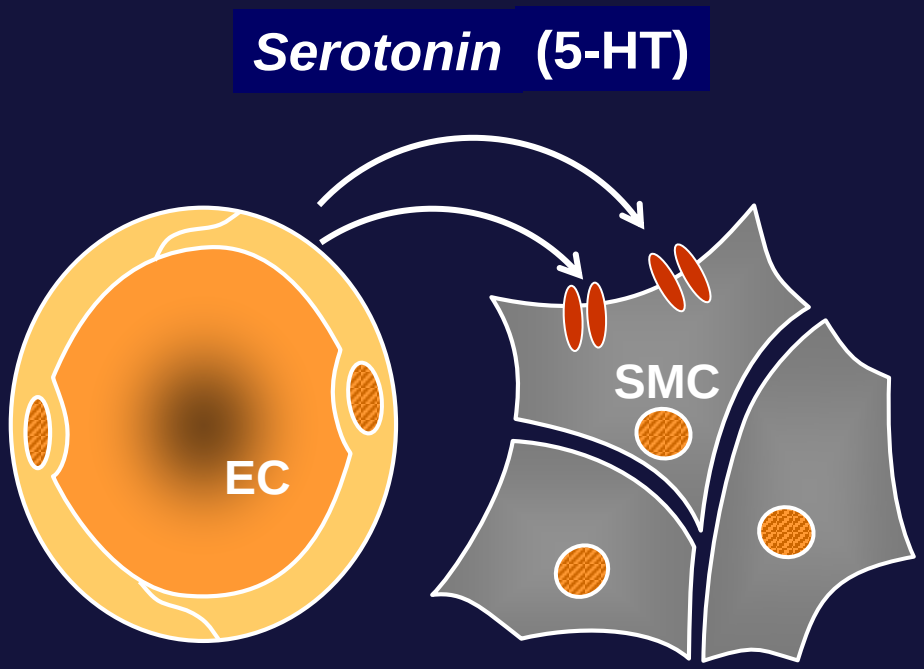
Drug	Mode of action	Phase of development	Results
Simvastatin	Anti –proliferative Increasing apoptosis	2 Phases II	2 negative trials
Terguride	5-HT2B/2A receptors antagonists	1 phase II	negative result
Imatinib	Tyrosine kinase inhibitor	III	Benefit/risk ratio questionable

www.clinicaltrials.gov

STATINS IN PAH: Rational

- In addition to ↘cholesterol, statins have antiproliferative, antithrombotic, antiinflammatory, and antioxidant effects.
- Simvastatin, have been reported to attenuate the development of PH and to reverse established PH and vascular remodeling in a number of experimental animal models
- There is some evidence that this is achieved through increased apoptosis as well as reduced proliferation of SMCs.

2 negative trials in humans



✓Serotonin(5-HT) is a potent growth Factor of SMCs in humans

✓Patients with IPAH have increased circulating 5-HT levels

✓5-HT Transporters and 5-HT2B receptors are overexpressed on human PA SMCs

Two ways for blocking the action of serotonin:

- Specific Serotonin reuptake inhibitors (SSRIs)
- 5-HT2B Antagonists

Terguride is a potent 5-HT2B/2A receptors antagonists

- Indications: Ovulation disorders due to hyperprolactinemia, puerpural lactation, hyperprolactemic pituitary adenoma.
- Mode of action: Terguride acts as a partial dopamine receptor agonist in the pituitary gland.
- More than 10 years clinical experience with Terguride.
- All adverse effects seen, even after overdose, are reversible and can be explained by the dopamine agonistic activity of terguride.

Proof-Of-Concept Study of Terguride In PAH (TERPAH)

- Double-blind, randomized, placebo-controlled, proof-of- concept study in patients with either idiopathic or connective- tissue (scleroderma or systemic lupus erythematosus) associated PAH (NYHA FC II-IV).
- Patients on specific PAH mono-therapy (or combination-therapy not exceeding two PAH specific drugs) with either endothelin receptor antagonists or phosphodiesterase type 5 (PDE5) inhibitors or non-parenteral prostanoids (i.e. inhaled, oral, s.c.) were recruited (pre-treated patients). Treatment naive patients were not specifically excluded

Results: negative study (6’ WD + 4 meters)

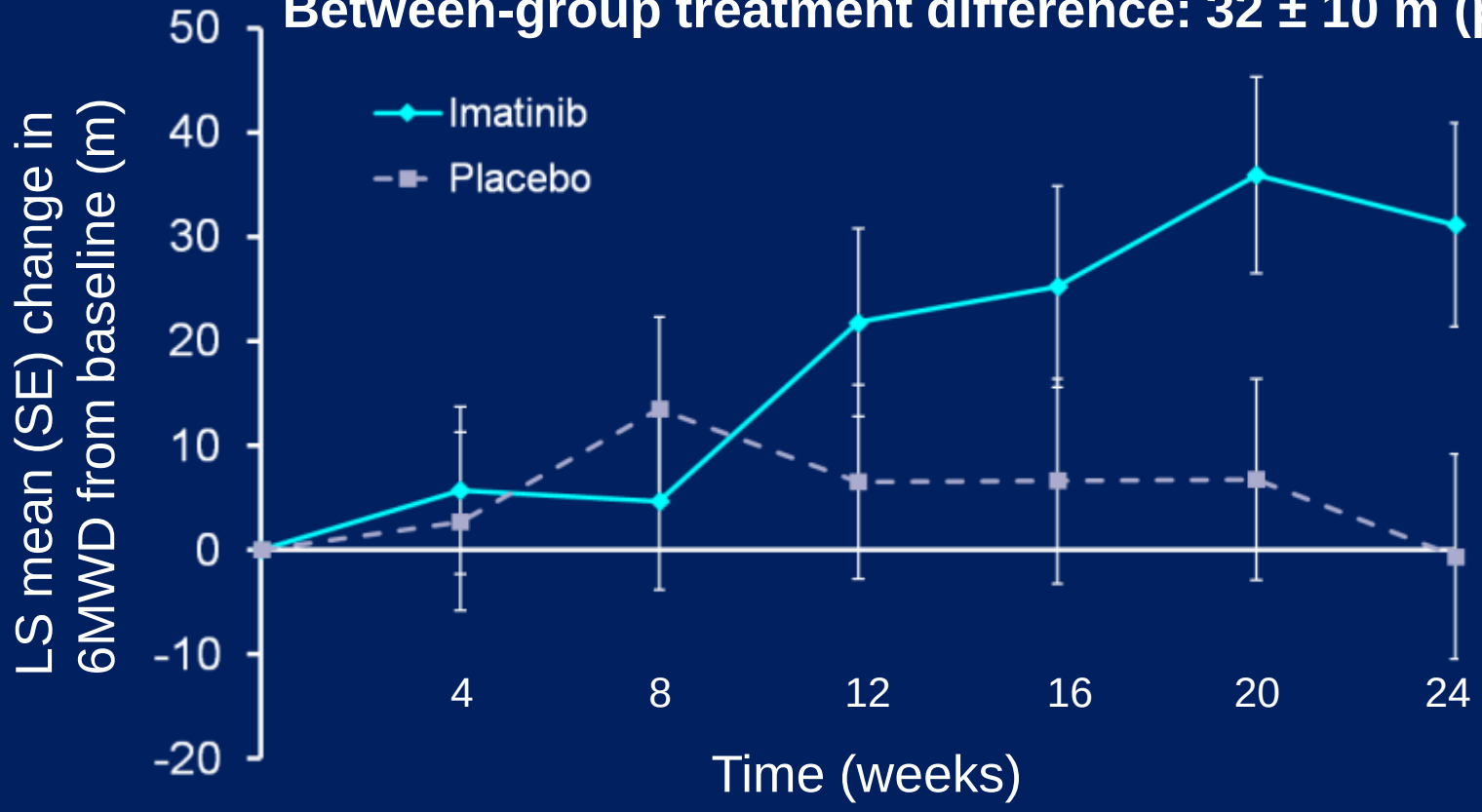
Ghofrani et al ATS 2012

Imatinib in pulmonary arterial hypertension, a randomized, efficacy study (IMPRES)

Marius M Hoeper,[1] Robyn J Barst,[2] Nazzareno Galiè,[3] Paul M Hassoun,[4] Nicholas W Morrell,[5] Andrew J Peacock,[6] Gérald Simonneau,[7] Victor F Tapson,[8] Fernando Torres,[9] Keith Liu,[10] Debbie Quinn,[11] Hossein-Ardeschir Ghofrani[12]

Primary endpoint: change in 6MWD

Between-group treatment difference: 32 ± 10 m (p=0.002)



No. of patients							
Imatinib	92	89	84	76	71	72	66
Placebo	93	93	91	88	82	84	80

Subdural hematomas

- Unexpectedly, SDH occurred in 9 patients in clinical trials with imatinib
  - 2 in IMPRES core study plus 6 in open-label extension study
  - 1 in Phase II study
- All patients were on imatinib and anticoagulations
- Outcome
  - 7 patients with SDH recovered (1 died 8 mos. later of RV failure)
  - 1 patient died of SDH
  - 1 patient died of unrelated causes

FDA requests Novartis to provide additional data regarding benefits and risks of imatinib in advanced PAH

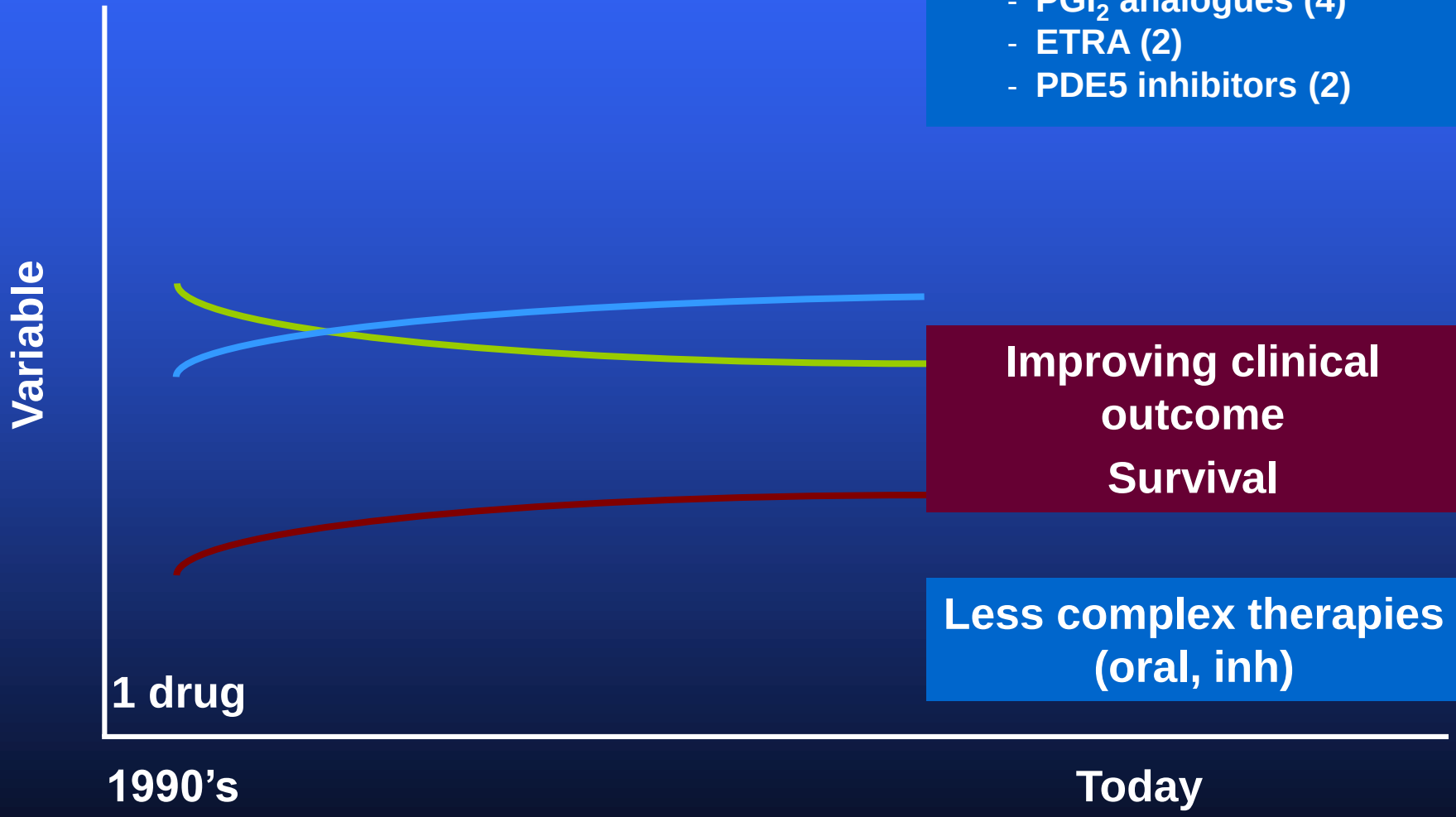
PAH - What progress in the last 20 years?

Lung transplantation

iv epoprostenol

8 drugs available

- **PGI_2 analogues (4)**
- **ETRA (2)**
- **PDE5 inhibitors (2)**



Improving clinical outcome

Survival

Less complex therapies (oral, inh)