PAH: Standard of Care

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TF 7 Therapy - Standard of Care Questions

A. Do we have additional information on the role of rehabilitation in PAH patients?

B. Should first-line combination therapy be the gold standard of severe WHO FC IV PAH (and what about other FC)?

C. How can we modify the current treatment algorithm including the new approved drugs?

D. Should we adapt the treatment algorithm to the different PAH types and to different countries (country organization)?

1st WHO PH

Geneva

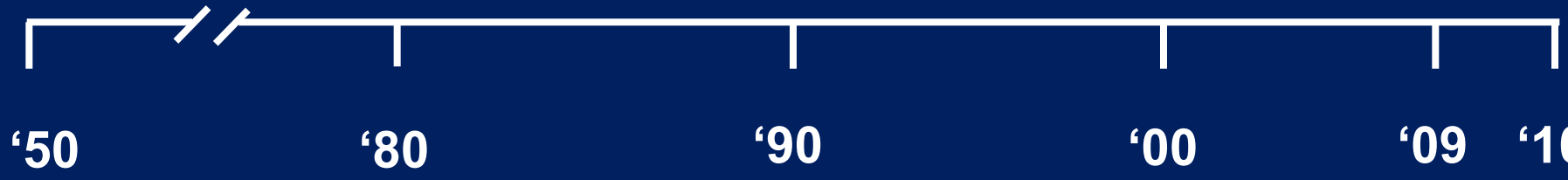
1973

PH Classification 1950-1998

(1st WHO PH Geneva 1973)

1. Primary Pulmonary Hypertension
2. Secondary Pulmonary Hypertension
3. Associated Pulmonary Hypertension

PAH time course of Treatments



Tolazoline, Hydralazine, Acetylcholine, Phentolamine, Isoproterenol, Diazoxide, Nitrates,…

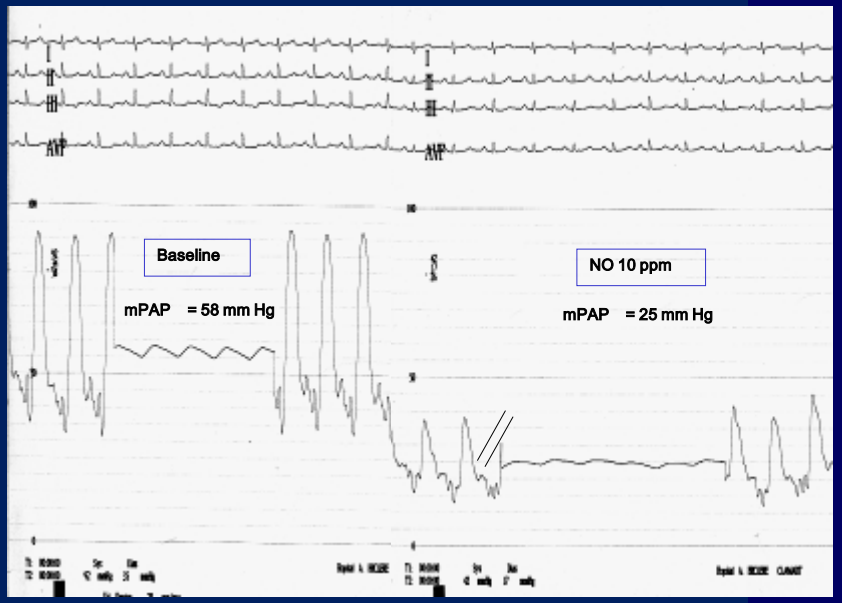
Calcium Channel Blockers in vasoreactive pts

Calcium Channel Blockers

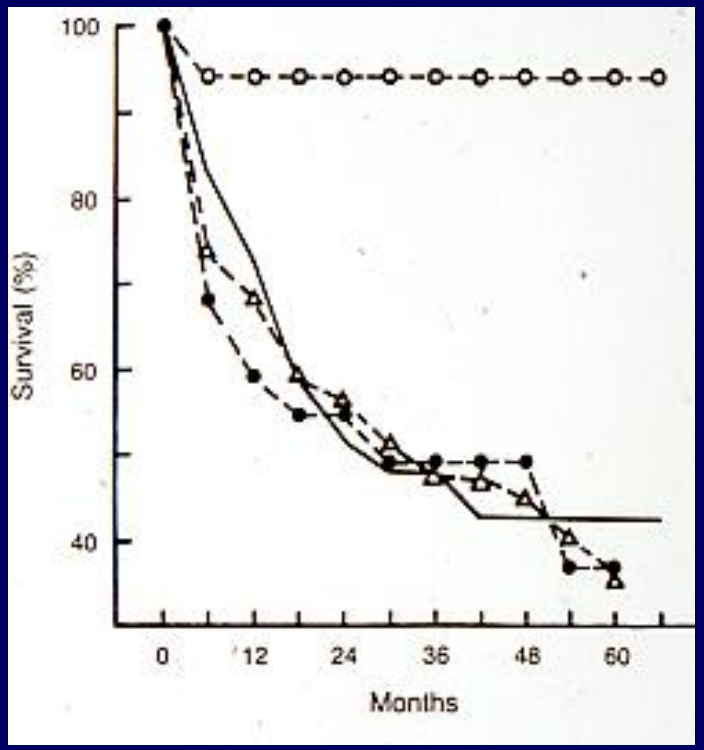
Vasoreactivity – NO test

Definition

↓ mPAP > 10, < 40 mmHg abs; CO =/↑

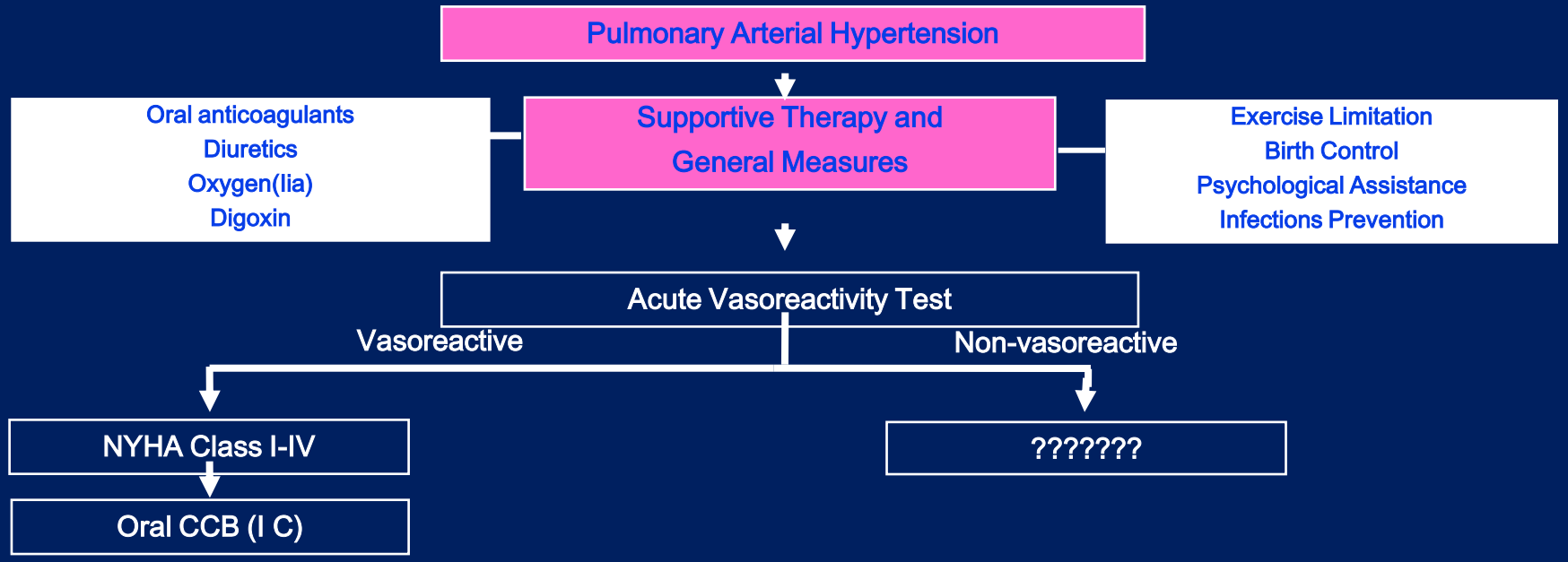


~ 10%



Rich S et al. N Engl J Med 1992, 32:76-81

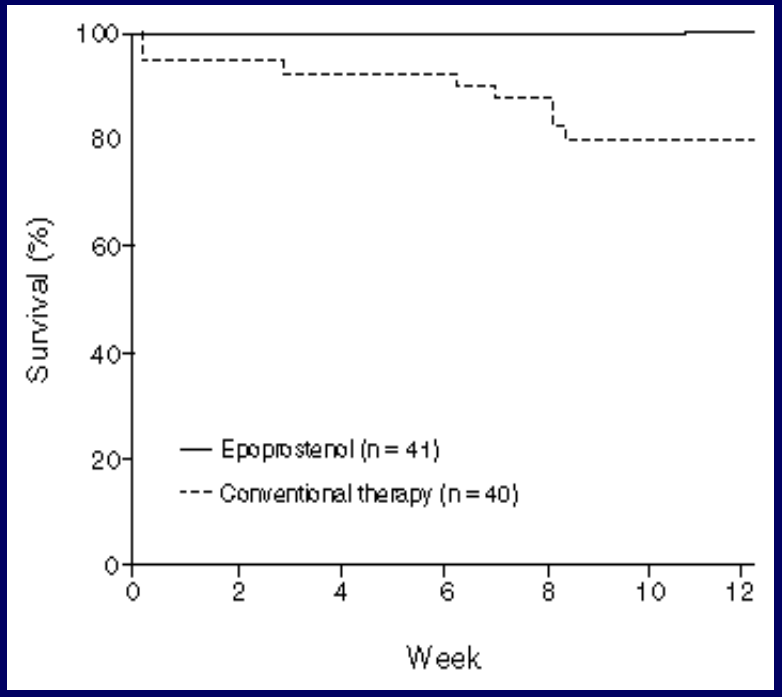
Treatment Algorithm before 1998

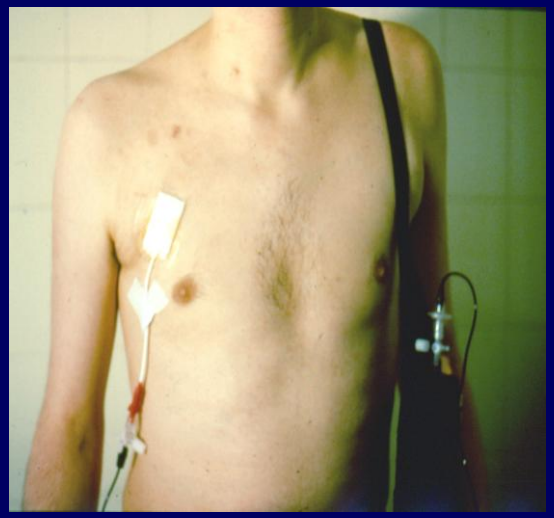


A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

ROBYN J. BARST, M.D., LEWIS J. RUBIN, M.D., WALKER A. LONG, M.D., MICHAEL D. MCGOON, M.D., STUART RICH, M.D., DAVID B. BADESCH, M.D., BERTRON M. GROVES, M.D., VICTOR F. TAPSON, M.D., ROBERT C. BOURGE, M.D., BRUCE H. BRUNDAGE, M.D., SPENCER K. KOERNER, M.D., DAVID LANGLEBEN, M.D., CESAR A. KELLER, M.D., SRINIVAS MURALI, M.D., BARRY F. URETSKY, M.D., LINDA M. CLAYTON, PHARM.D., MARIA M. JÖBSIS, B.A., SHELMER D. BLACKBURN, JR., B.A., DENISE SHORTINO, M.S., JAMES W. CROW, PH.D., FOR THE PRIMARY PULMONARY HYPERTENSION STUDY GROUP*

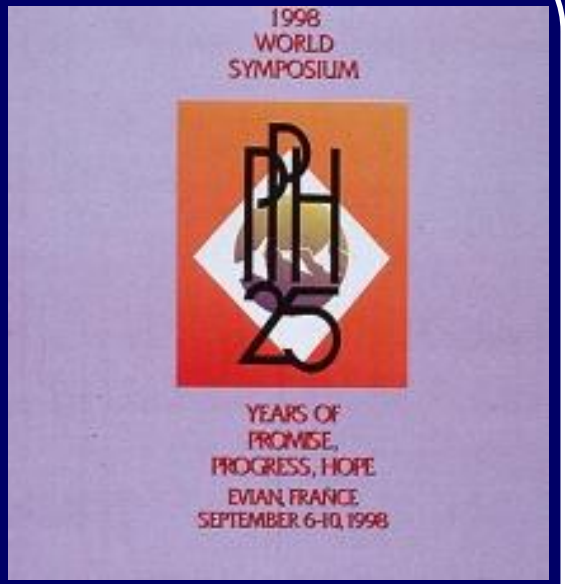
New Engl J Med 1996; 334:296-301





Published RCTs in PAH

1. Rubin, **Epoprostenol** in PPH. Ann Intern Med 1990
2. Barst, **Epoprostenol** in PPH. N Engl J Med 1996
3. Badesch, **Epoprostenol** scleroderma PAH. Ann Intern Med 2000

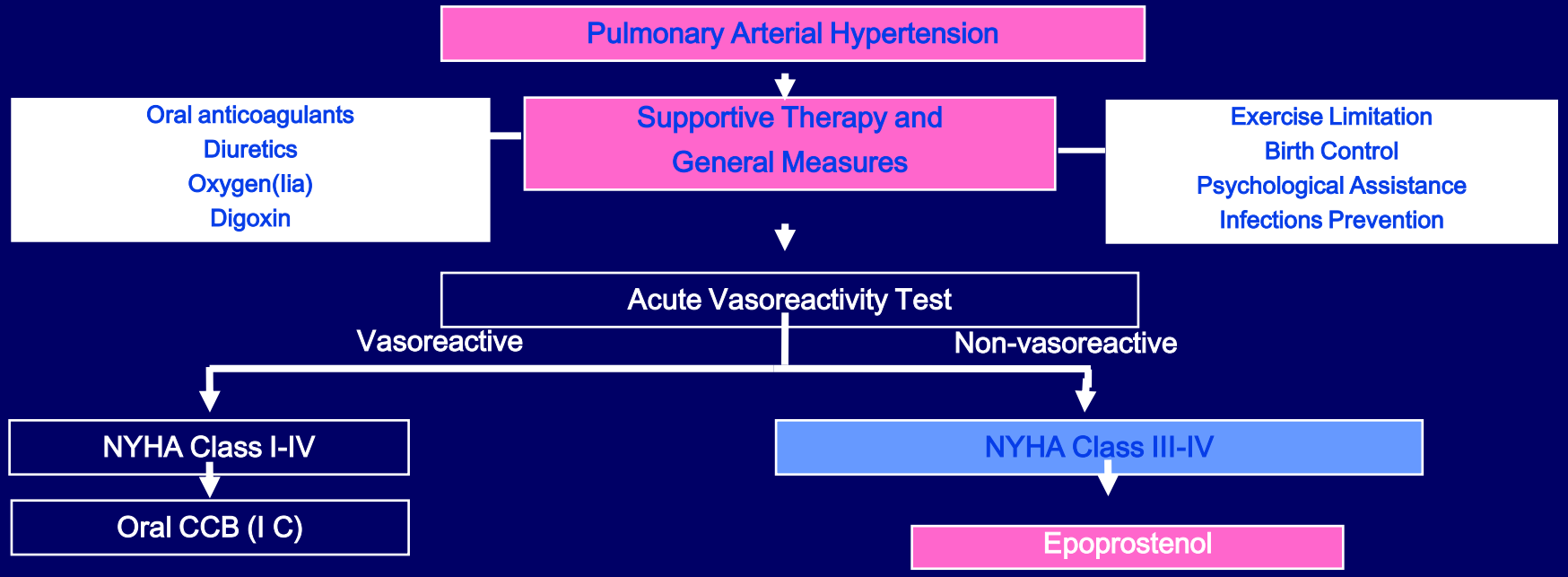


2nd WHO PH

Evian

1998

Treatment Algorithm …1998 - 2003



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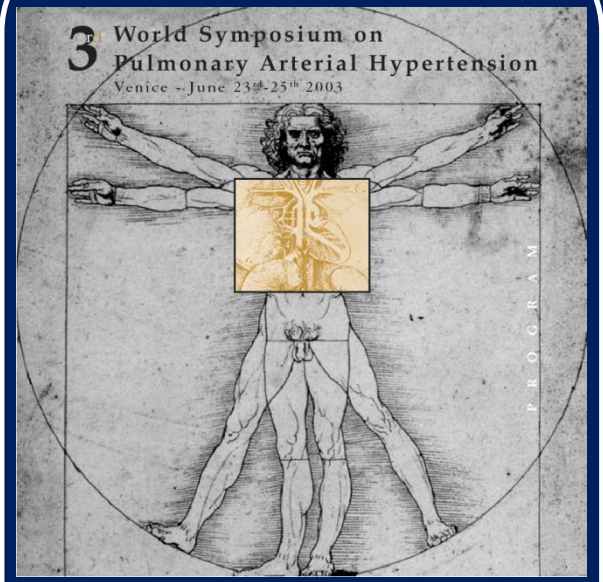
3. Badesch, **Epoprostenol** scleroderma PAH. Ann Intern Med 2000
4. Channick, **Bosentan** in PAH. Lancet 2001
5. Langleben, **Terbogrel** in PPH. Am J Cardiol 2002
6. Simonneau, **Treprostinil** in PAH. Am J Respir Crit Care Med 2002
7. Galié, **Beraprost** in PAH. J Am Coll Cardiol 2002
8. Olschewski, **Inhaled Iloprost** in PH. N Engl J Med 2002
9. Rubin, **Bosentan** in PAH. N Engl J Med 2002
10. Barst, **Beraprost** in PAH. J Am Coll Cardiol 2003
11. Sastry, **Sildenafil** in IPAH. J Am Coll Cardiol 2004
12. Humbert, **Bosentan + Epoprostenol** in PAH. Eur Respir J 2004
13. Barst, **Sitaxsentan.** Am J Respir Crit Care Med 2004
14. Galié, **Sildenafil** in PAH. N Engl J Med 2005



3rd WSPAH

Venice

2003

Approved Drugs for PAH

European Medicines Agency

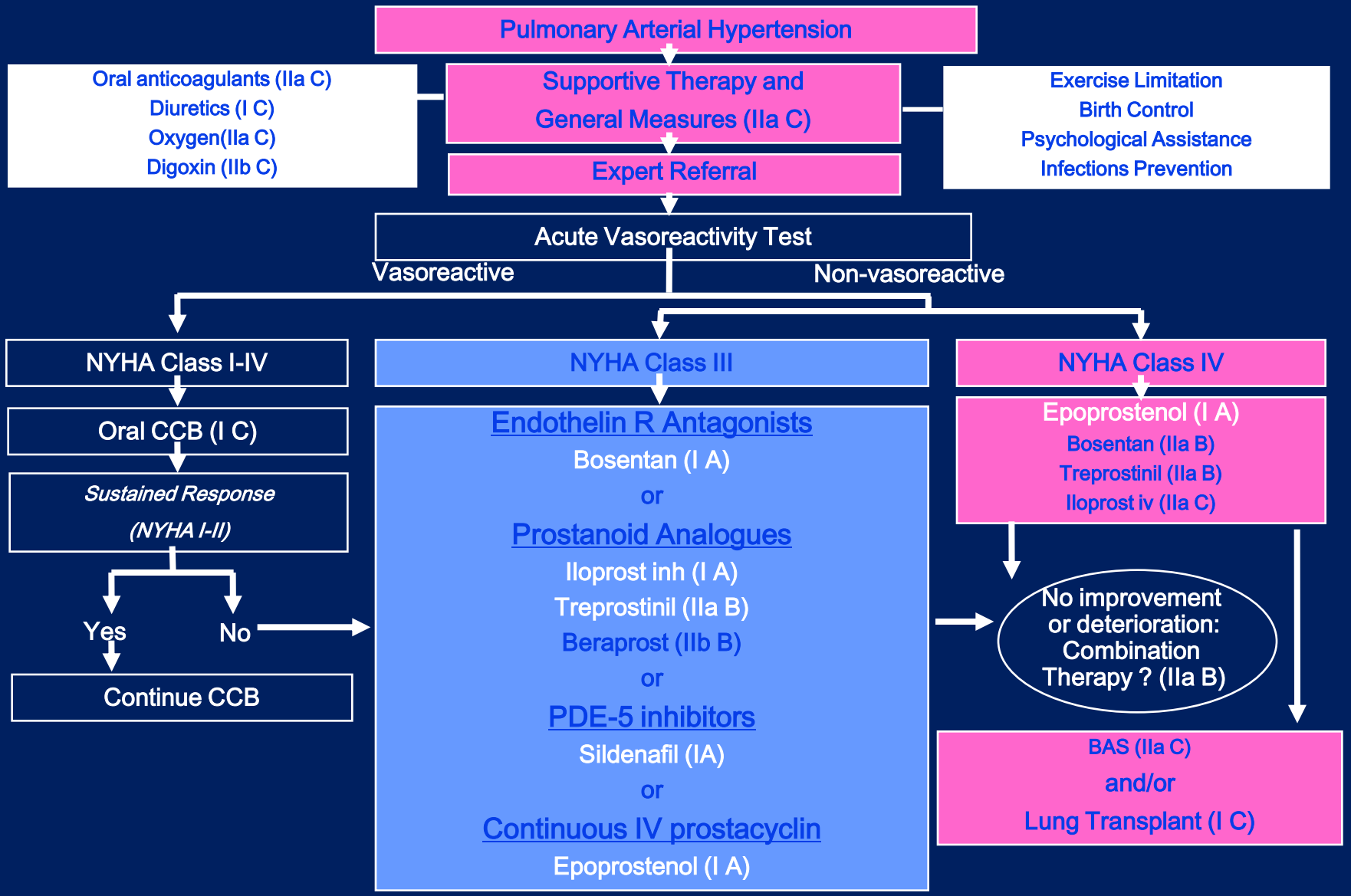
emea

FDA

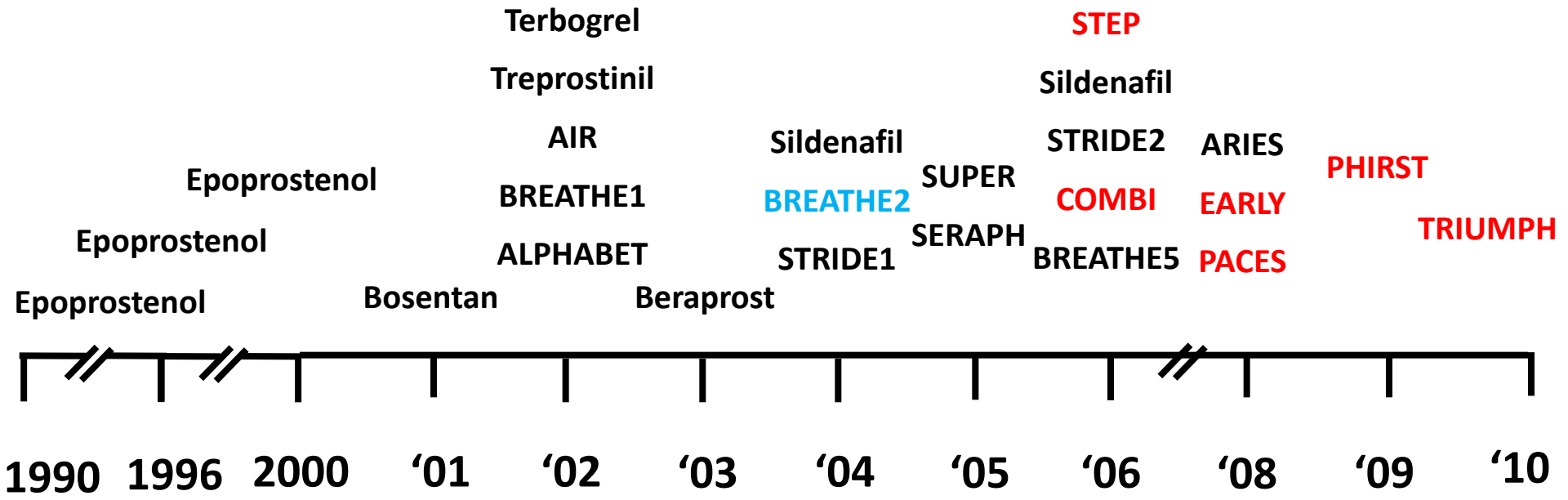
Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
Treprostinil sc

Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
Treprostinil sc

PAH treatment algorithm - 2004



Galiè N, *et al. Eur Heart J* 2004; 25:2243-2278.



Monotherapy

Monotherapy and/or Sequential Combination

Upfront Combination

N.Galiè, M.Palazzini, A.Manes, Eur Heart J 2010

Approved Drugs for PAH

European Medicines Agency

emea

Ambrisentan
Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
~~Sitaxentan~~
Tadalafil
Treprostinil sc

FDA

Ambrisentan
Bosentan
Epoprostenol iv
Iloprost inhal
Sildenafil
Tadalafil
Treprostinil sc, iv, inhal

European Heart Journal

EUROPEAN SOCIETY OF CARDIOLOGY®

CURRENT OPINION

Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses

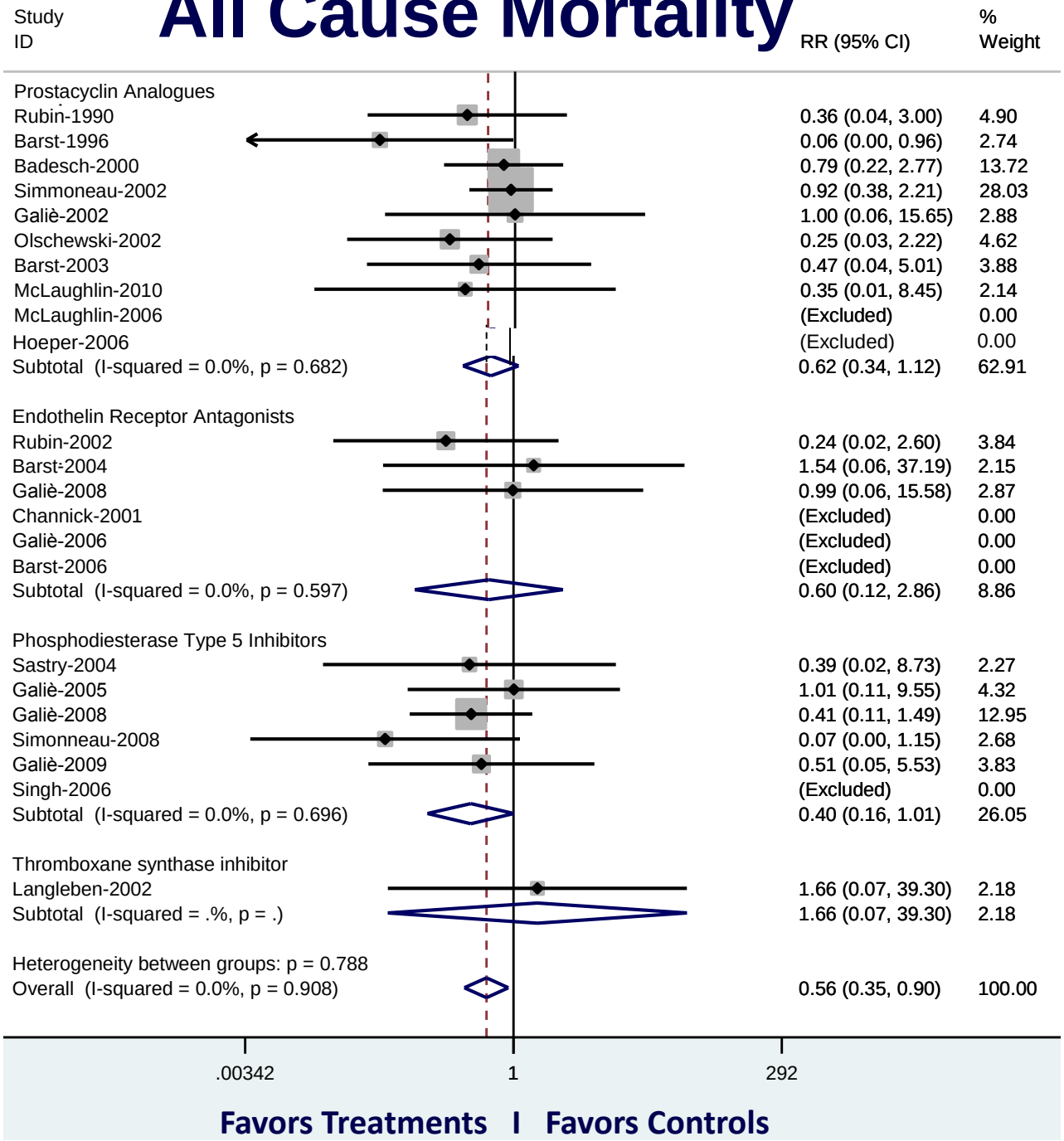
Nazzareno Galiè*, M Palazzini, A Manes

Institute of Cardiology, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

Received 9 December 2008; revised 18 December 2008; accepted 9 January 2009

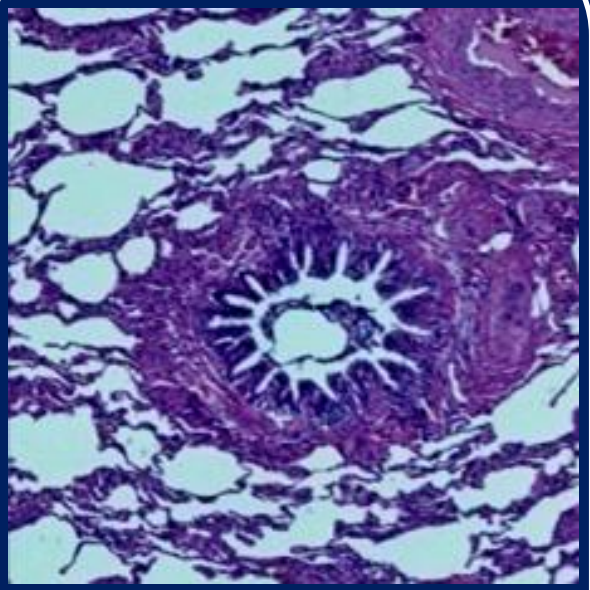
- **Medline search from January 1990 to April 2010**
- **25 RCTs, 3839 patients**

All Cause Mortality

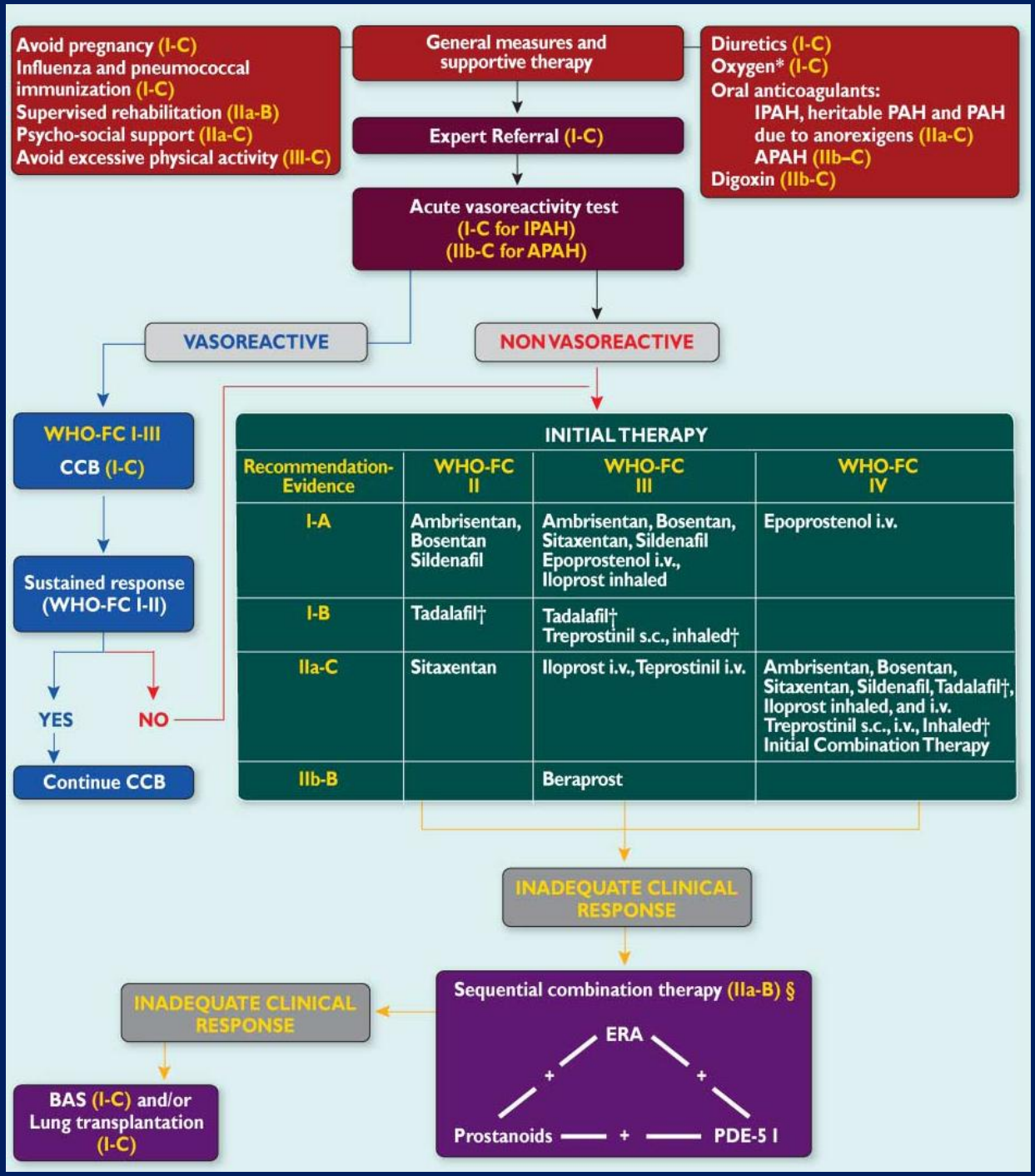


RR = - 44%

P = 0.016



4th WSPH
Dana Point
2008



Galiè.N et al Eur Heart J and Eur Respir J, 2009

Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan Riociguat, Selexipag)
- Transplantation indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization

Areas of Algorithm Improvement

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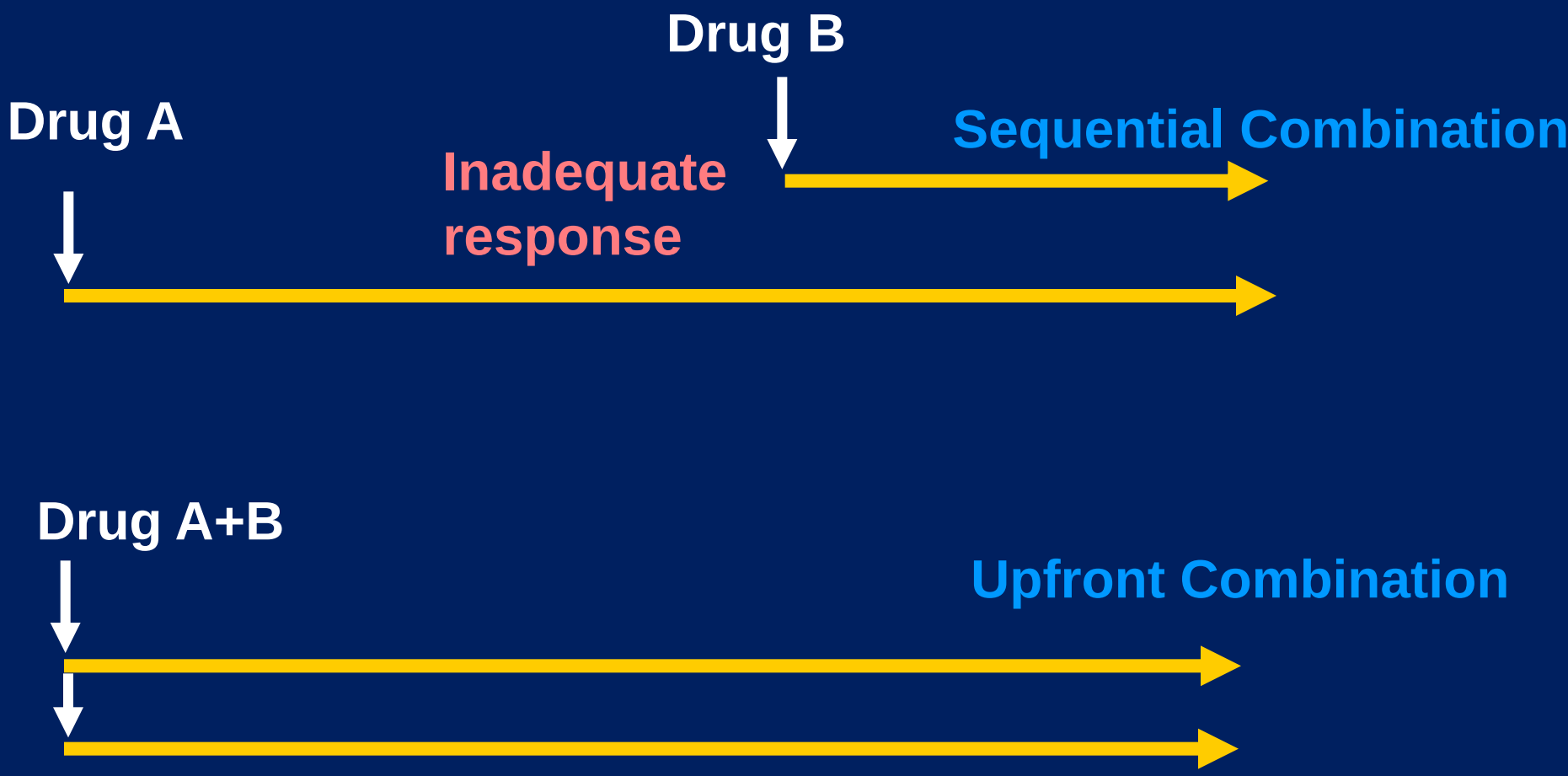
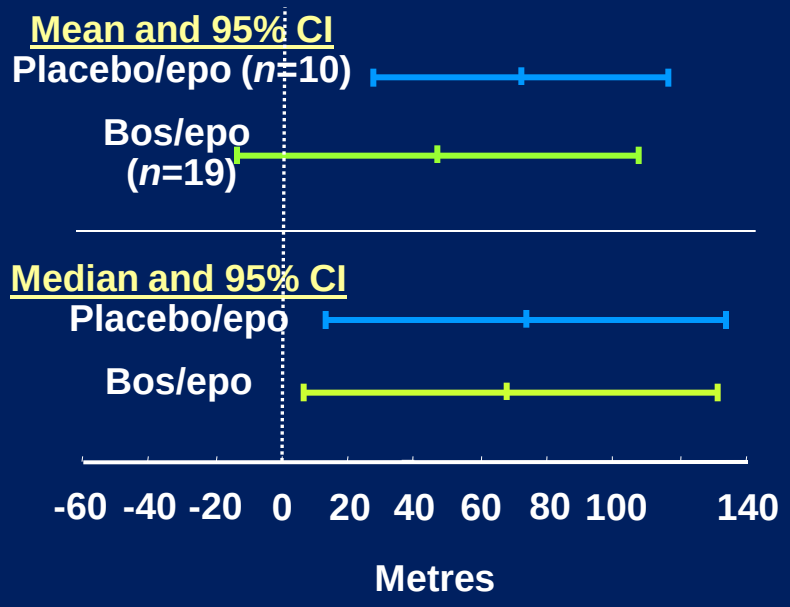
Combination Strategies

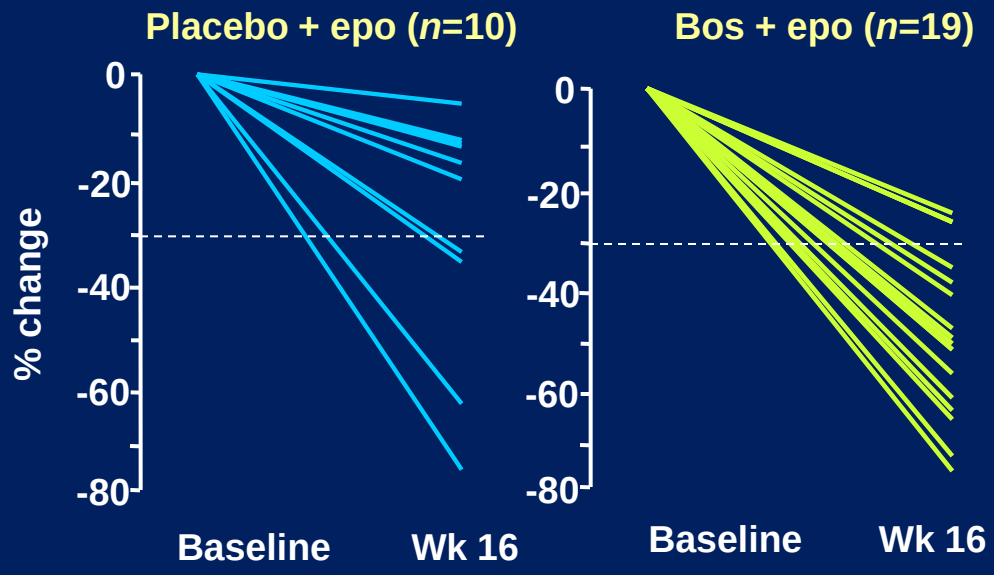


BREATHE-2
Epoprostenol + bosentan

6-MWD (metres)



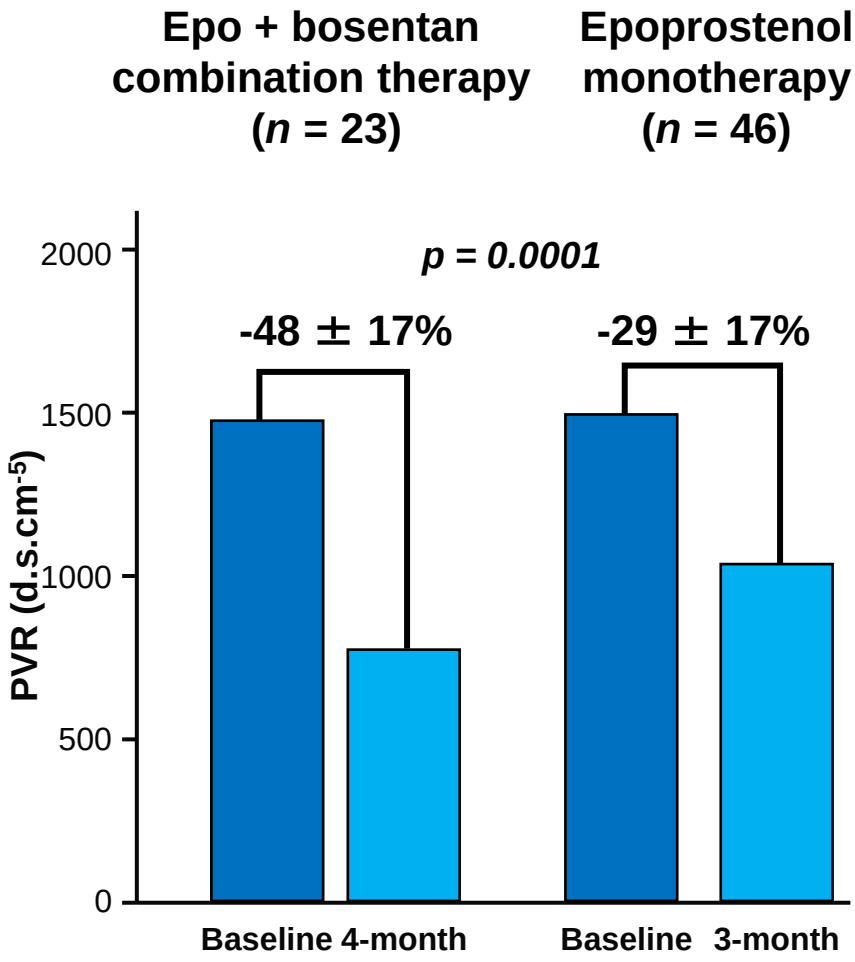
TPR change from baseline (%)

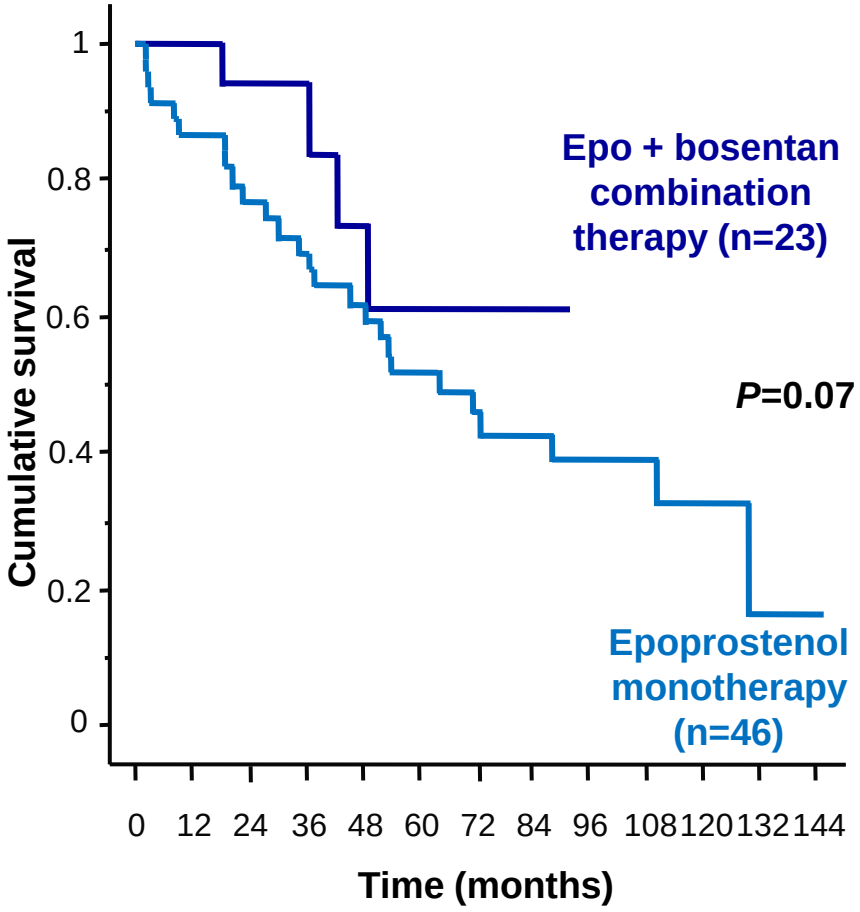


29 of 32 patients completed at week 16

Humbert M, *et al. Eur Respir J* 2004; 24:353-9.

Effect of up-front combination therapy



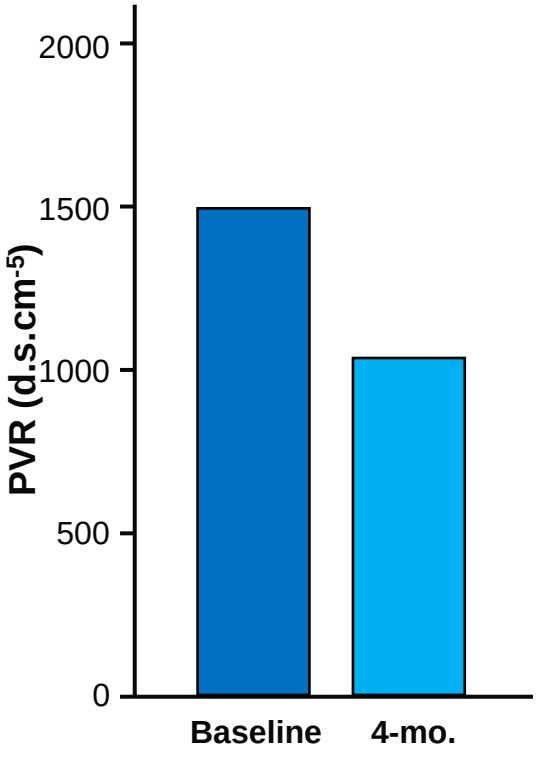


Kemp K, *et al. J Heart Lung Transpl. In press.*

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

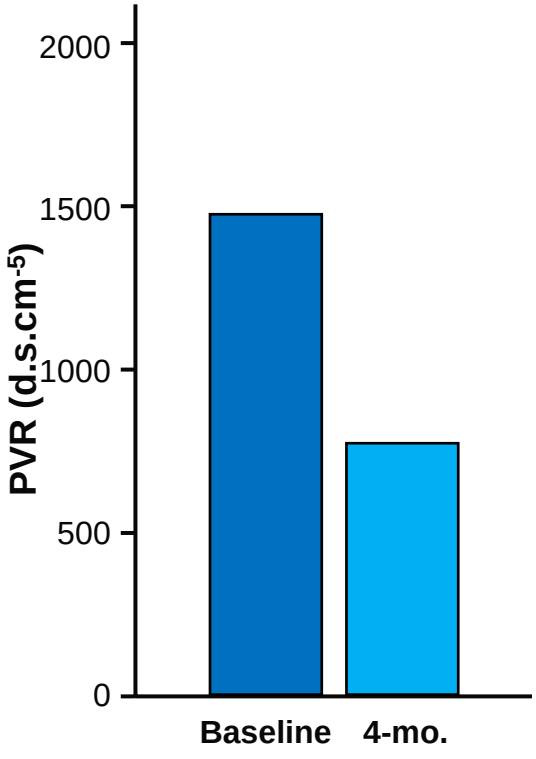
Up-front triple combination therapy in PAH

Epoprostenol monotherapy (n=46)



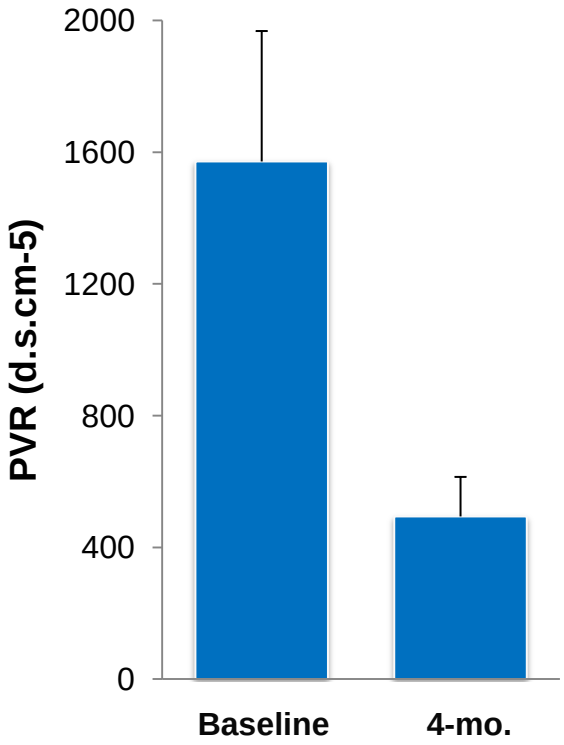
-29 ± 17%

Epoprostenol + bosentan combination therapy (n=23)



-48 ± 17%

Epo + bosentan + sildenafil combination therapy (n=11)



- 69 ± 8%

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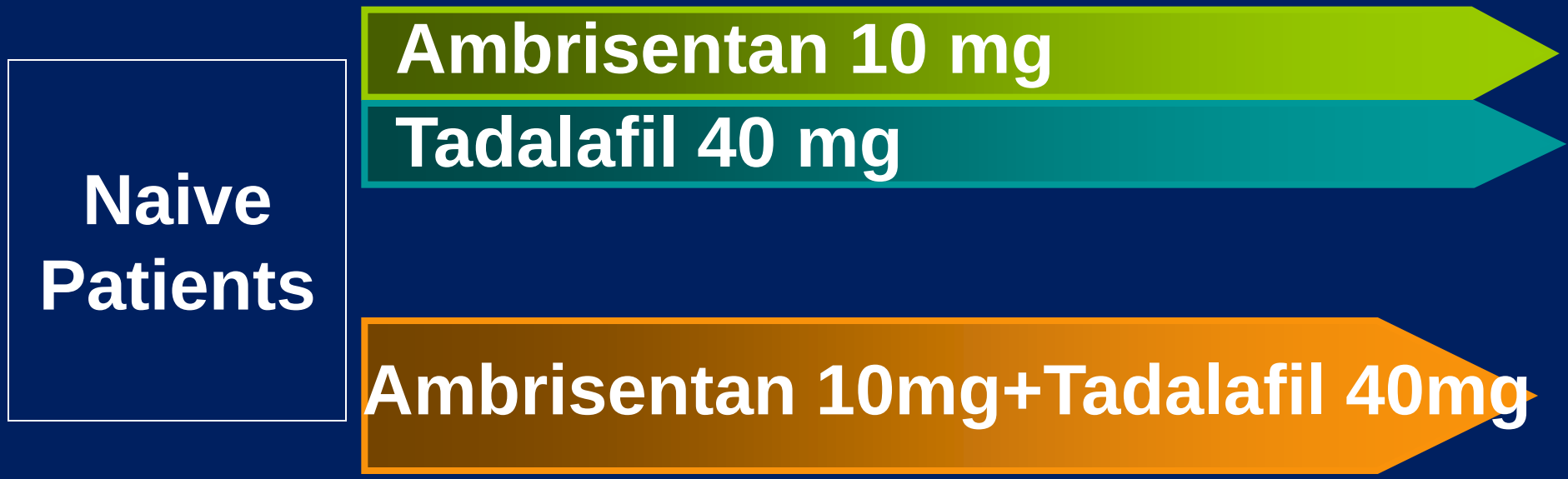
Ambition Study

A randomized, double-blind, placebo-controlled, multicenter study of first-line combination therapy with **AMB**r**I**sentan and **T**adalafil vs. monotherapy in subjects with pulmonary arterial hypertens**ION**

- **Phase III randomised controlled study comparing upfront combination therapy (Ambrisentan+Tadalafil) to initial monotherapy (Ambrisentan or Tadalafil)**
- **Time to treatment failure as primary end-point**
- **Event driven sample size and duration starting with 510 patients and a minimum F-U of 10 months**

Efficacy of up-front combination



Phase III: AMBITION

Primary End Point "Time to Clinical Failure"

Time to clinical failure is defined as the time from randomization to the first occurrence of:

- Death (all-cause)
- Hospitalization for worsening PAH (adjudicated)
  - Non-elective hospitalization for worsening PAH
  - Lung or heart/lung transplant
  - Atrial septostomy
  - Initiation of parenteral prostanoid therapy
- Disease progression (adjudicated)
  - >15% decrease from baseline in 6MWD combined with WHO class III or IV symptoms (at two consecutive post-baseline clinic visits separated by ≥14 days)
- Unsatisfactory long-term clinical response (adjudicated, all criteria required)
  - Receiving randomized treatment for at least 6 months
  - Any decrease from baseline in 6MWD at two consecutive post-baseline clinic visits separated by ≥14 days
  - Sustained WHO class III symptoms for ≥6 months (WHO class III symptoms assessed at two clinic visits separated by ≥ 6

Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan Riociguat, Selexipag)
- Transplantation indication
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Treatments

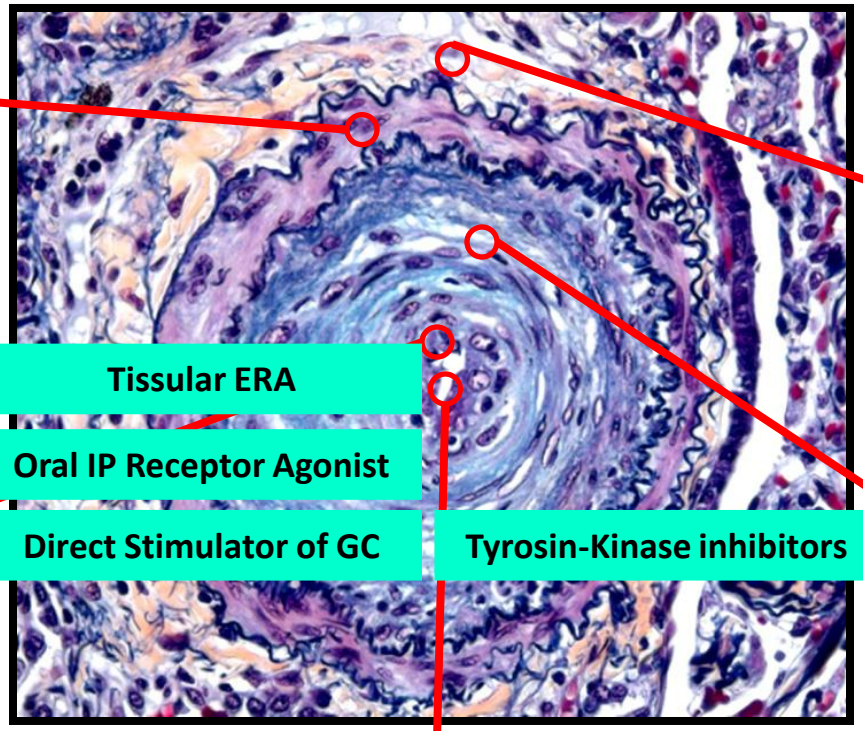
Ca^{++} -Channel blockers

(Vasoreactivity responders)

Pathobiology

*Vasoconstriction;
†Proliferation/migration;
‡Inflammation;
§Thrombosis

MEDIA
SMC Hyperplasia*†
K^+ch dysfunction and related ↑ $[Ca^{++}]$*
↓BMPRs†
↑Angiopoietin†



ADVENTITIA
Inflammatory Cells†‡
Fibrosis
↑Cyto/Chemokines†‡
↑MMP and tenascin†‡
↑B-FGF†

ENDOTELIUM
↑Endothelin*†
↓Prostacyclin*†
↓Nitric Oxide/cGMP*†
↑TxA_2*†§
↑VEGF†
↓BMPRs†

Tissular ERA

Oral IP Receptor Agonist

Direct Stimulator of GC

Tyrosin-Kinase inhibitors

INTIMA
MFB Hyperplasia†
Fibrosis†
↑PDGF receptors†
↑Cyto/Chemokines†‡

Endothelin Receptor Antagonists

PDE-5 inhibitors

Prostanoids

Upfront Combo Therapy

BLOOD
Hypercoagulability §
Platelets Dysfunction §
↑Serotonin*†
↑PDGF†
↓VIP*†

Anticoagulants

Seroto[illegible]ntagonists

Vasoactive [illegible]estinal Peptide

N.Galiè, M.Palazzini, A.Manes, Eur Heart J 2010

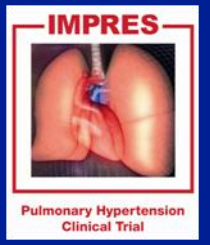
RCTs in PAH with new oral therapies

	Pathway
IMPRES (imatinibI)	TK inhibitor PDGF-R inhibitor
SERAPHIN (macitentan)	Endothelin Tissue-specific ERA
PATENT (riociguat)	Nitric oxide GC stimulator
FREEDOM (treprostinil)	Prostacyclin
GRIPHON (selexipag)	Prostacyclin P-R agonist

RCTs in PAH with new oral therapies

	Primary EP
IMPRES (imatinib-TKI)	6-MWD
SERAPHIN (macitentan-ERA)	M/M
PATENT (riociguat-GS)	6-MWD
FREEDOM (treprostinil-P)	6-MWD
GRIPHON (selexipag-PRS)	M/M

Enrolment of patients and completion of the study

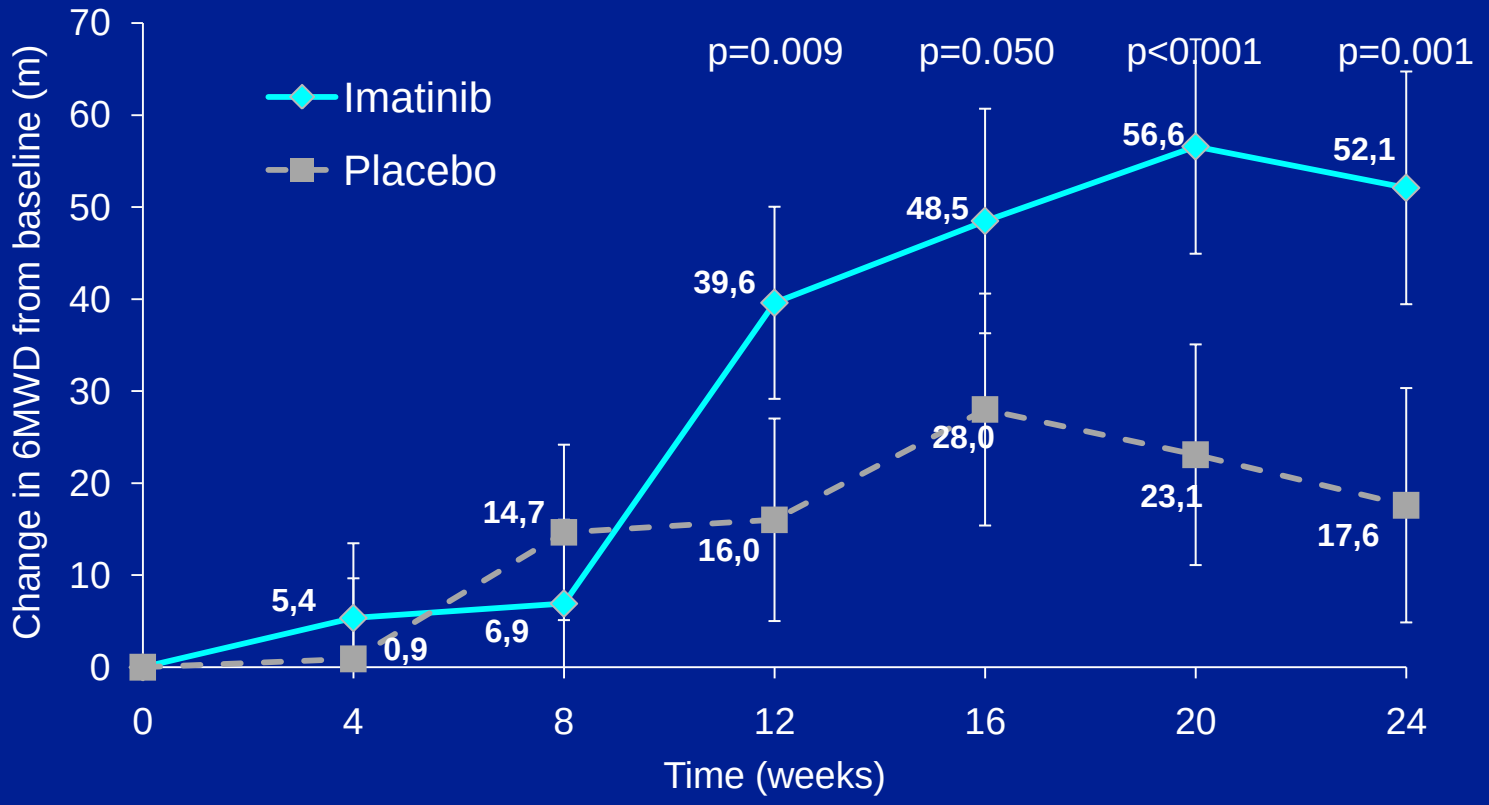


Screened
n=326

Randomized
n=202

Imatinib n=103	Placebo n=99
Discontinued: n=34 (33.0%)	Discontinued: n=18 (18.2%)
• AEs: 27 (26.2%)	• AEs: 7 (7.1%)
• Unsatisfactory therapeutic effect: 1 (1.0%)	• Unsatisfactory therapeutic effect: 5 (5.1%)
• Death: 2 (1.9%)	• Death: 2 (2%)
• Withdrew consent: 2 (1.9%)	• Withdrew consent: 1 (1%)
• Abnormal laboratory value: 1 (1.0%)	• Abnormal laboratory value: 1 (1%)
• Protocol deviation: 1 (1.0%)	• Protocol deviation: 1 (1%)
• Administrative problems: 0 (0.0%)	• Administrative problems: 1 (1%)
Completed 24 weeks n=69 (67.0%)	Completed 24 weeks n=81 (81.8%)

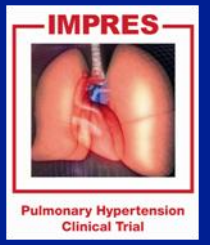
Primary endpoint: change in 6MWD



- LS mean 6MWD was significantly higher at Week 24 in patients receiving imatinib (383±9.8 m) than in those receiving placebo (351±9.8 m)
  - between-group difference: **31.8±10.1 m (p=0.002)**

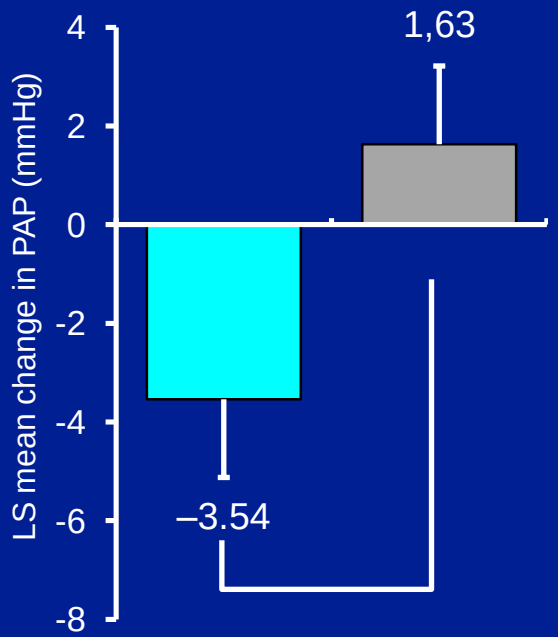
Values are means and standard errors. p-values are for between-group comparisons.
The primary variable was analyzed using the full analysis set and a mixed effects model for repeated measures.
Missing values imputed with plausible values. LS = least squares

Change in haemodynamic parameters at Week 24



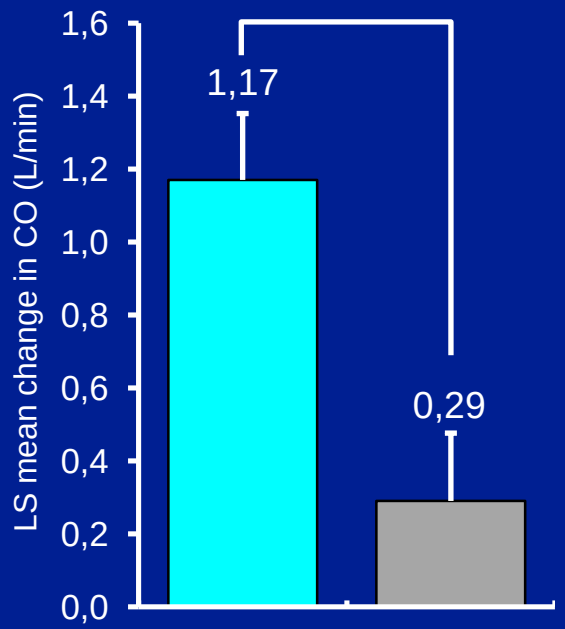
Pulmonary arterial pressure

Δ–5.18 mmHg, p<0.001



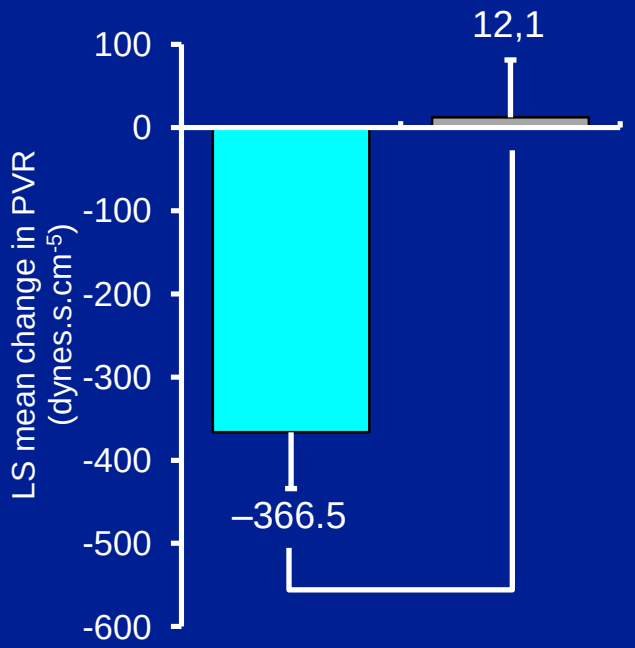
Cardiac Output

Δ+0.88 L/min, p<0.001



Pulmonary Vascular Resistance

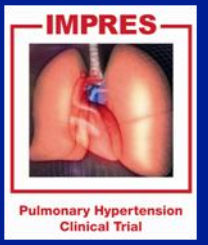
Δ–378.6 dynes.sec.cm^{-5}, p<0.001

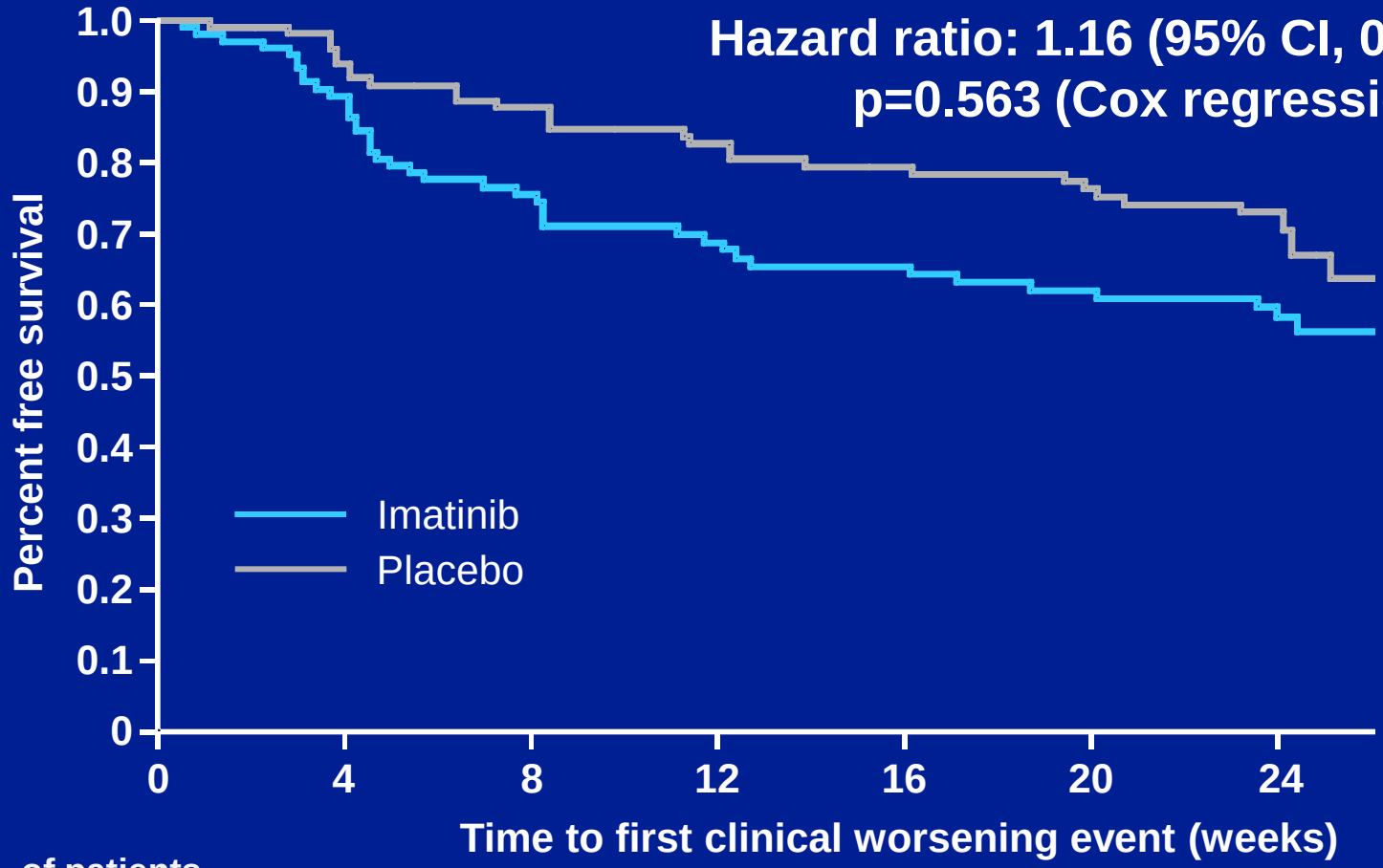


Imatinib Placebo

Data is least squares (LS) means, full analysis set

Time to clinical worsening





No. of patients							
Imatinib	103	93	70	66	60	58	45
Placebo	98	91	85	80	75	72	54

Subdural Hematomas in the QTI Clinical Program

- There have been 11 cases of subdural hematoma (SDH)s:
  - 9 in the QTI571 clinical trials
    - 8 Phase III trial: core and extension (n=181)
    - 1 Phase II trials core (n= 45)
    - 0 Drug-drug interaction trial (n=18)
  - 1 spontaneous report in Patient Supply Programs (requests from physicians for drug)
    - 0 Japan Named Patient Program (n=9)
    - 0 Individual Patient Supply Program UK (n=4)
    - 1 Individual Patient Supply Program Switzerland (n=23)
  - 1 spontaneous report from off label use in patient with prior h/o SDH
- 7 females and 2 males between the ages of 47-66 years old
- Time to event ranges from 12 days to 18 months
- All SDH cases were also anticoagulated; no SDH cases have occurred in non-anticoagulated patients

Macitentan in the SERAPHIN trial
Study objectives

Primary objective
To demonstrate that macitentan prolongs the **time to the first morbidity or mortality event** in patients with symptomatic PAH

www.clinicaltrials.gov, NCT00660179.

Primary efficacy endpoint

Macitentan reduced the risk of a morbidity and mortality event

Dose of macitentan (mg)	Observed risk reduction (%)	*p* value
3	30	0.0108

Actelion. *Press release* 2012

Primary efficacy endpoint

A dose-related effect has been observed

Dose of macitentan (mg)	Observed risk reduction (%)	*p* value
10	45	< 0.0001
3	30	0.0108

Actelion. *Press release* 2012

Secondary efficacy endpoints

Both doses of macitentan demonstrated a statistically significant effect on secondary objectives:

- Change from baseline to month 6 in 6-MWD
- Change from baseline to month 6 in WHO functional class
- Time to either death due to PAH or hospitalisation due to PAH*

*Over the whole treatment period.

Actelion. *Press release* 2012

Macitentan: Aminotransferase elevations

	Placebo	Macitentan 3 mg	Macitentan 10 mg
ALT or AST > 3 x upper limit of normal	4.5%	3.6%	3.4%

ALT: alanine transaminase
AST: aspartate transaminase

Actelion. *Press release* 2012

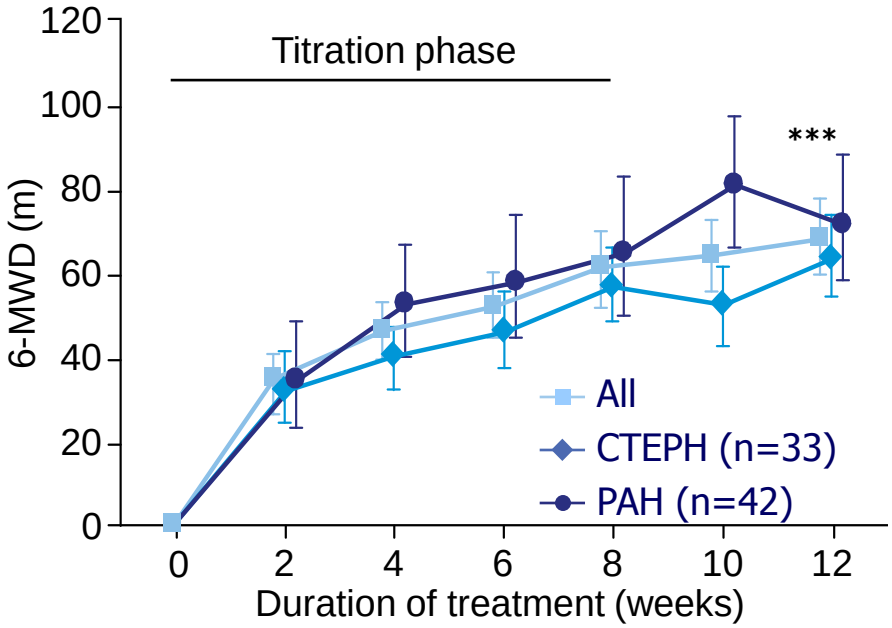
Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study.

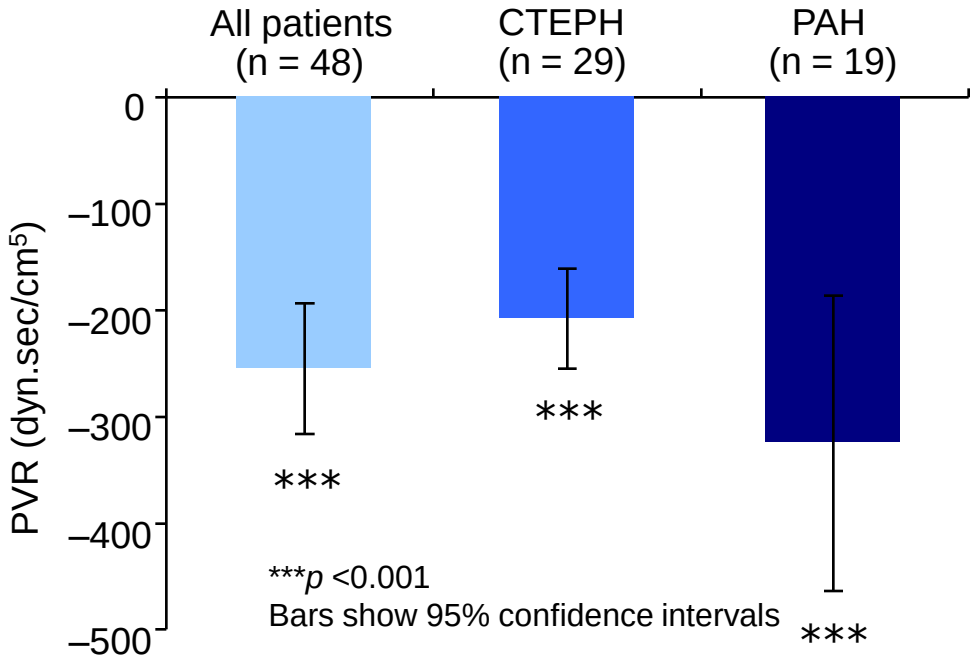
Ghofrani HA, Hoeper MM, Halank M, Meyer FJ, Staehler G, Behr J, Ewert R, Weimann G, Grimminger F.

N=75 patients with PAH or CTEPH

No PDE5i or PGI2 – 6 on bosentan

Most tolerated a dose of 2.5 mg tid





Ghofrani A et al. *Eur Respir J* 2010;36:792-9.

Freedom Studies

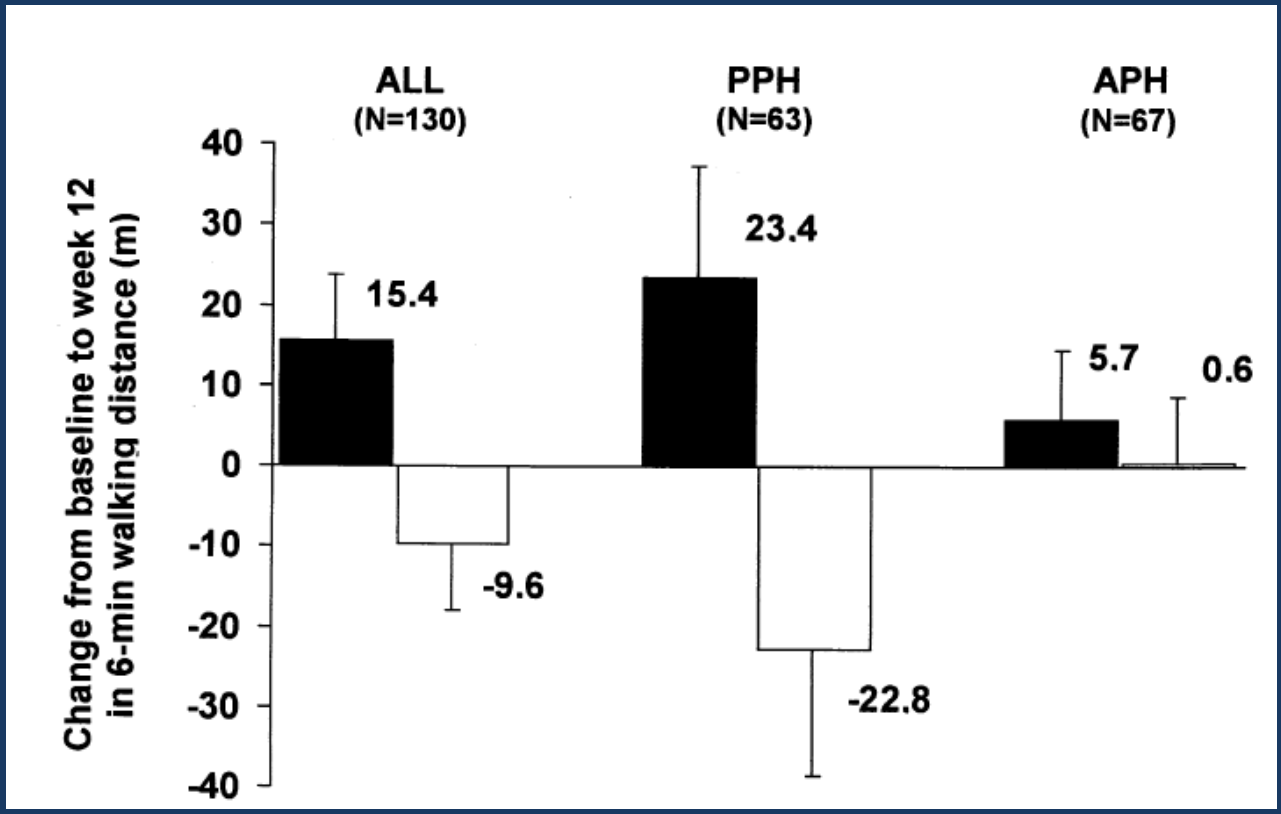
Author	Acronym	Study drug	Patients	N	Duration (wks)	1 EP	Efficacy 1EP	Efficacy TtCW
Tapson V CHEST 2012	**FREEDOM C**	UT 15 C	PAH	354	16	**6MWD**	-	-
Tapson V ATS 2012	**Freedom M**	UT 15 C	PAH	300	16	**6MWD**	+	-
Tapson V ATS 2012 A2493	**FREEDOM C [2]**	UT 15 C	PAH	310	16	**6MWD**	-	-

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.

Effects of Beraprost Sodium, an Oral Prostacyclin Analogue, in Patients With Pulmonary Arterial Hypertension: A Randomized, Double-Blind, Placebo-Controlled Trial

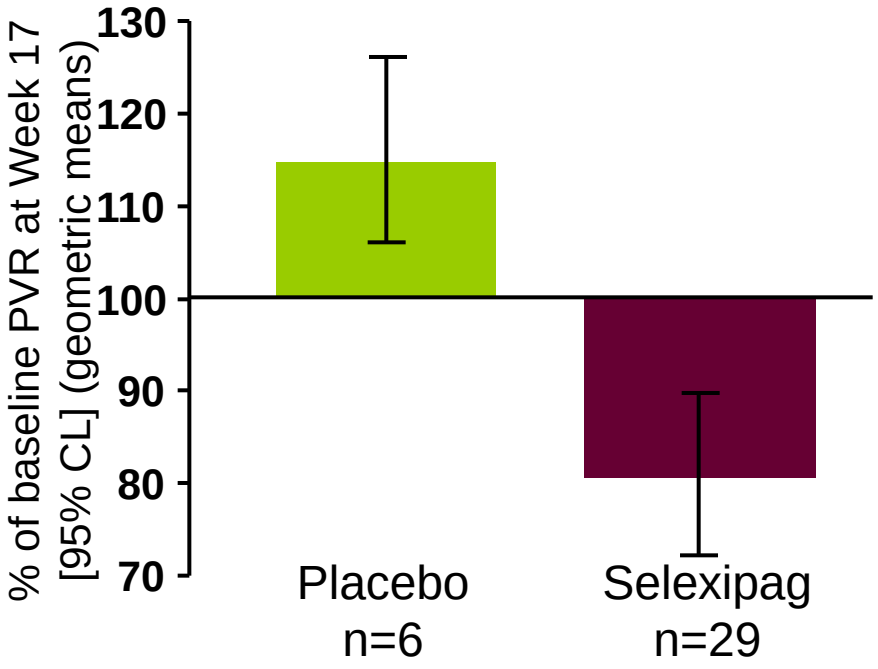
Nazzareno Galiè, MD,* Marc Humbert, MD,† Jean-Luc Vachiéry, MD,‡ Carmine Dario Vizza, MD,§ Meinhard Kneussl, MD,‖ Alessandra Manes, MD,* Olivier Sitbon, MD,† Adam Torbicki, MD,¶ Marion Delcroix, MD,# Robert Naeije, MD,‡ Marius Hoeper, MD,** Ari Chaouat, MD,†† Sophie Morand, MD,‡‡ Bruno Besse, MD,‡‡ Gerald Simonneau, MD,† for the Arterial Pulmonary Hypertension and Beraprost European Trial (ALPHABET) Study Group

JACC Vol. 39, No. 9, 2002
May 1, 2002:1496–502



Selexipag Phase II study

N=43 patients with PAH on ERA, PDE5i or both
3:1 randomization selexipag (200-800 µg bid) vs pbo
Final optimized dose at day 35 – assessment at 17 weeks



Treatment effect: −30.3%
(95% CL: −44.7, −12.2;
p=0.0045*)

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

*Wilcoxon rank-sum test

Simonneau G, et al. Eur Respir J 2012 Feb 23 (Epub ahead of print)

Question C :How can we modify the current treatment algorithm including the new approved drugs?

(Nazzareno Galiè)

- **First line therapy, if any**
- **Place for newly approved drugs** (inhaled remodulin, iv sildenafil)
- **Place for new drugs with available phase III data** (imatinib, macitentan, oral treprostinil, riociguat)
- **Place for upfront combination therapy**

Question C :How can we modify the current treatment algorithm including the new approved drugs?

<u>First line therapy</u> should be based on the following principles:

- Benefit to risk ratio (first more safe drugs, last drugs with more side effects)
- Specific labeling (exercise capacity vs outcome)
- Experience of the treating physician
- Pharmacoeconomy (drug costs, hospitalizations costs, etc)
- Country approvals
- Head to head comparison?

Question C :How can we modify the current treatment algorithm including the new approved drugs?

The place of new drugs in the algorithm should be based on:

- Grade of recommendation (I, IIa, IIb, III) and level of evidence (A, B, C)
- Characteristics of the pivotal(s) RCT(s) (primary end-point, secondary end-points, patients population, background therapy,…)
- Innovation as compared to already existing drugs in the same (class or group)

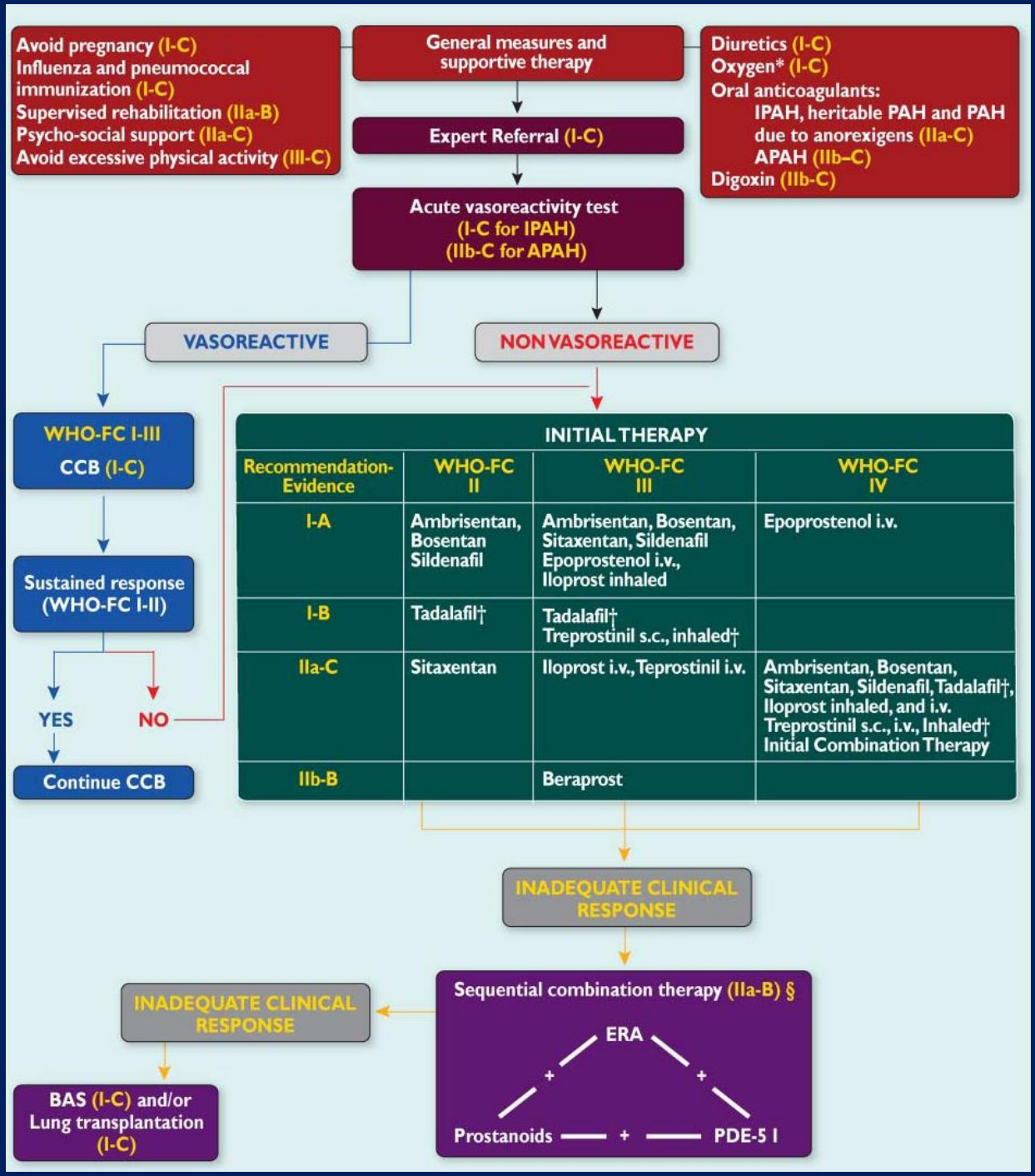
Table 1 Classes of recommendations

Classes of Recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Table 2 Levels of evidence

Level of Evidence A	Data derived from multiple randomized clinical trials[a] or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial[a] or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[a]Or large accuracy or outcome trial(s) in the case of diagnostic tests or strategies.



Galiè.N et al Eur Heart J and Eur Respir J, 2009

Question C :How can we modify the current treatment algorithm including the new approved drugs?

Some uncertanties

- Is it appropriate an algorithm based on the primary end-point (exercise capacity vs outcome/effect on mortality?
- Are PDE-5 inhibitors & GC stimulators in the same group of drugs?
- Place of imatinib if approved (issue of transplantation?)
- Can we include iv sildenafil in the treatment algorithm without clinical data on PAH patients for the theoretical indication (forced fasting in patients already treated with the oral form due to surgery etc.)?
- BAS? Still to be included??? Survey?
- If oral treprostinil is approved (1 RCT positive in monotherapy and 2 RCTs negative in combo) should be indicated only in naïve patients? Should then we re-evaluate oral beraprost?

Areas of Algorithm Improvement

- Upfront combination therapy
- Place for new drugs (Imatinib, Macitentan Riociguat, Selexipag)
- Transplantation indication
- RV assistance
- Indications for complications
- Definition of expert center/Country organization

PAH complications

- PA aneurisms/Rupture/Dissection
- PA thrombosis
- Left main CA compression
- Emopthysis
- Supraventricular arrhythmias

Areas of Algorithm Improvement

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Definitions of PH Expert Center

Background-1

- Pulmonary hypertension is a rare chronic progressive condition which is lethal, disabling, costly and treatable.
- Diagnosis and treatment options are complex.
- Patients often look well, even when they are deteriorating, and in inexperienced hands this may result in missed opportunities for treatment
- Current therapies slow disease progression and are not curative.
- There are many novel drugs which may be effective but require testing in clinical trials.

Definitions of PH Expert Center

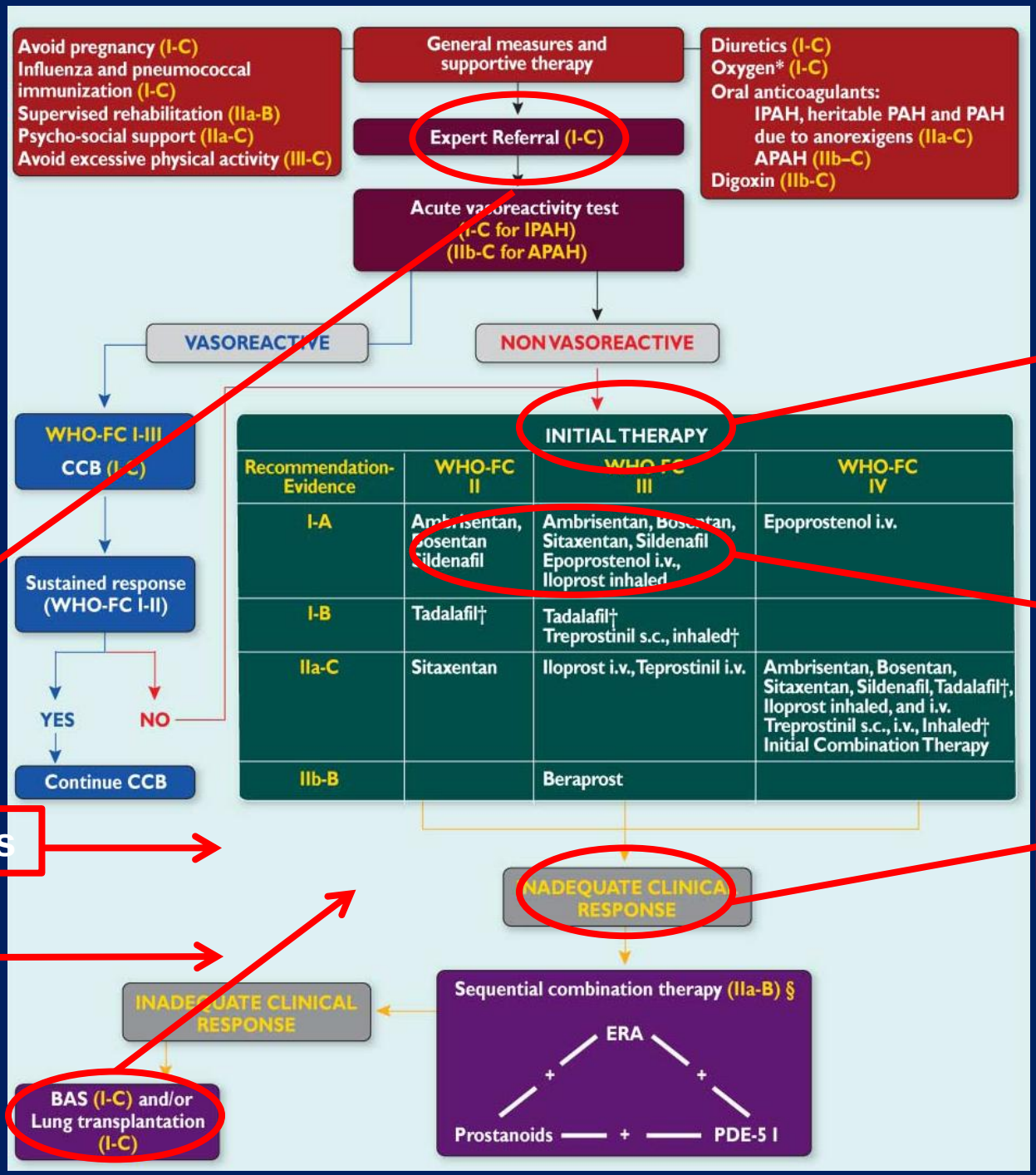
Background-2

- High volume units have been recurrently shown in medicine to obtain best outcomes for patients while maintaining greatest patient satisfaction, lowest complication rates, shortest length of hospital stay and best value for healthcare payors

Definitions of PH Expert Center

Proposal

1. Each country should have at least two adult expert centres.
2. Each country should have at least one paediatric expert centre.
3. The ideal number of patients seen by an adult or paediatric centre per annum should be no less than 200 (either PAH or CTEPH)
4. In countries with a population >10 million, adult centres should ideally expand to >300 patients seen per annum



New Definition

Upfront – combo
2 d Class II
3 d Class III-IV

Macitentan
Riociguat
Selexipag

Complications

Imatinib?

RV Assistance

Galiè.N et al Eur Heart J and Eur Respir J, 2009