# Designing the future of PAH: ongoing trials, new drugs

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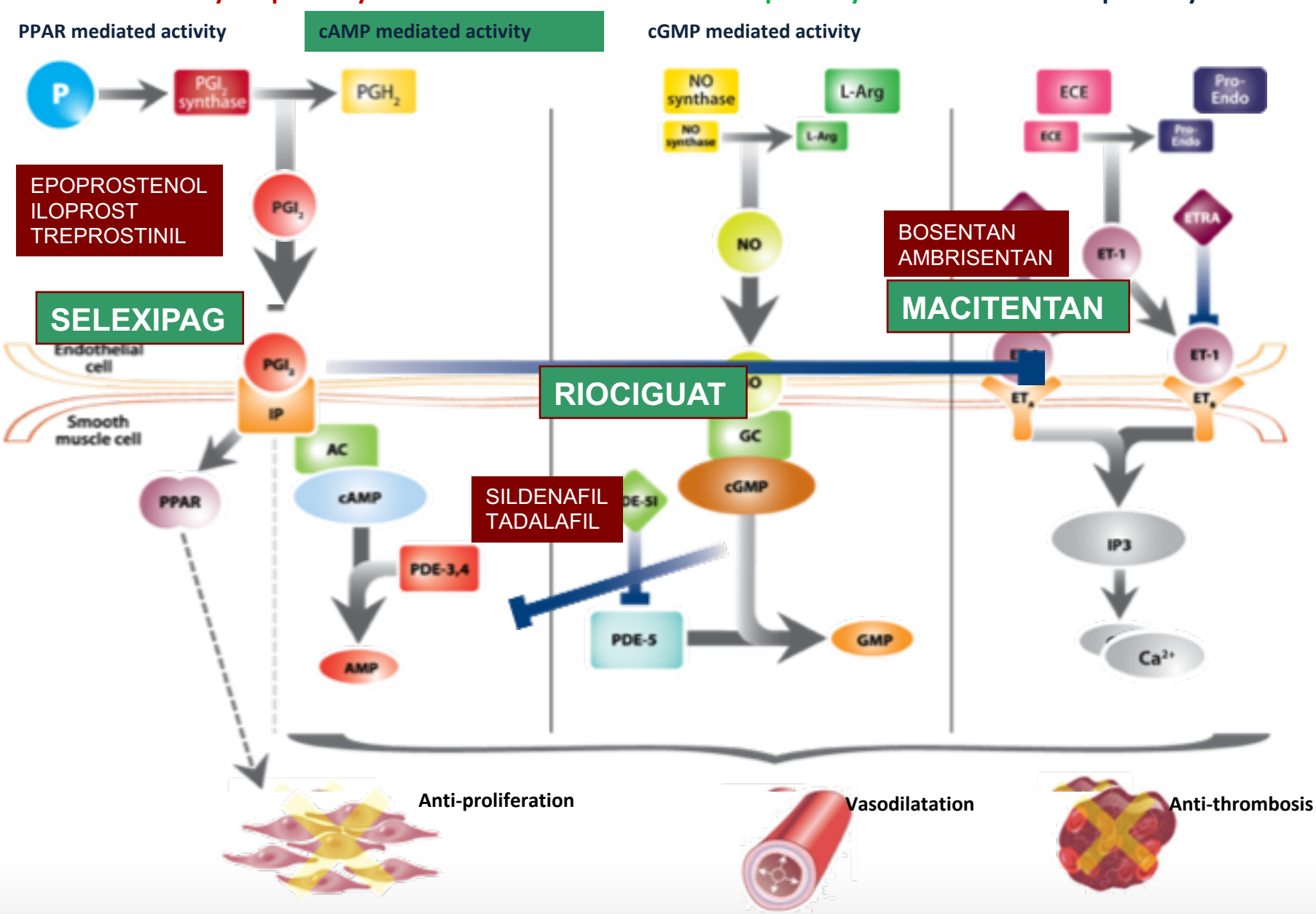
## PREAMBLE - 1

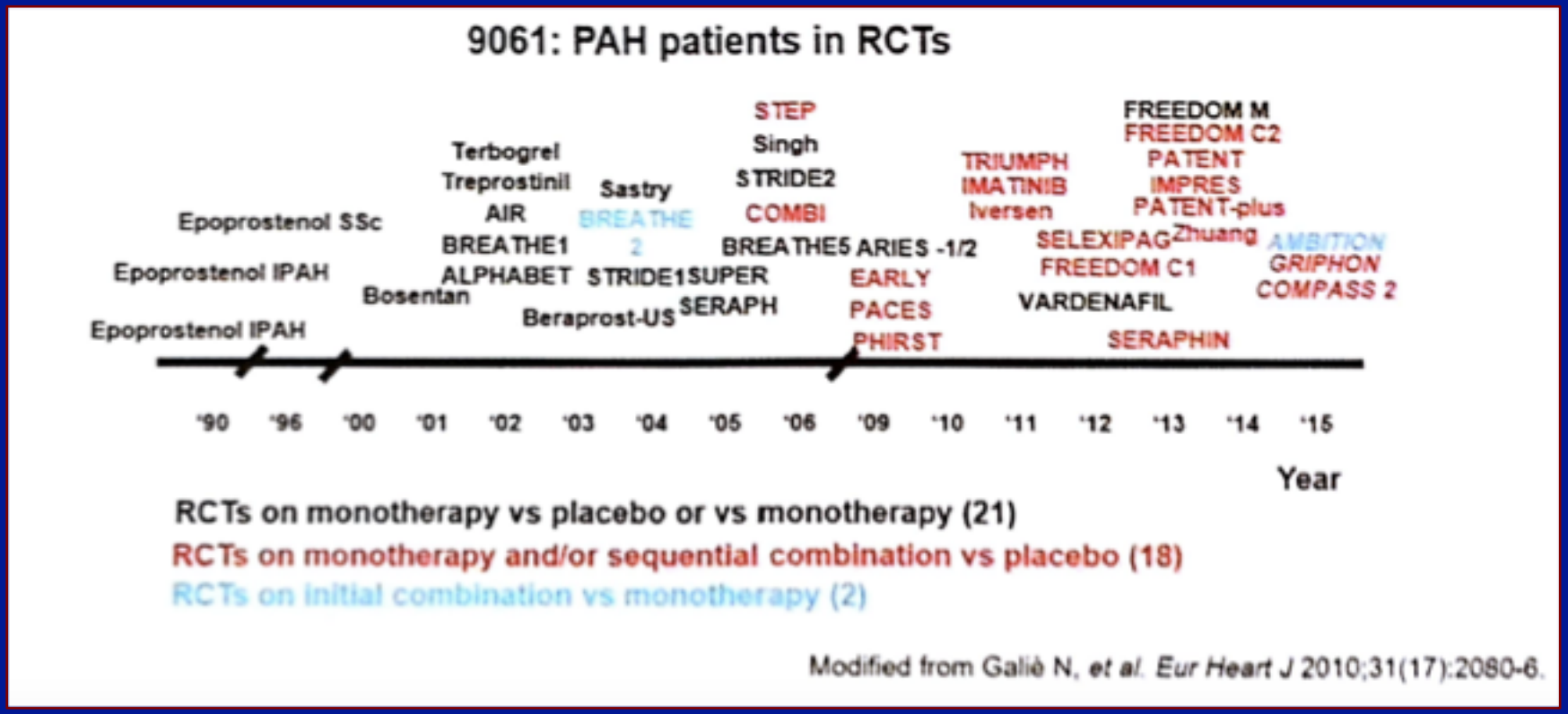
- Over the last 10-15 years we have witnessed significant advances in the management of pulmonary arterial hypertension (PAH).

- More than 10 drugs targeting the endothelin, nitric oxide, and prostacyclin pathways have been developed and commercialized.



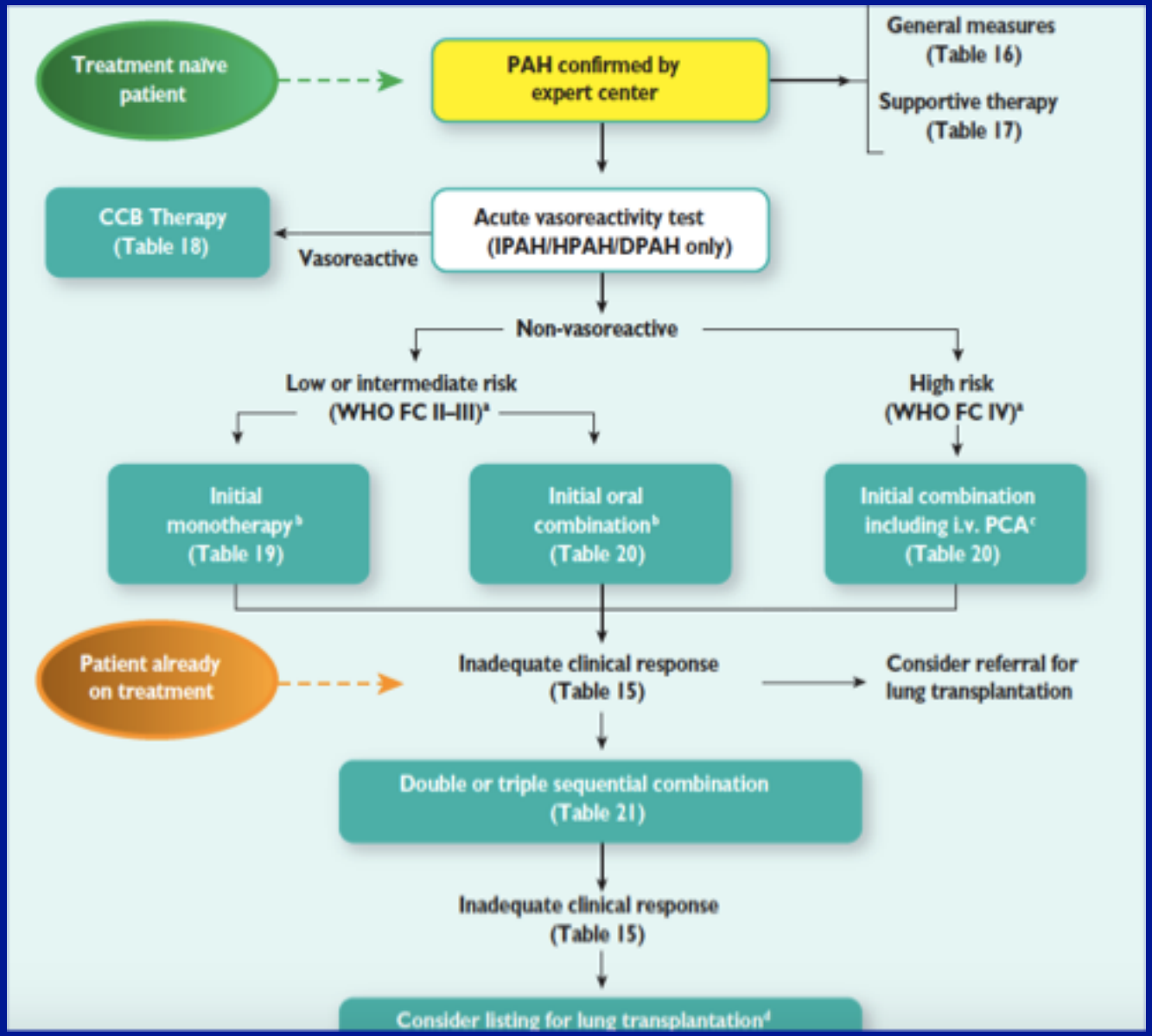

AC, adenylyl cyclase; AMP, adenosine monophosphate; $Ca^{2+}$, calcium; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ECE, endothelin converting enzyme; ET-1, endothelin-1; $ET_{A/B}$, endothelin receptor; ETRA, endothelin receptor antagonists; GC, guanylyl cyclases; GMP, guanosine monophosphate; IP; prostaglandin receptor; IP3, inositol trisphophate; L-Arg, L-Arginine; NO, nitric oxide; P, arachidonic acid; PDE, phosphodiesterase; PDE-5I, phosphodiesterase type 5 inhibitor; $PGH_2$, prostaglandin $H_2$; $PGI_2$, prostacyclin; PPAR, peroxisome proliferator-activated receptor; Pro-Endo, pro-endothelin

1. Humbert et al. *N Engl J Med*. 2004;351:1425-1436; 2. Ghofrani et al. *J Am Coll Cardiol*. 2004;43:68S-72S; 3. Mitchell et al. *Exp Physiol*. 2007;93:141-147



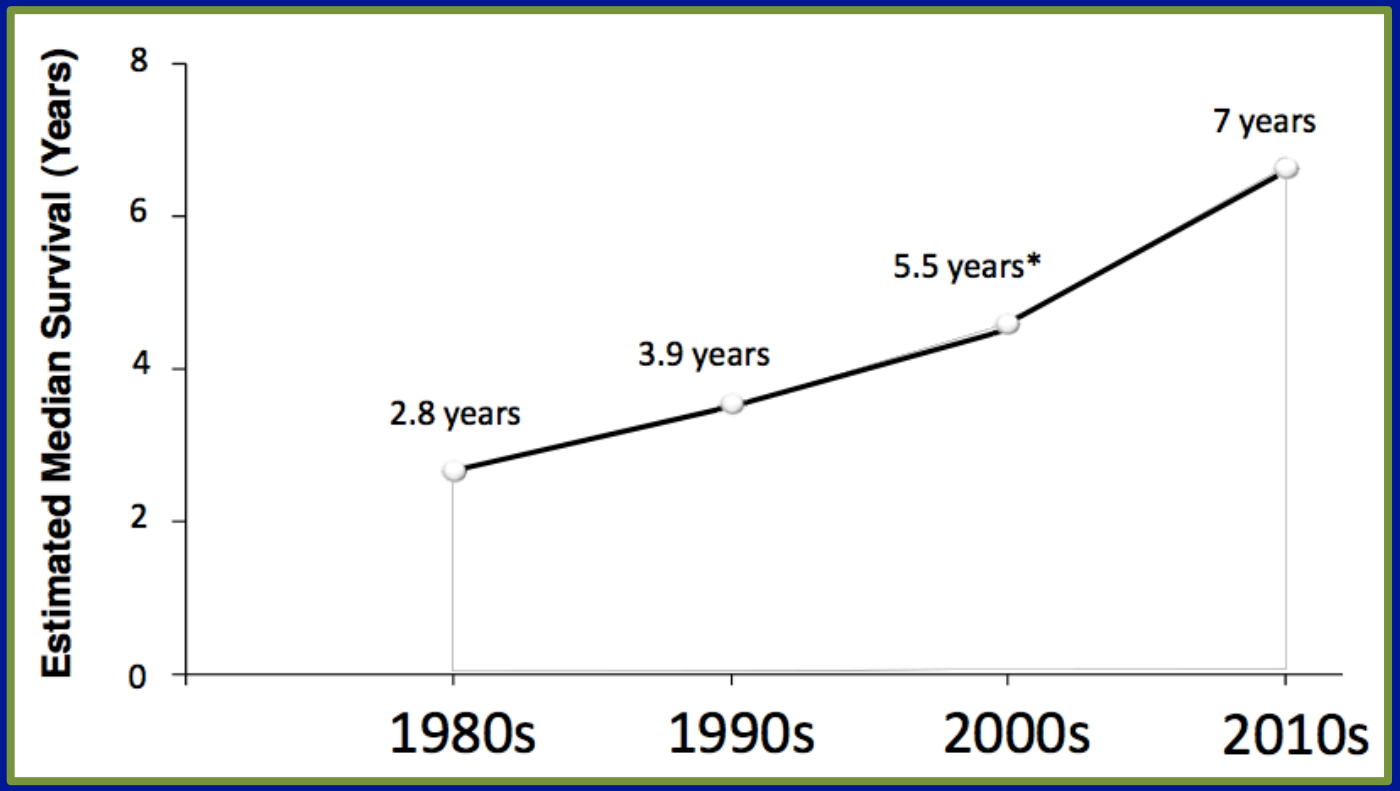

*RCT trial designs and end-points have substantially changed over the years, aiming at harder end-points to better demonstrate drug efficacy (TTCW). This process for sure is not ended with the composite morbi-mortality end points.*

# Treatment algorithm 2015




ESC/ERS Guidelines 2015

# PAH: improvement in survival




Available therapies have been shown to decrease patients' risk of short-term mortality and clinical worsening. However, despite these advances with modern treatment modalities, survival remains poor.

D'Alonzo GE, Ann Intern Med 1991
Thenappan T, Eur Resp J 2010
Humbert M, Eur Respir J 2010
Benza RL, Chest 2012

# Ongoing trials with approved PAH therapies

- **TRITON** (Selexipag +ERA+PDE5i)
- **ADP811-301** (Ralinepag)
- **BEAT** (Beraprost+inhaled treprostinil)

# TRITON

*The efficacy and safety of initial Triple Versus Initial Dual Oral Combination Therapy in Patients with newly diagnosed PAH*

- Initial triple oral treatment regimen (macitentan, tadalafil, selexipag) vs an initial dual oral treatment regimen (macitentan, tadalafil, placebo)
- Multi-center, double-bind, placebo-controlled, Phase 3b study
- 238 partecipants
- Recruitment status: recruiting
- Primary outcome measure: PVR at baseline to week 26, measured by RHC

# ADP811-301

*A study evaluating the Efficacy and Safety of Ralinepag to improve Treatment outcomes in PAH patients*

- Ralinepag vs Placebo
- Double-bind, placebo-controlled, Phase 3 study
- 700 partecipants
- Recruitment status: recruiting
- Primary outcome measures: time from randomization to the first adjudicated protocol-defined clinical failure event (death, hospital admission for worsening PAH, disease progression or unsatisfactory long-term clinical response)

# BEAT

*Beraprost-314D Added-on to Tyvaso*

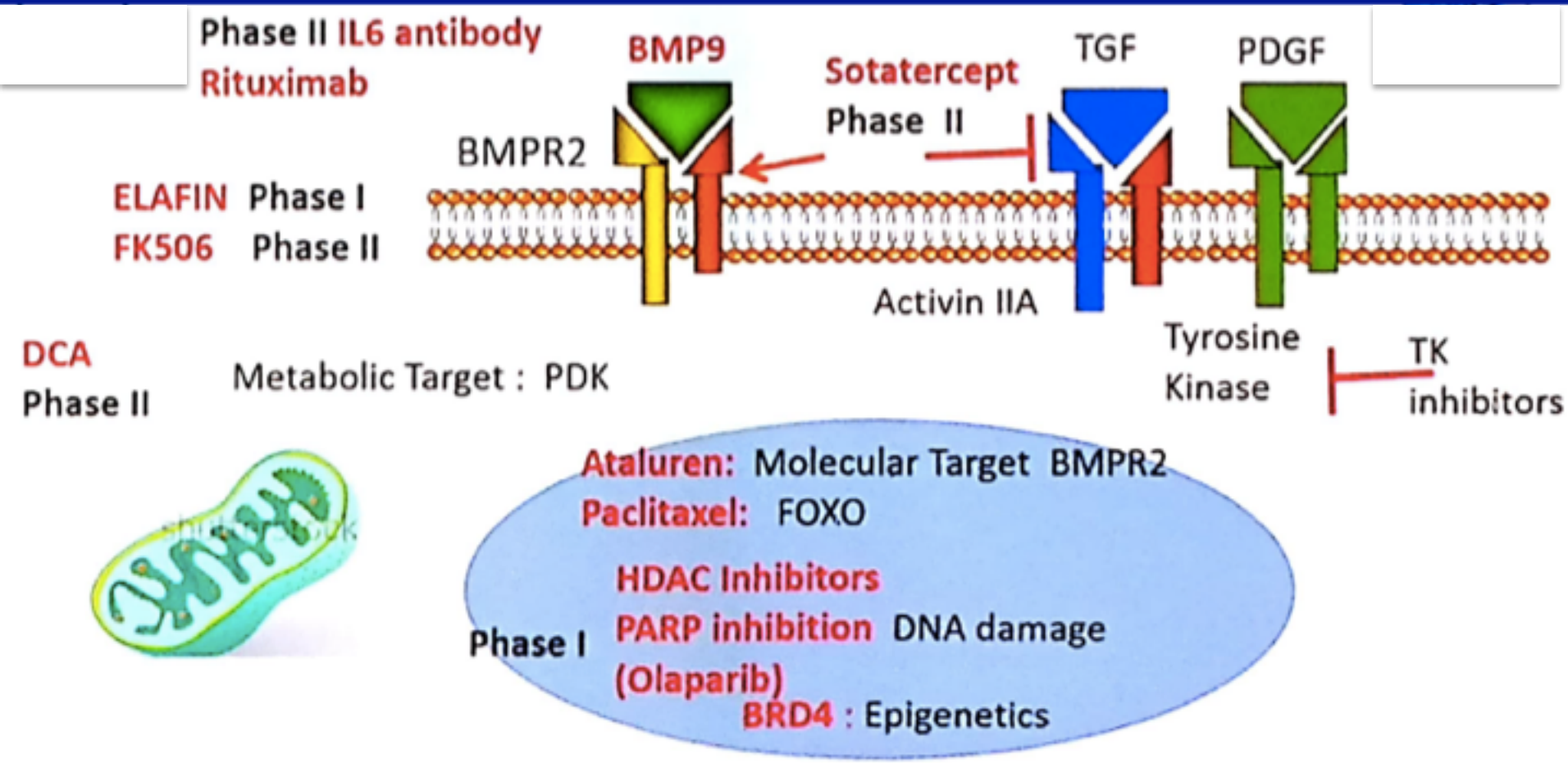
- Beraprost vs Placebo in patients treated with inhaled Treprostinil (Tyvaso)
- Multicenter, double-bind, placebo-controlled, Phase 3 study
- 240 partecipants
- Recruitment status: active, non recruiting
- Primary outcome measures:

- Time to clinical worsening (death, hospitalization due to worsening PAH, initiation of a parenteral prostacyclin, disease progression, unsatisfactory long-term clinical response)

## PREAMBLE - 2

- Intriguingly, despite the publication of numerous preclinical studies proposing new therapeutic targets for PAH, few have reached clinical trial phases and none of these innovative therapies are currently approved for clinical use.

# New therapeutic strategies



# New PH drugs

| TRIAL NAME | PHASE | TREATMENT | DOSE | MECHANISM OF ACTION | PARTICIPANTS | RESULTS |
|---|---|---|---|---|---|---|
| **NCT02587325** | I | **ABI-009, nab-rapamycin** | | mTOR inhibitor | 25 | Ongoing |
| **LIBERTY (NCT02736149)** | II | **Ubenimex (Bestatin)** | 150 mg TID | Inhibitor of leukotriene A4 hydrolase | 51 | Terminated (lack of efficacy by PVR) |
| **NCT02829034** | NA | **Ranolazine** | Starting dose: 500 mg BID<br>Maximal dose: 1000 mg BID | Specific inhibitor of late sodium current | 10 | Ongoing |
| **NCT00964678** | I/II | **Carvedilol** | Starting dose: 3.125 mg BID<br>Maximal dose: 25 mg BID | Non selective β-blocker with vasodilatator properties | 10 | Significant improvement in RVEF and stroke volume in 6 patients |
| **NCT02279160** | II | **Ralinepag** | Starting dose: 50 mcg OD<br>Maximal dose: 1450 mcg OD | Non-prostanoid, prostaglandin I2 receptor agonist | 60 | Improvement from baseline in PVR |
| **ASCO1 (NCT01086540)** | II | **Rituximab** | 1000 mg IV | Murine-derived monoclonal antibody and antineoplastic agent that binds specifically to the CD20 antigen | 57 | Ongoing |
| **PHANTOM (NCT03229499)** | II | **Anastrozole** | 1mg OD | Aromatase inhibitor | 84 | Ongoing |
| **LARIAT (NCT02036970)** | II | **Bardoxolone Methyl** | 1-2-3-4 mg OD | Induction of Nrf2 and suppression of NF-κ | 166 | Study completed (no results posted) |
| **CATALYST (NCT02657356)** | II | **Bardoxolone Methyl** | Starting dose: 5 mg<br>Maximum dose: 10 mg | Induction of Nrf2 and suppression of nf-κ | 200 | Ongoing |

# New PH drugs

| TRIAL NAME | PHASE | TREATMENT | DOSE | MECHANISM OF ACTION | PARTICIPANTS | RESULTS |
|---|---|---|---|---|---|---|
| NCT03556020 | II | PB1046 | Starting dose: 0.2 mg/Kg; Target dose: at least 1.2 mg/Kg - Subcutaneous Injection | Sustained-release vasoactive intestinal peptide (VIP) analogue | 63 | Ongoing |
| ARROW (NCT02234141) | II | Selonsertib | 2-6-18 mg OD | Inhibitor of ASK-1 | 151 | Negative |
| PRIMEx (NCT03449524) | II | CXA-10 | 75-150 mg OD | Specific isomer of nitro-oleic acid | 96 | Ongoing |
| PULSAR (NCT03496207) | II | Sotatercept | 0.3 mg/Kg or 0.7 mg/kg every 21 days – subcutaneous injection | Novel activin receptor type IIA fusion protein | 90 | Ongoing |
| NCT00832507 | II | Cicletanine | 150mg-300 mg OD or BID | Antagonist of type 2 serotonin receptors | 162 | No improvements in exercise tolerance, symptoms or hemodynamics |
| ASA-STAT (NCT00384865) | II | Aspirin and simvastatin | Aspirin 81 mg OD Simvastatin 40 mg OD | | 64 | Lack of efficacy by 6MWT |
| | II | Terguride | 5-HT receptor antagonist | | | Lack of efficacy by 6MWT |
| BEAT (NCT01908699) | III | Beraprost added-on to inaled treprostinil (Tyvaso) | 15 or 30 mcg QID | Orally active prostacyclin analogue added to inhaled treprostinil, a synthetic analogue of prostacyclin | 240 | Ongoing |
| NCT03496623 | III | Inhaled Treprostinil | Target dosing 12 breaths (72 mcg) QID | Prostacyclin analogue | 314 | Ongoing |

## Low-Dose FK506 (Tacrolimus) in End-Stage Pulmonary Arterial Hypertension

*To the Editor:*

Edda Spiekerkoetter, M.D.

American Journal of Respiratory and Critical Care Medicine Volume 192 Number 2 | July 15 2015

- Dysfunctional BMPR2 signaling is implicated in the pathogenesis of PAH
- FK506 (tacrolimus) as an effective upregulator of BMP signaling, and low-dose FK506 was an effective treatment for experimental PAH. Preliminary data also suggested that compassionate use of low-dose FK506 in three patients with endstage PAH might have been associated with clinical benefit. On the basis of these findings, a phase 2a RCT in PAH was initiated to evaluate the safety and tolerability of FK506 in stable patients with PAH (clinicaltrials.gov, NCT01647945).

Trial ASCO1 - RITUXIMAB

The first multicenter blinded, randomized, placebo-controlled clinical trial (RCT) to evaluate an immunotherapy in PAH began enrolling patients in 2010 and is testing the efficacy of B-cell depletion with rituximab in systemic sclerosis–associated PAH. ASC01 is a National Institutes of Health–sponsored trial scheduled to complete enrolment this year (clinicaltrials.gov, NCT01086540). *This trial includes a number of mechanistic studies including evaluating B-cell phenotype and clonality, multiplex cytokine assays, and regulatory T-cell properties. For this study, as for other emerging PAH therapies, there is anticipation that this careful phenotyping may provide biomarkers that may help predict which patients will benefit most from a given adjuvant therapy.*

# Translating Research into Improved Patient Care in Pulmonary Arterial Hypertension

Sébastien Bonnet[1,2], Steeve Provencher[1,2], Christophe Guignabert[3,4], Frédéric Perros[3,4], Olivier Boucherat[1], Ralph Theo Schermuly[5], Paul M. Hassoun[6], Marlene Rabinovitch[7], Mark R. Nicolls[8,9], and Marc Humbert[3,4,10]

Am J Respir Crit Care Med
195, 583–595, 2017

The journey from the discovery of a potential therapeutic target to its commercialization is long, complex, and costly. The series of clinical trials can cost hundreds of millions of dollars. Moreover, patient time commitment for current and upcoming PAH clinical trials is in the range of months to years, thus limiting the number of patients with PAH to be enrolled in trials testing for other therapies. In addition, even when animal studies show promising results, more than 80% of these therapies ultimately fail when tested in humans.

**Translating Research into Improved Patient Care in Pulmonary Arterial Hypertension**

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Importantly, this is not unique to PAH, because translating research into improved patient care exists across diseases . Nonetheless, given the limited financial resources, the persistent medical need for improved therapy in PAH, and the restricted study population available for clinical trials, there is a need to reduce the number of false positive signals in preclinical studies and to optimize the development of innovative therapeutic targets through performance of clinical trials based on more robust experimental data.

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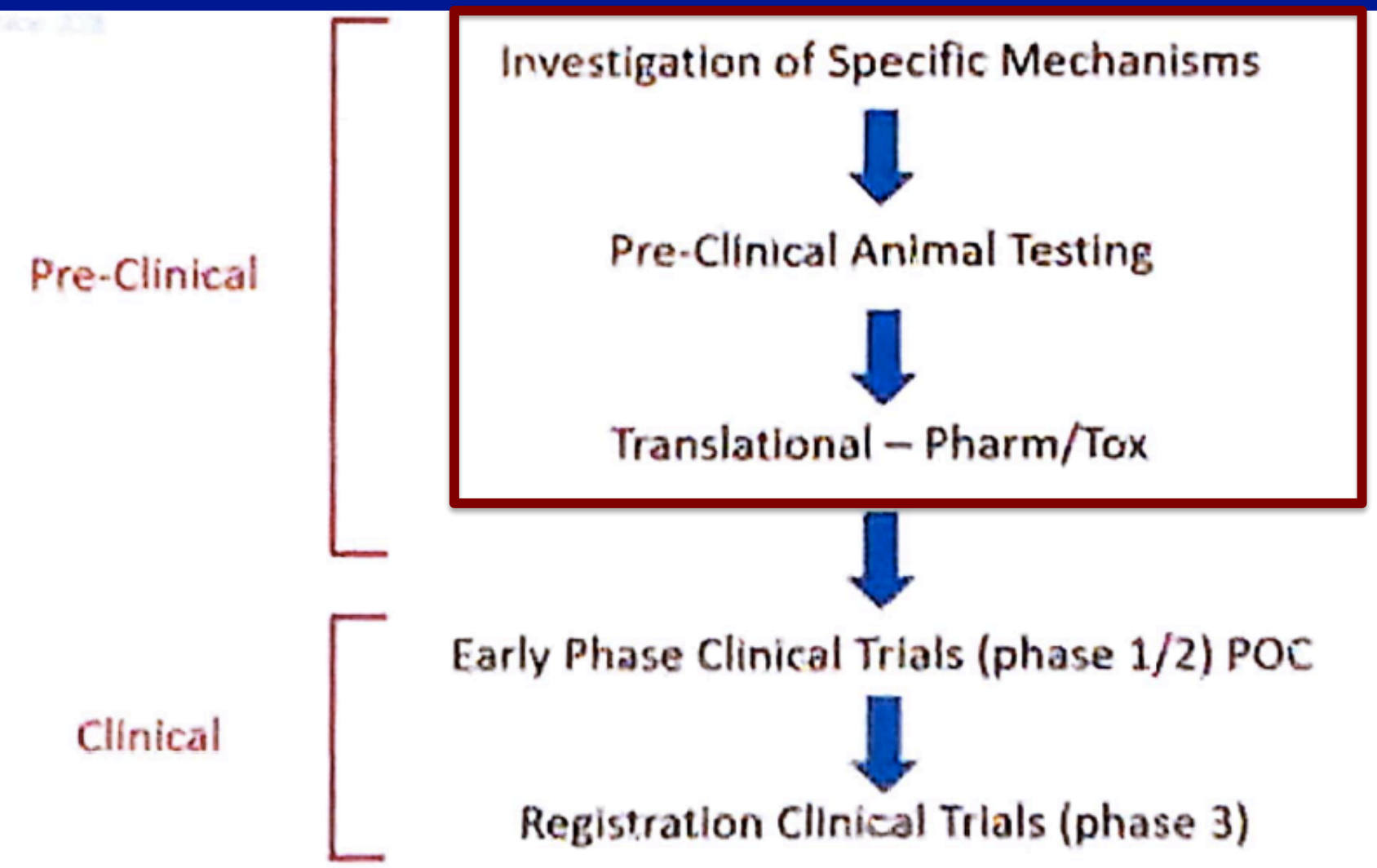
## Conclusions

A better translation of preclinical research findings into sustainable improvements in patient outcomes is clearly needed, but remains a substantial obstacle for many human diseases, including PAH. At present, research on PAH is characterized by significant discordance between preclinical findings and clinical results. Bridging this translational gap is thus vital and can be achieved only by rigorous use and characterization of human PAH tissues, a better design of preclinical studies, significant governmental and foundational support and funding, and close collaboration and significant commitment from clinical trial sites.

# Why do most clinical trials fail?

- Current animal models are useful but non perfect: they mimic only part of the PAH pathophysiological process and they don't entirely encompass the typical features of human PAH.
- Trial population is not representative of future patients to be treated
- The choice of endpoints is inappropriate
- Lack of blinding

# The phases of pre-clinical and clinical trials

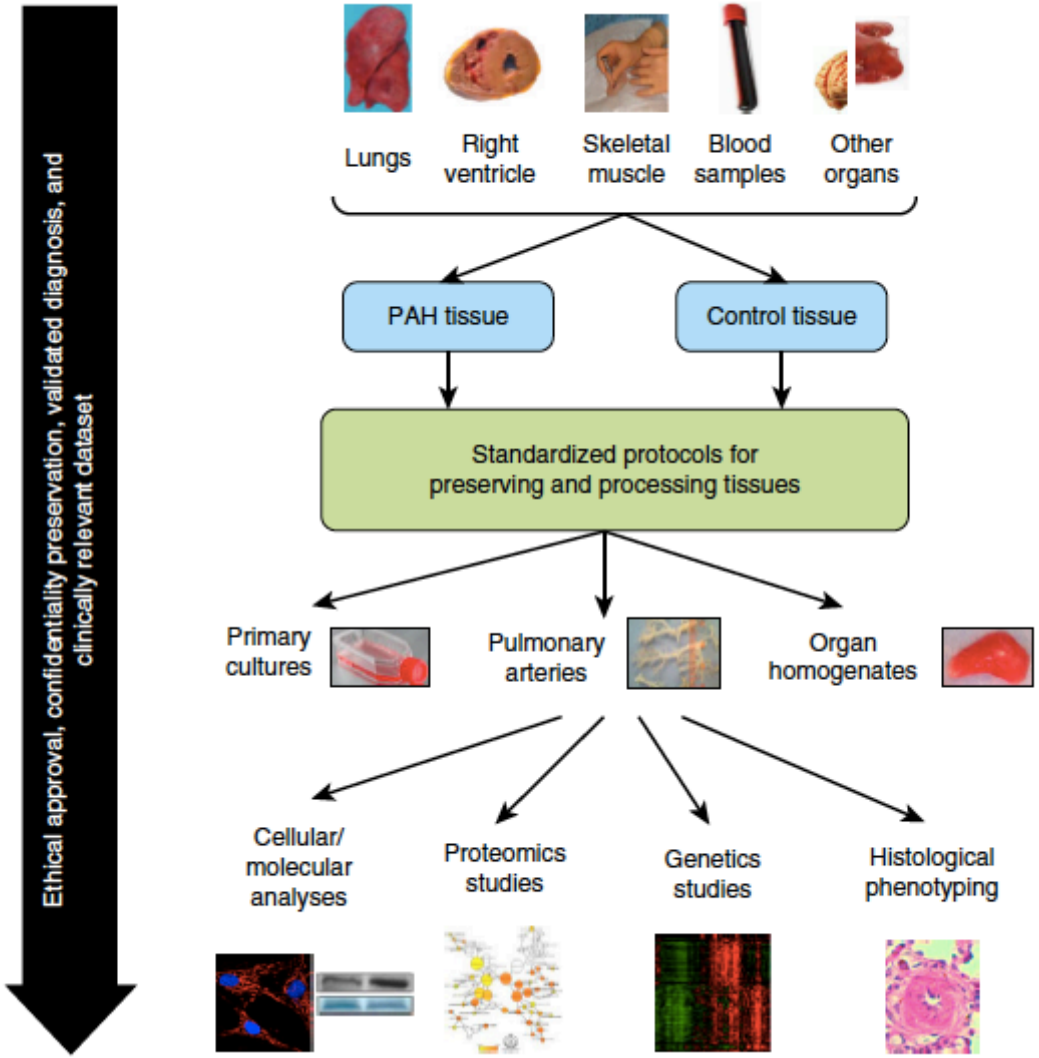


# Current animal models are useful but non perfect

| SPECIE | MODEL | ADVANTAGES | DISADVANTAGES |
|---|---|---|---|
| **Rat** | Induced monocrotaline | Inexpensive<br>Important vascular remodeling and RVF | Pulmonary interstitial edema, some feuatures of myocarditis and hepatic veno-occlusive disease not tipically present in human PAH |
| **Rat** | Chronic hypoxia and widely available | No obstructive intimal lesions<br>Pulmonary vascular remodeling induced by chronic hypoxia exposure alone is reversible after cessation of hypoxia | Representative of group 3 rather than PAH |
| **Rat** | Sugen-hypoxia | Intensify of vascular remodeling process, leading to the appearance of plexiform lesions | Sugen induces an emphysema-like phenotype |
| **Rat** | Mitomycin | May allow the understandinf of PVOD | |
| **Rat** | Spontaneous fawn-hooded rats | Spontaneously develop PH in a serotonin-dependent fashion that replicates seme PAH features | Developmental of lung anomalies |
| **Rat** | Genetically modified BMPR2 | Powerful tool to dissect PAH pathophysiological mechanisms | Low penetrance and expressivity |

*Provencher S., Rabinovitch et al, Am J Respir Critic Care Med Vol 195 Number 5 , 2017*

# PAH Preclinical studies using human specimens



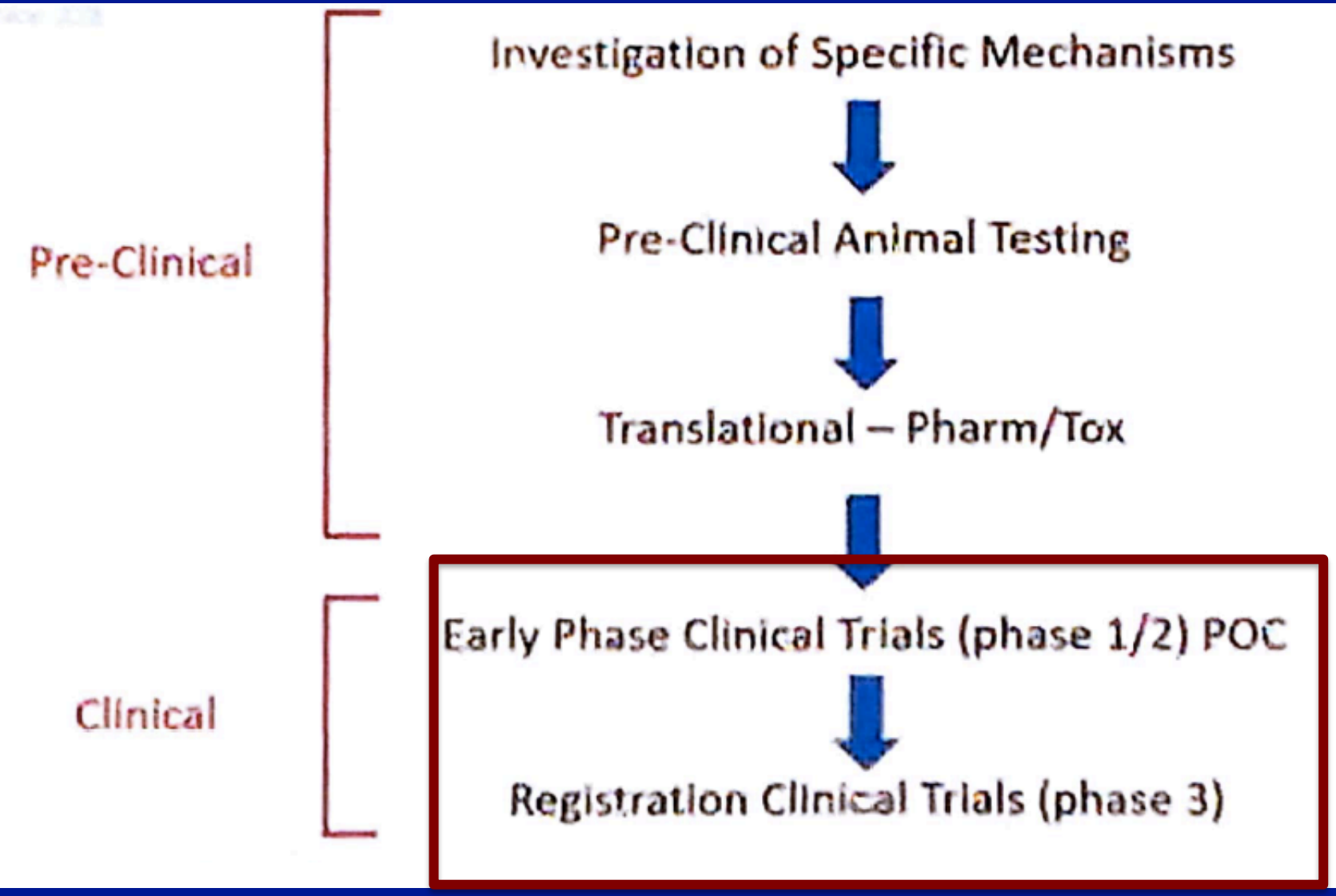

Tissues obtained:

- before cellular and protein degradation occurs;
- From patients with early-stage PAH→ at end-stage, proteins and signaling pathways may be influenced by the patient's treatment.

→ **Future**: **development of specialized endoarterial biopsy catheters.**

*Bonnet S., Provencher S. et al, Am J Respir Critic Care Med Vol 195 Number 5 , 2017*

# The phases of pre-clinical and clinical trials



# Why do most clinical trials fail?

- Phenotype is different than prior:

- Older
- Higher BMI
- More comorbidities
- Different etiologies
- Functional class of patients enrolled in clinical trials more II than III

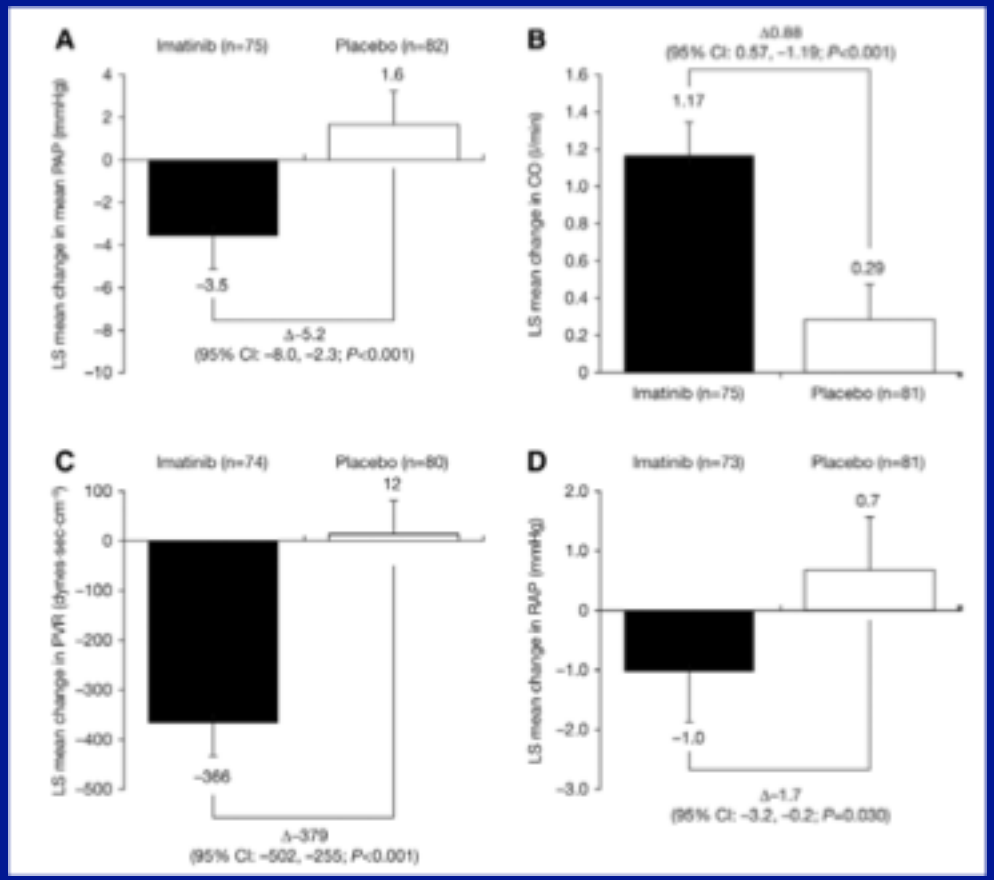
- Approved therapies may have contributed to rate of disease progression
- Achieving balance between clean phenotypes vs relevant populations

# Imatinib Mesylate as Add-on Therapy for Pulmonary Arterial Hypertension

## Results of the Randomized IMPRES Study

Marius M. Hoeper, MD; Robyn J. Barst, MD; Robert C. Bourge, MD; Jeremy Feldman, MD; Adaani E. Frost, MD; Nazzareno Galié, MD; Miguel Angel Gómez-Sánchez, MD; Friedrich Grimminger, MD; Ekkehard Grünig, MD; Paul M. Hassoun, MD; Nicholas W. Morrell, MD; Andrew J. Peacock, MD; Toru Satoh, MD; Gérald Simonneau, MD; Victor F. Tapson, MD; Fernando Torres, MD; David Lawrence, PhD; Deborah A. Quinn, MD; Hossein-Ardeschir Ghofrani, MD

(*Circulation*. 2013;127:1128-1138.)



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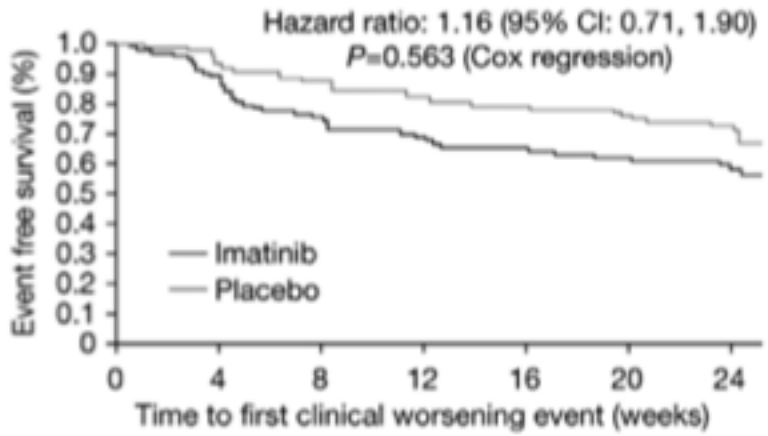



**Figure 4.** Time to clinical worsening. CI indicates confidence interval. Values below the graph are the number of patients remaining in the study at each time point.

**Subdural hematoma occurred in 8 patients (2 in the core study, 6 in the extension) receiving imatinib and anticoagulation.**

# Take home messages

- Despite the commercialized 10 drugs, long-term prognosis of PAH remains poor.
- None of the innovative therapies proposed are currently approved for clinical use (significant discordance between preclinical findings and clinical results).

→ To achieve this translational gap:

- characterization of human PAH tissues,
- better design of preclinical studies;
- close collaboration.

*Bonnet S., Provencher S. et al, Am J Respir Critic Care Med Vol 195 Number 5 , 2017*

# While waiting for new drugs …

**While waiting for new drugs …**
**…there is  lot we can do!!!**

## How to improve outcomes in PAH:

# 1- early diagnosis and early treatment

# Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial

N Galiè, L J Rubin, M M Hoeper, P Jansa, H Al-Hiti, G M B Meyer, E Chiossi, A Kusic-Pajic, G Simonneau

Lancet 2008; 371: 2093–100

185 pz con IPAH o PAH associata a CTD, HIV, CHD - classe WHO II - randomizzati a bosentan o placebo. Follow-up 6 mesi. End-points: TTCW

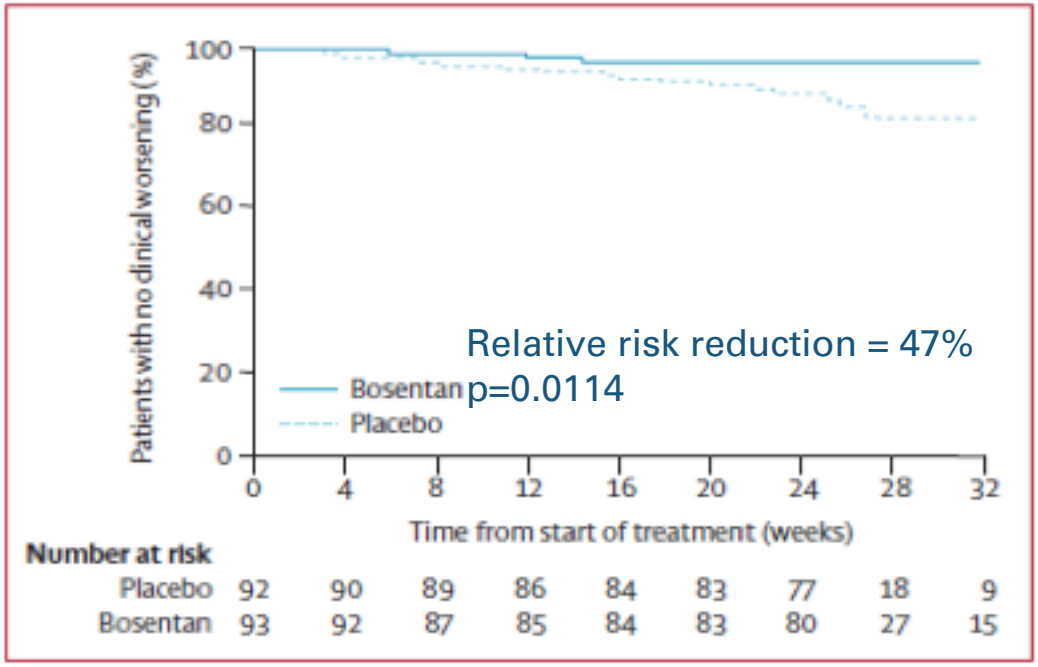



*Figure 4:* Time to clinical worsening

## How can we make early diagnosis?

## GL: screen populations at risk for PAH

## Which technique can we use for screening?

- Echo is the only technique we have (Echo has inherent limitations: it allows to estimate systolic PAP, while PH definition is based on mean PAP).
- Echo can perform much better if it is performed by “echocardiographists with PH experience”

# How to improve outcomes in PAH:

## 2- stratify the risk and treat aggressively high risk and also intermediate risk patients

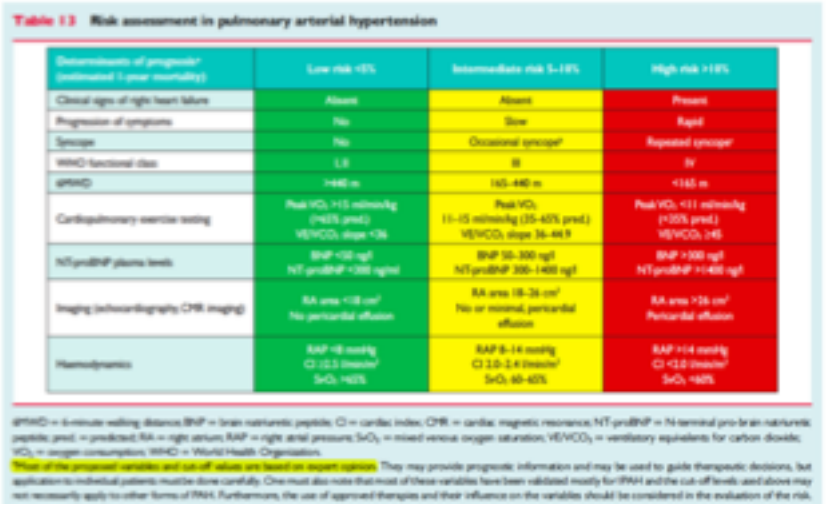



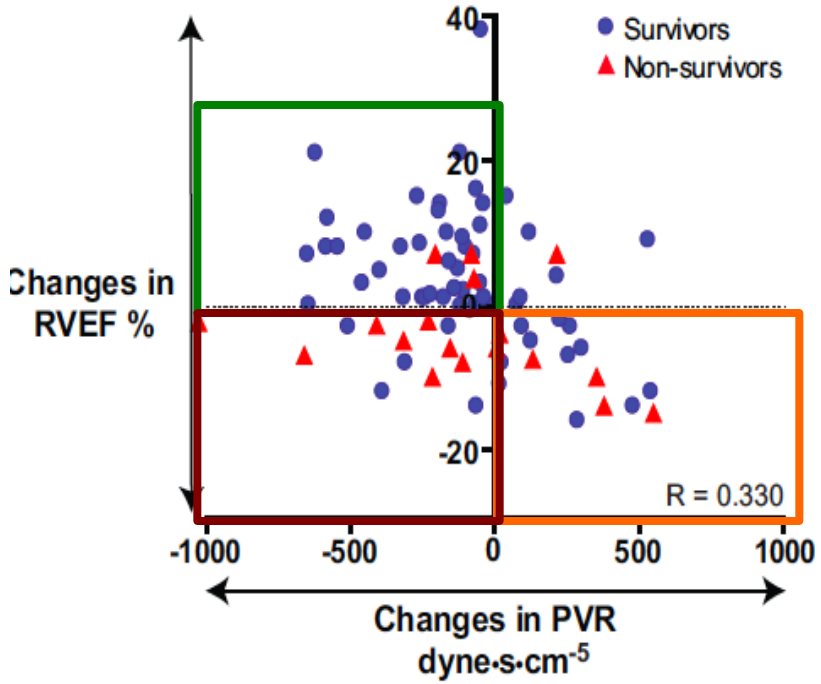
**Table 13 Risk assessment in pulmonary arterial hypertension**

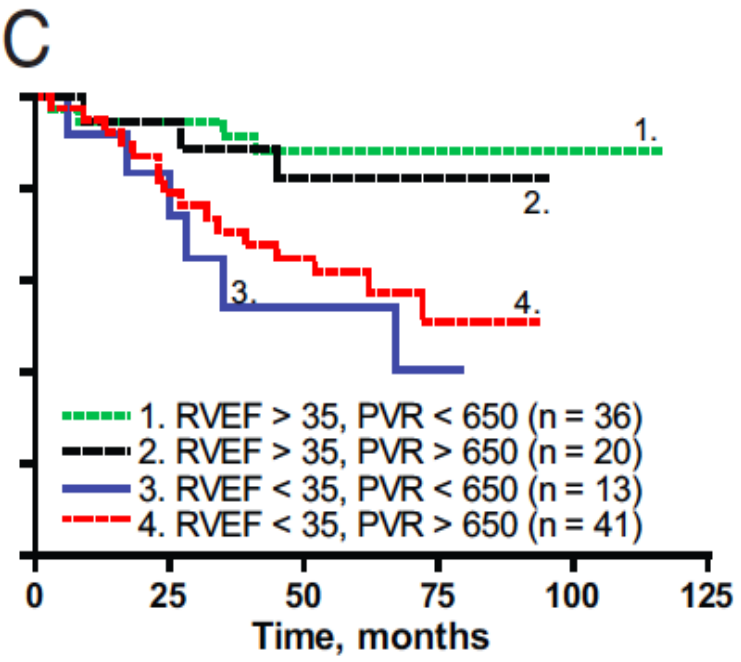
| Determinants of prognosis[a] (estimated 1-year mortality) | Low risk <5% | Intermediate risk 5–10% | High risk >10% |
|---|---|---|---|
| Clinical signs of right heart failure | Absent | Absent | Present |
| Progression of symptoms | No | Slow | Rapid |
| Syncope | No | Occasional syncope[a] | Repeated syncope[a] |
| 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% |

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; $SvO_2$ = mixed venous oxygen saturation; $VE/VCO_2$ = ventilatory equivalents for carbon dioxide; $VO_2$ = oxygen consumption; WHO = World Health Organization.

[a]None of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

# Impact of RVEF and PVR changes after therapy on survival

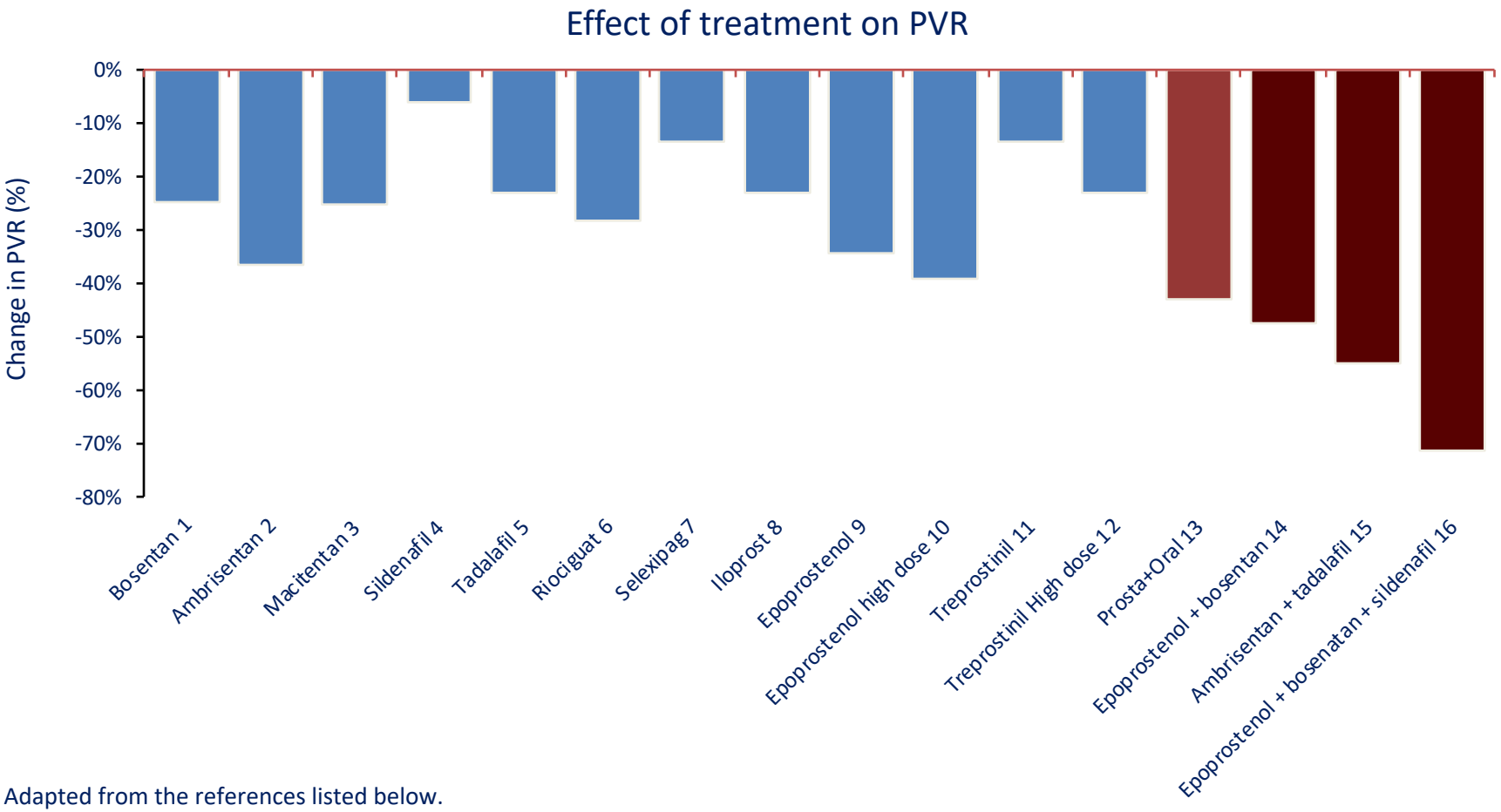



- Significant PVR reduction in order to obtain RVEF improvement
- RVEF may drop despite PVR reduction (myocardial damage)

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

# The impact of current treatments on PVR




Adapted from the references listed below.

**1**. Channick RN, *et al. Lancet* 2001 358;1119–23. **2.** Galiè N, *et al. J Am Coll Cardiol* 2005; 46:529–35. **3.** Pulido T, *et al. N Engl J Med* 2013; Supplementary information.**4.** Galiè N, *et al. N Engl J Med* 2005;353:2148–57. **5.** Galiè N, *et al. Circulation* 2009;119:2894–2903. **6.** Ghofrani HA, *et al. N Engl J Med* 2013; 369:319–40. **7.** Simonneau G, *et al. Eur Resp Journal* 2012;40:874–80. **8.** Olschewski H, *et al. N Engl J Med* 2002;347:322–9. **9.** Barst RJ, *et al. N Engl J Med* 199;334:296–301. **10** McLaughlin VV, Circulation 2002;106:1477–82 **11.** Simonneau G, *et al. Am J Respir Crit Care Med* 2002;165:800–4. **12** Sadushi-Koliçi R J Heart Lung Transplant. 2012;31:735-43 **13** Badagliacca R.et al . *J Heart Lung Transplant. 2012;31:364-372* **14.** Kemp K, *et al. J Heart Lung Transplant* 2012;31:150–8. **15** Hassoun PM, *et al. Am J Respir Crit Care Med* 2015;192:1102–10. **16.** Sitbon O, *et al. Eur Respir J* 2014;43:1691–7.

# *The pathway to improve long-term outcomes in PAH has not changed in 2018*

*Humbert M, et al. Eur Respir Rev 2012;21:126,306-312*