# Klinische Studien PH 2015

## Beispiel der Prostanoide

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ECCPS
EXCELLENCE CLUSTER CARDIO-PULMONARY SYSTEM

Actelion

AstraZeneca

Bayer

BMS

GSK

Janssen Cilag

Lilly

OMT

Pfizer

United Therapeutics

# Updated Clinical Classification

## 1 Pulmonary Arterial Hypertension

- IPAH
- Heridetable PAH: BMPR2,ALK1, ENG, SMAD9, CAV1, KCNK3, unknown
- drugs and toxins induced
- associated with:
- Connective tissue diseases
- HIV infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis

## 1’ PVOD and/or PCH

## 1´´ PPHN

## 2 Pulmonary hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease
- Cong./acq. LH inflow/outflow tract obstruction and congenital CMP

## 3 Pulmonary hypertension due to lung diseases and/or hypoxia

- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Other lung dis mixed obstr./restr. Ventilatory pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

## 4 Chronic Thromboembolic pulmonary hypertension (CTEPH)

## 5 Pulmonary Hypertension with unclear and/or multifactorial mechanisms

- Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- Systemic disorders: Sarcoidosis, histiocytosis, LAM
- Metabolic disorders: Glycogen storage disease, Gaucher disease, thyroid disorders
- Others: obstruction by tumors, fibrosing mediastinitis,Chronic Renal failure on dialysis, segmental PH

Simonneau JACC 2013

# Updated Clinical Classification

**1 Pulmonary Arterial Hypertension**

**2 Pulmonary hypertension due to left heart disease**

**3 Pulmonary hypertension due to lung diseases and/or hypoxia**

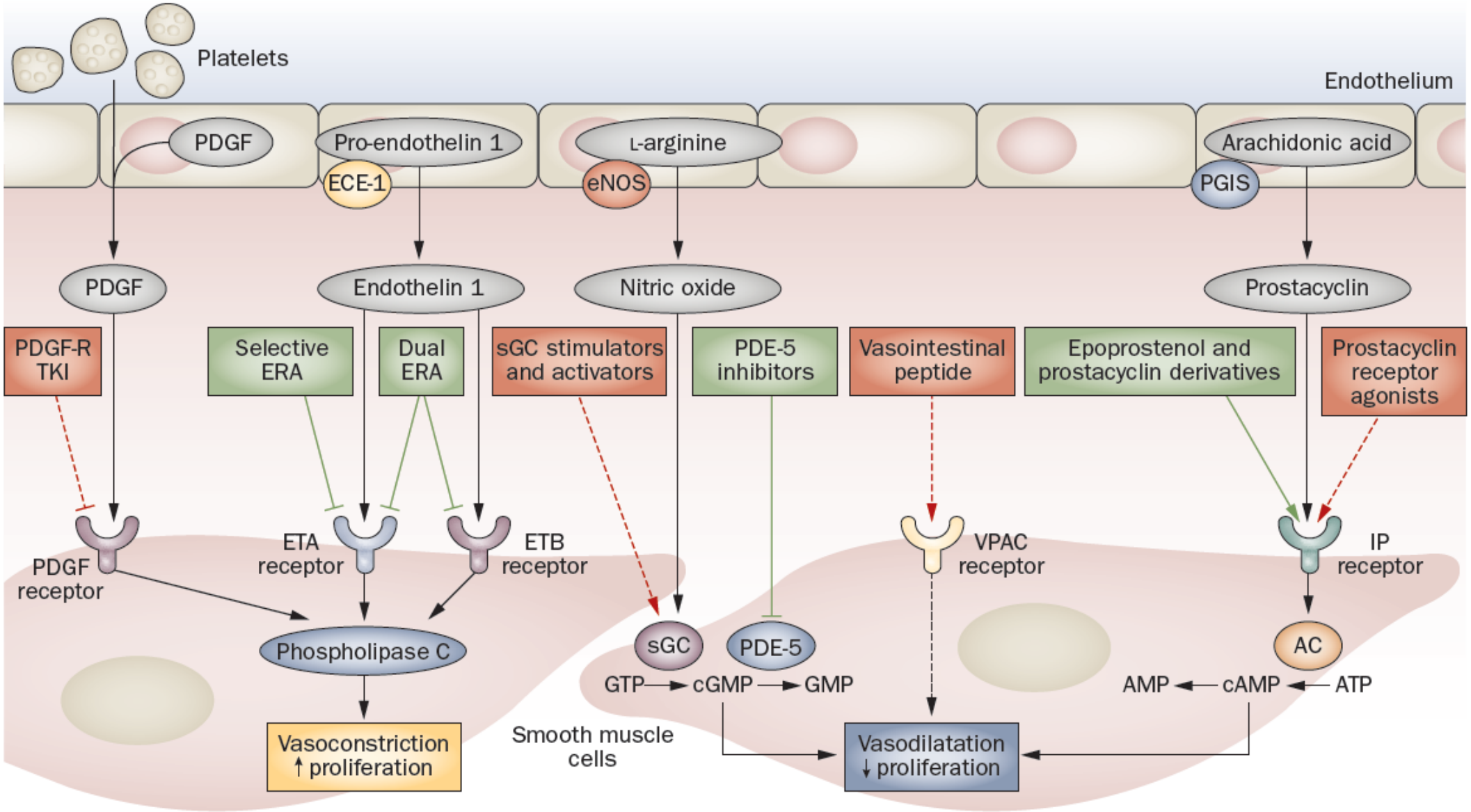
RISE IIP

**4 Chronic Thromboembolic pulmonary hypertension (CTEPH)**

MERIT

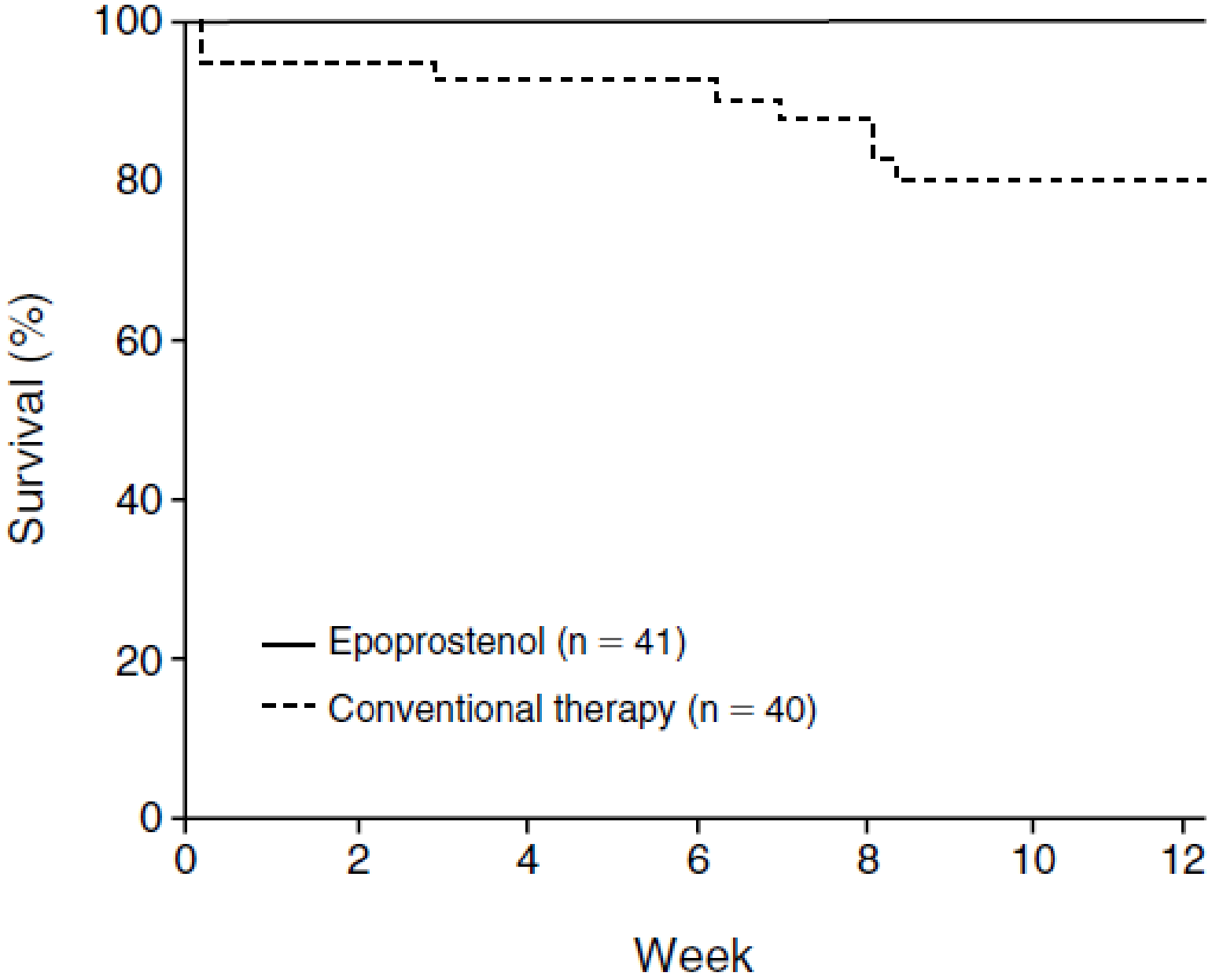
**5 Pulmonary Hypertension with unclear and/or multifactorial mechanisms**

Simonneau JACC 2013




O'Callaghan Nat Rev Cardiol 2011

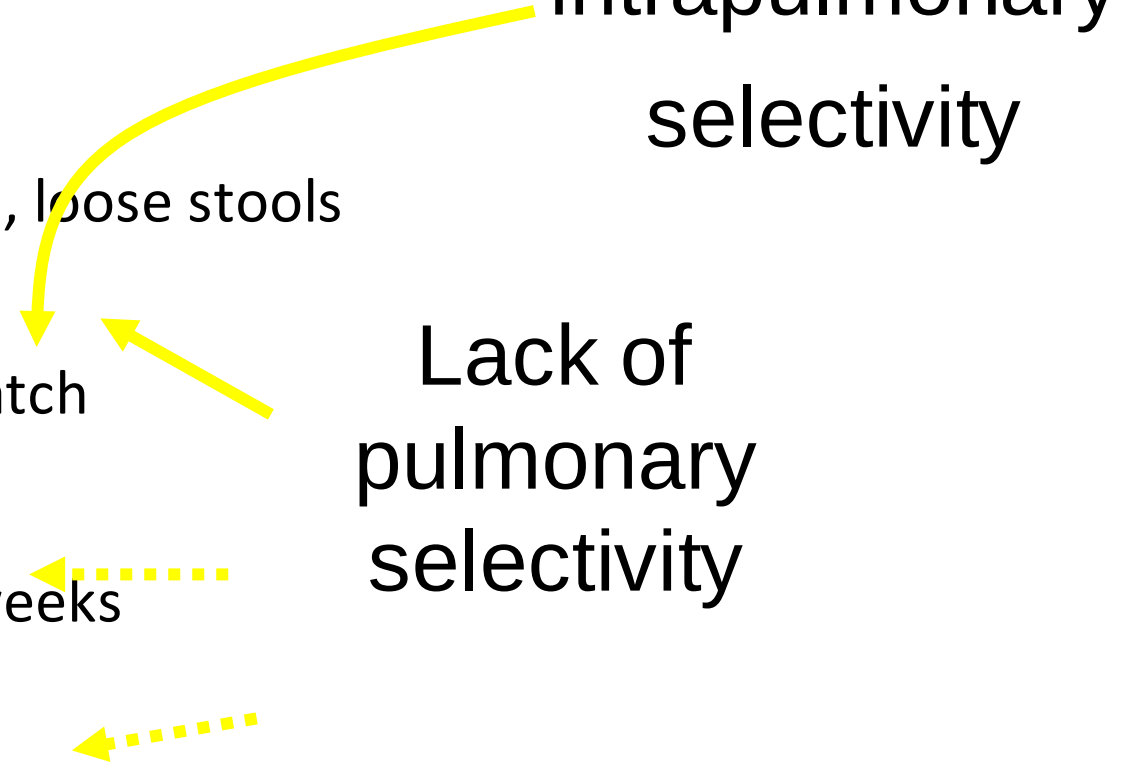
B




Barst NEJM 1996

# Problems with systemic prostacyclines

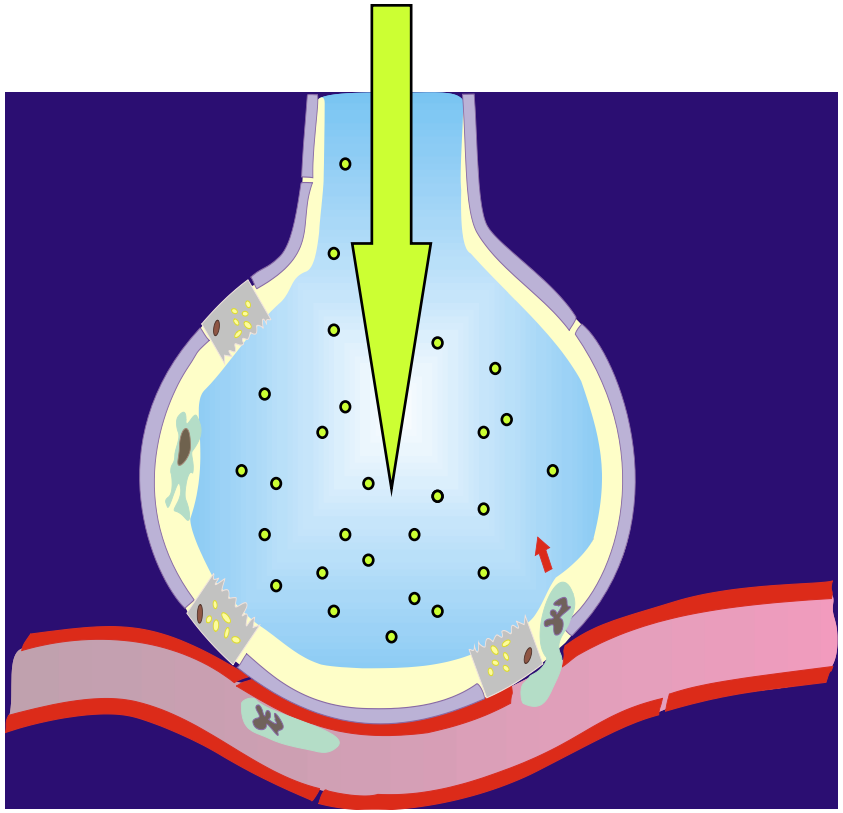
- Catheter complications
  - septic events
  - discontinuation of infusion
- Systemic side effects
  - jaw pain, leg pain, headache, loose stools
  - systemic hypotension
  - ventilation/perfusion mismatch
- Tachyphylaxis
  - dose increase every 2 to 4 weeks
- Costs of therapy

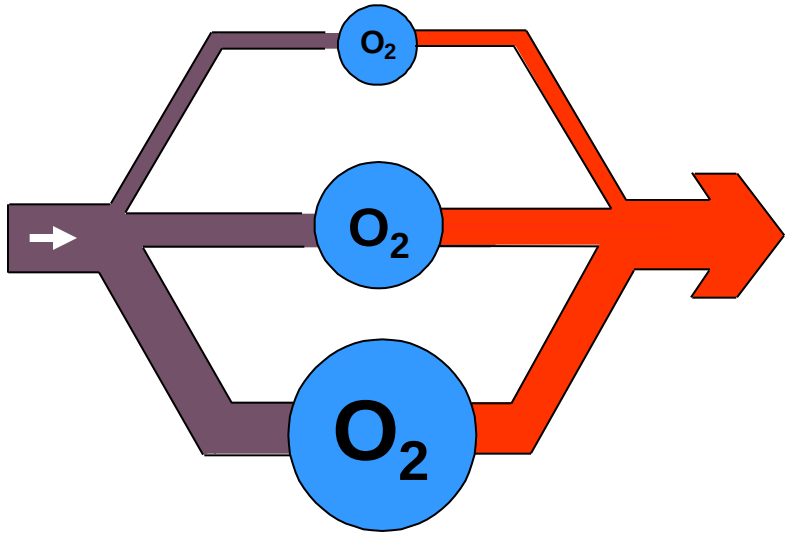


# Goals of inhalative therapy for PH

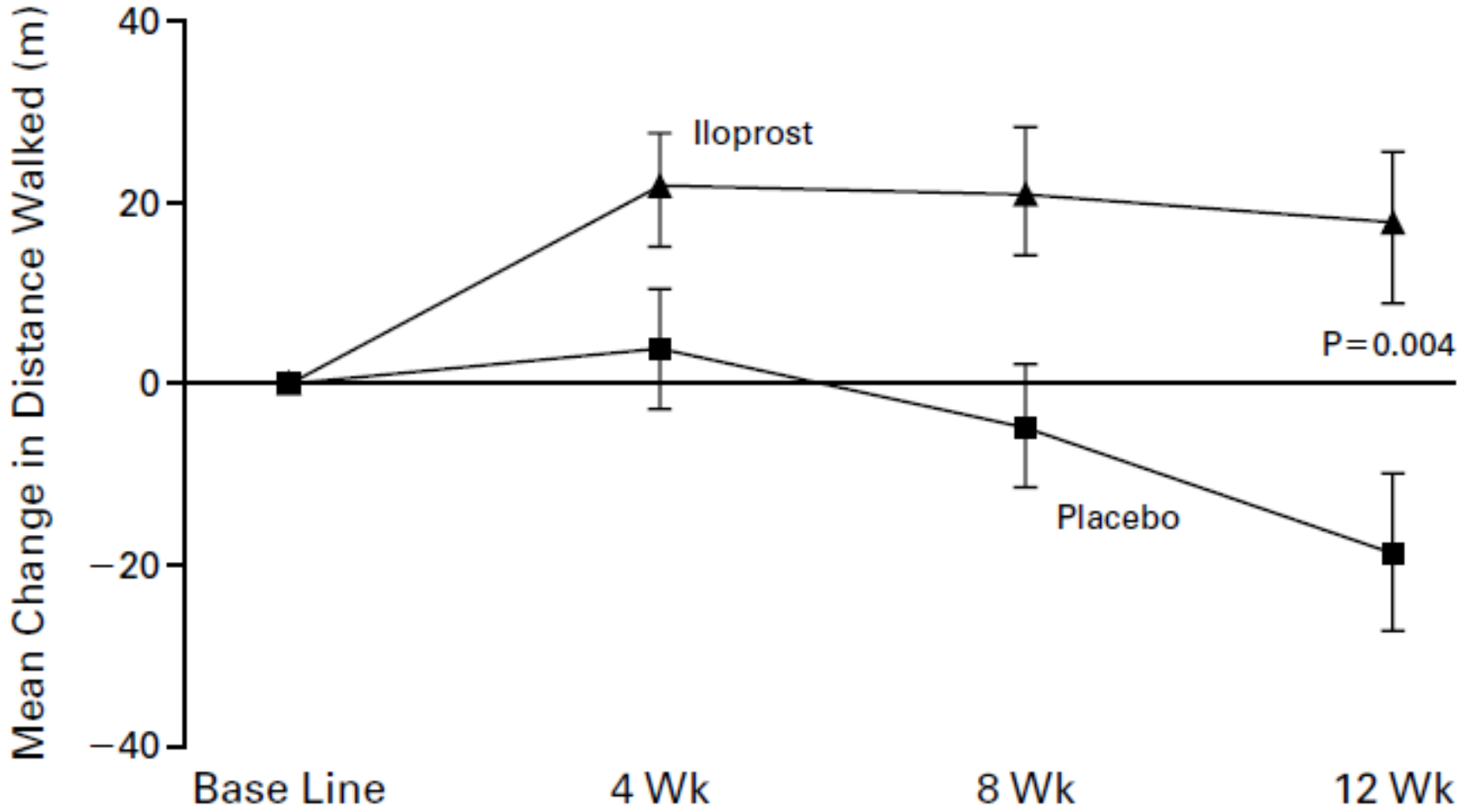
pulmonary selectivity
intra-pulmonary selectivity

Vasodilator



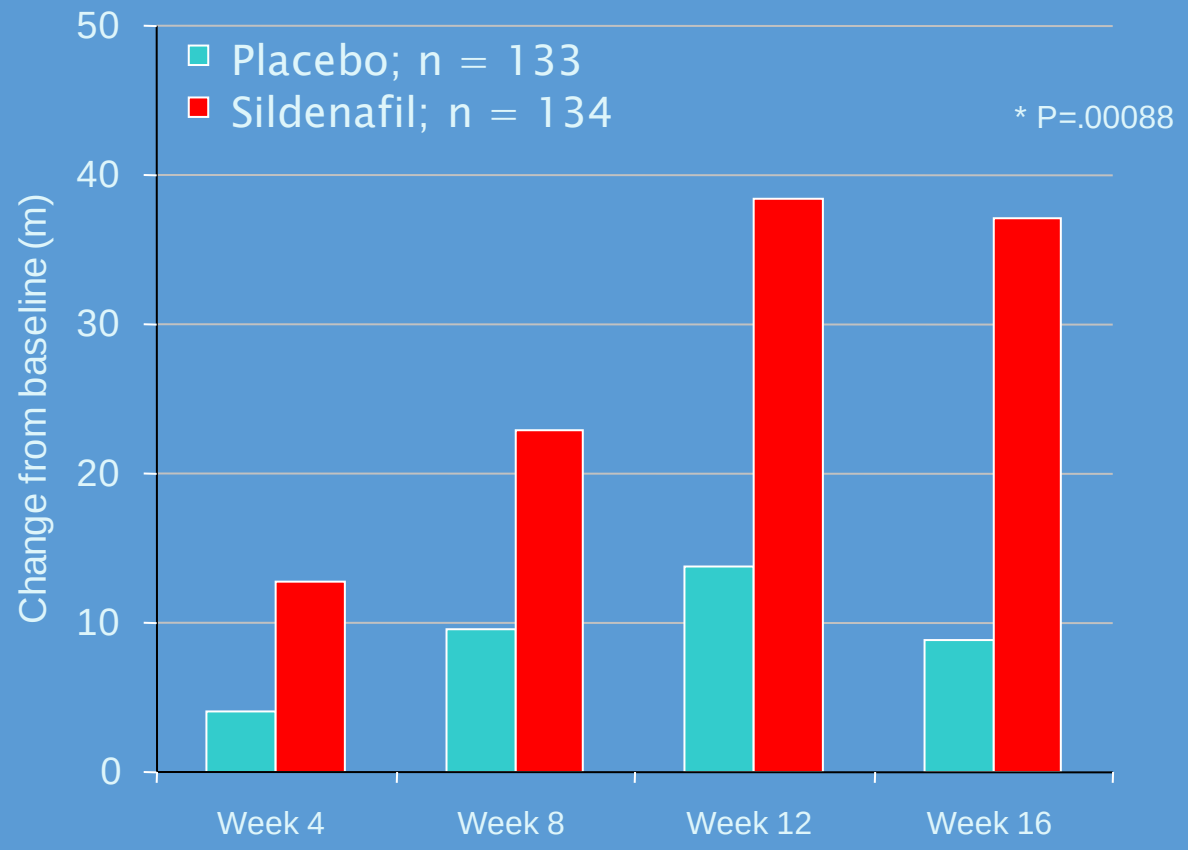



**V/Q matching**




Olschewski NEJM 2002

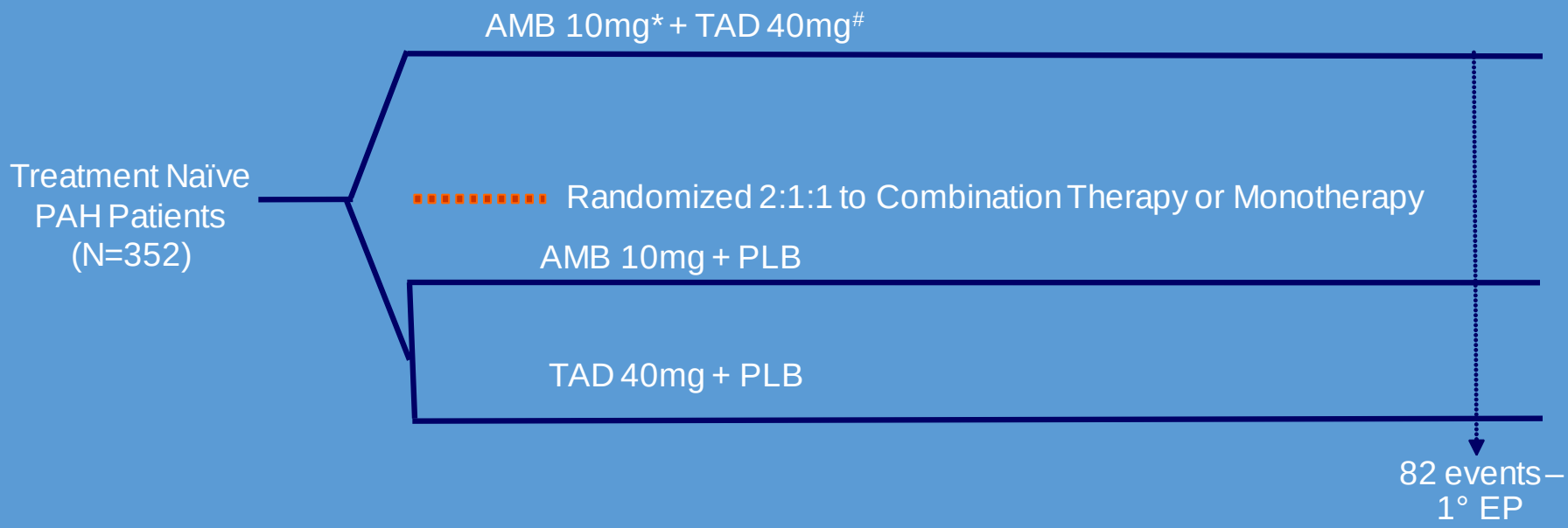
# PACES: Adding sildenafil to epoprostenol




- Significant improvement in time to clinical worsening
- 7 deaths, all in the placebo group

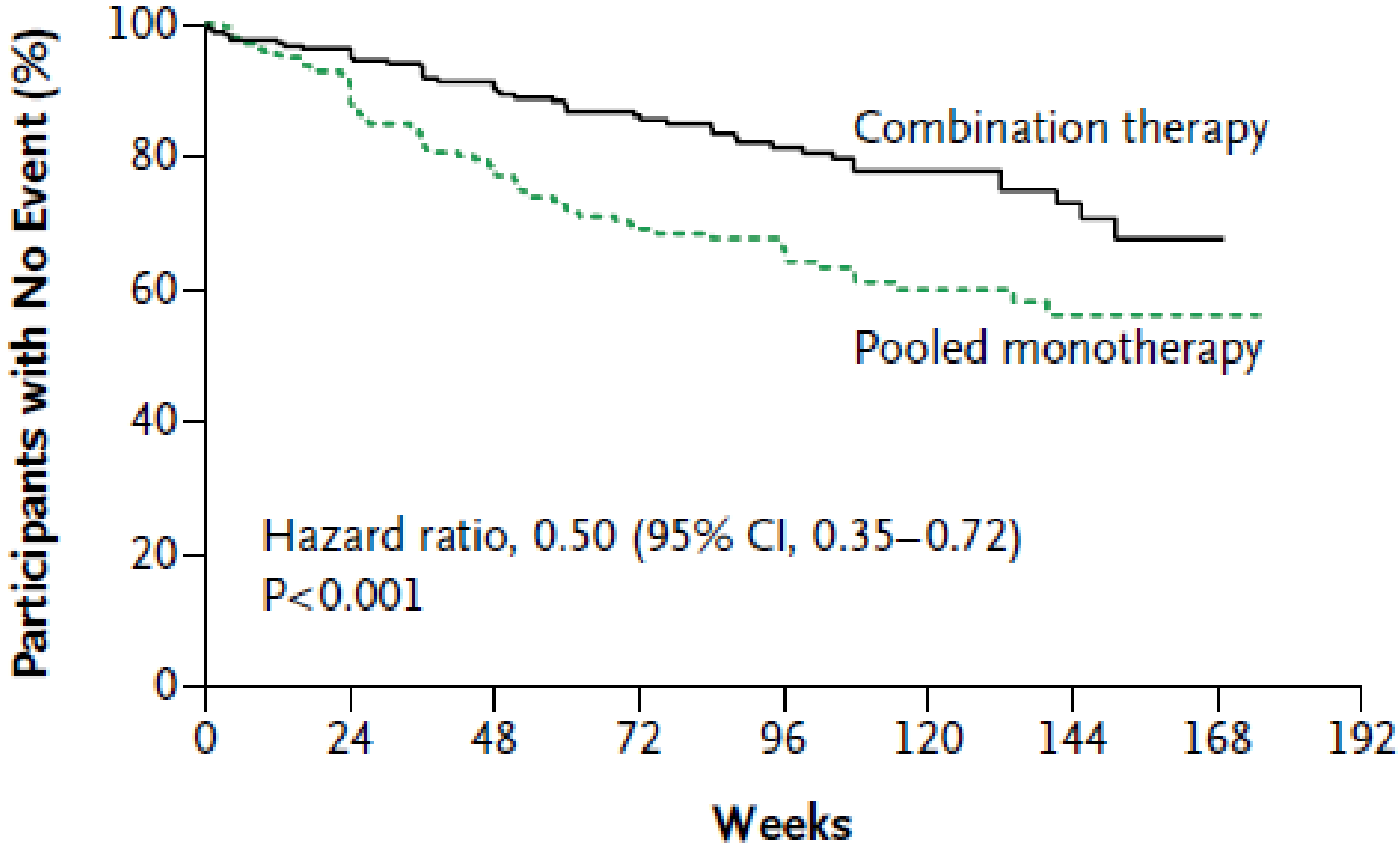
Simonneau G et al. ATS 2007 Ann Int Med 2008

# AMBITION: Studiendesign




*Target dose. 5mg first 8 weeks forced uptitration to 10mg unless tolerability issues
# 20mg for first 4 weeks, 40mg thereafter

- **Population:** ~352 PAH patients – treatment-naïve
- **Treatment:** AMB ***and*** TAD vs. AMB ***or*** TAD
- **1° Endpoint:** Time to clinical failure
  - Death, hospitalization for PAH, disease progression, treatment failure
- **2° Endpoints – Change from baseline at Week 24:**
  - 6MWD, BDI, WHO class, BNP, etc.
- **Study Goal:**
  - Demonstrate superiority of first-line combo therapy compared to monotherapy
- **Clinic Visits:**
  - Screen, Baseline, Weeks 4, 8, 16, 24, every 12 weeks




Galie NEJM 2015

Primary Outcome:
Time to first adjudicated morbidity or mortality event defined as:
Death or
Hospitalization for worsening of PAH or
Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy or
Initiation of parenteral prostanoid therapy or chronic oxygen therapy or
Disease progression..

Selexipag decreased the risk of a morbidity/mortality event versus placebo by 40% ($p<0.0001$)

Comparative PK PD Study in PAH Patients (Fox vs. I-Neb)

Sponsors homepage, clinicaltrials.gov

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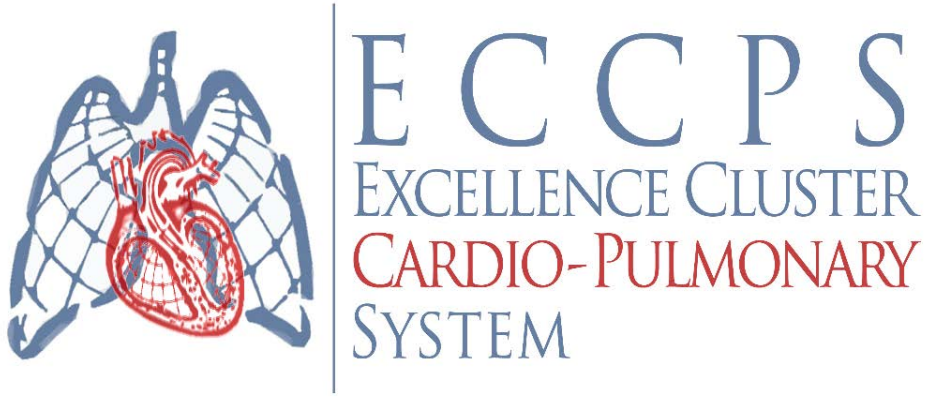

# 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Henning Gall

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# Recommendations for efficacy of drug monotherapy for PAH

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Prostacyclin analogues | Epoprostenol | Intravenous[e] | - | - | I | A | I | A | 220–222 |
| | Iloprost | Inhaled | - | - | I | B | IIb | C | 229–231 |
| | | Intravenous[g] | - | - | IIa | C | IIb | C | 232 |
| | Treprostinil | Subcutaneous | - | - | I | B | IIb | C | 233 |
| | | Inhaled[g] | - | - | I | B | IIb | C | 237 |
| | | Intravenous[f] | - | - | IIa | C | IIb | C | 234 |
| | | Oral[g] | - | - | IIb | B | - | - | 238–240 |
| | Beraprost[g] | | - | - | IIb | B | - | - | 218 |
| IP receptor agonists | Selexipag (oral)[g] | | I | B | I | B | - | - | 241,248 |

# Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension

| Measure/ treatment | Class[a]-Level[b] | | | | | | Ref.[c] |
|---|---|---|---|---|---|---|---|
| | WHO-FC I | | WHO-FC III | | WHO-FC IV | | |
| Ambrisentan + tadalafil[d] | I | B | I | B | IIb | C | 247 |
| Other ERA + PDE-5i | IIa | C | IIa | C | IIb | C | - |
| Bosentan + sildenafil + i.v. epoprostenol | - | - | IIa | C | IIa | C | 246 |
| Bosentan + i.v. epoprostenol | - | - | IIa | C | IIa | C | 198, 245 |
| Other ERA or PDE-5i + s.c. treprostinil | | | IIb | C | IIb | C | - |
| Other ERA or PDE-5i + other i.v. prostacyclin analogues | | | IIb | C | IIb | C | - |

# Recommendations for efficacy of sequential drug combination therapy for PAH

| Measure/ treatment | Class[a]-Level[b] | | | | | | Ref.[c] |
|---|---|---|---|---|---|---|---|
| | WHO-FC II | | WHO-FC III | | WHO-FC IV | | |
| Macitentan added to sildenafil[d] | I | B | I | B | IIa | C | 201 |
| Riociguat added to bosentan | I | B | I | B | IIa | C | 214 |
| Selexipag[e] added to ERA and/or PDE-5i[d] | I | B | I | B | IIa | C | 241, 248 |
| Sildenafil added to epoprostenol | – | – | I | B | IIa | B | 209 |
| Treprostinil inhaled added to sildenafil or bosentan | IIa | B | IIa | B | IIa | C | 237 |
| Iloprost inhaled added to bosentan | IIb | B | IIb | B | IIb | C | 230, 231 |
| Tadalafil added to bosentan | IIa | C | IIa | C | IIa | C | 211 |
| Ambrisentan added to sildenafil | IIb | C | IIb | C | IIb | C | 249 |
| Bosentan added to epoprostenol | – | – | IIb | C | IIb | C | 250 |
| Bosentan added to sildenafil | IIb | C | IIb | C | IIb | C | 251, 252 |
| Sildenafil added to bosentan | IIb | C | IIb | C | IIb | C | 252 |
| Other double combinations | IIb | C | IIb | C | IIb | C | – |
| Other triple combinations | IIb | C | IIb | C | IIb | C | – |
| Riociguat added to sildenafil or other PDE-5i | III | B | III | B | III | B | 215 |