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# Therapeutic approaches in P(A)H and the new ESC Guidelines

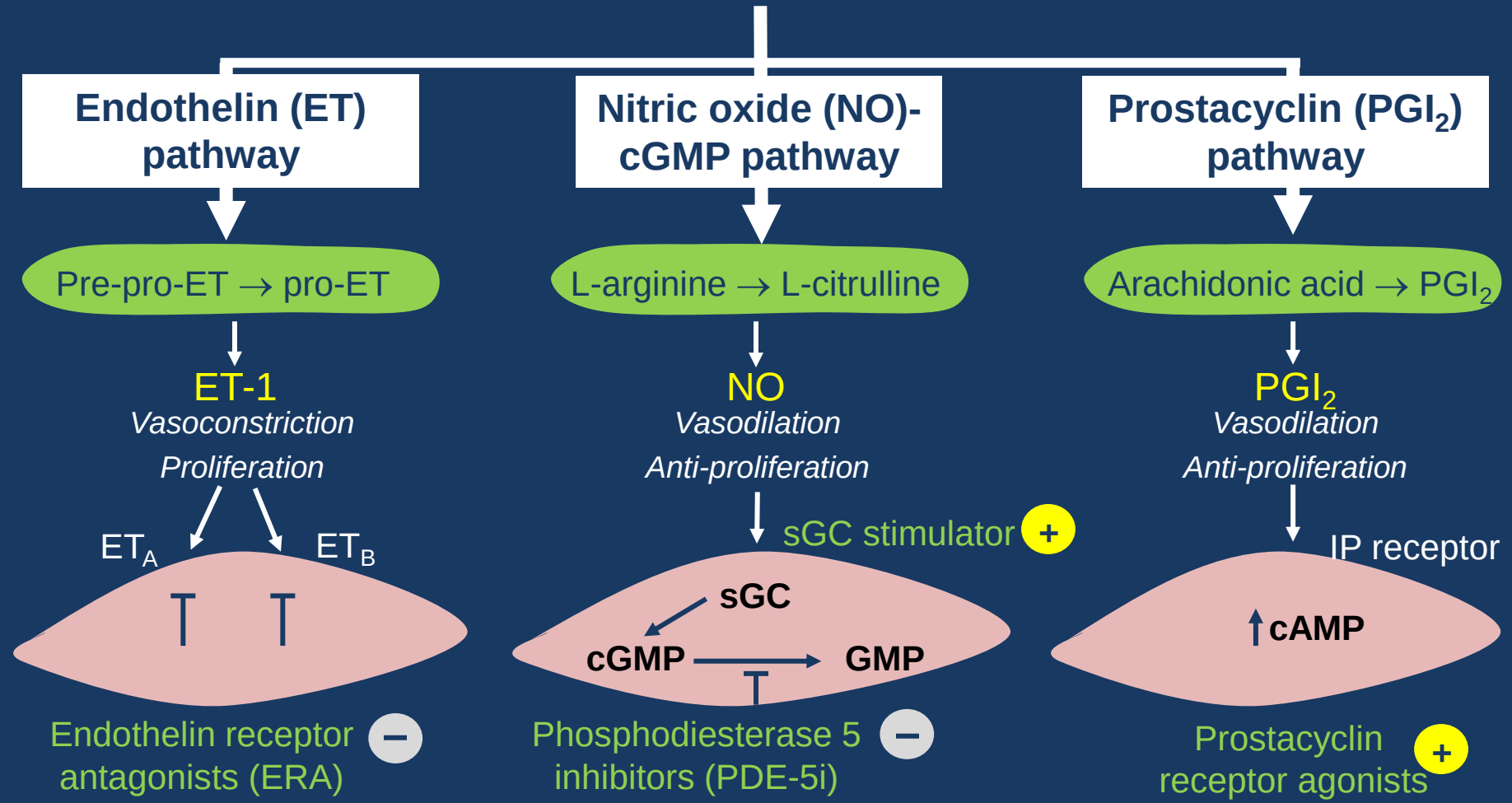
Jean-Luc Vachiéry, FESC

Head – Pulmonary Vascular Diseases and Heart Failure Clinic
Hôpital Universitaire Erasme
Université Libre de Bruxelles
Belgium

# Disclosures

- Name of companies with which relevant financial relationship exists:
  - Actelion Pharmaceuticals
  - Bayer Schering
  - GlaxoSmithKline
  - Pfizer
  - United Therapeutics
- Nature of relationship:
  - Consultant
  - Honoraria
  - Advisory Board Member

# PAH-specific therapies target the three signalling pathways involved in PAH




sGC: soluble guanylate cyclase
cAMP: cyclic adenosine monophosphate
cGMP: cyclic guanosine monophosphate

Adapted from Humbert M, *et al. N Engl J Med* 2004; 351:1425-36.

# Guidelines for treatment of PAH are based on evidence from 29 RCTs with > 5,000 patients

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**RCTs 1990-2005:**

- **Beraprost**
- **Bosentan**
- **Epoprostenol**
- **Sildenafil**
- **Treprostinil**

*1990* *2005* *2006* *2007* *2008* *2009* *2010* *2011* *2012* *2013* *2014*

**SUPER**
**SERAPH**

**STEP**
**STRIDE2**
**COMBI**
**BREATHE5**

**ARIES**
**EARLY**
**PACES**

**PHIRST**

**TRIUMPH**
**IMATINIB**
**Iversen**

**VARDENAFIL**

**FREEDOM C1**
**SELEXIPAG**

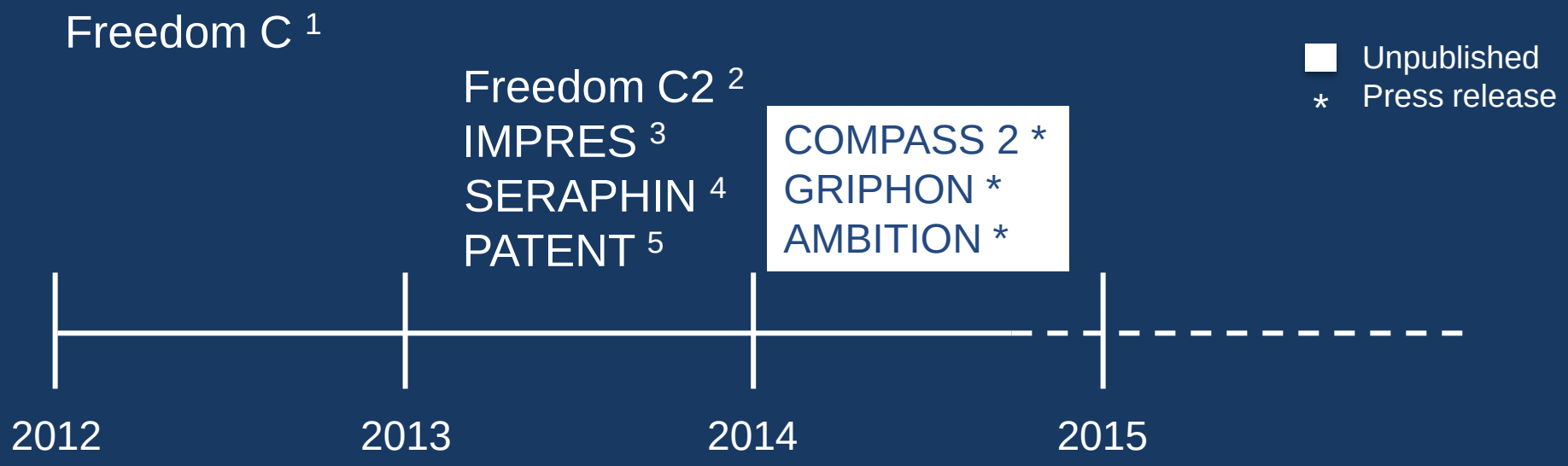
**SERAPHIN**
**PATENT**
**IMPRES**
**FREEDOM C2**
**FREEDOM M**

**COMPASS-2**
**AMBITION**
**GRIPHON**

**Monotherapy**
**Monotherapy and/or sequential combination**
**Initial combination**

Adapted from Galiè N, *et al. Eur Heart J* 2010; 31:2080-2086.

# RCTs in PAH 2012 – 2014
# From 6MWD to event-driven trial



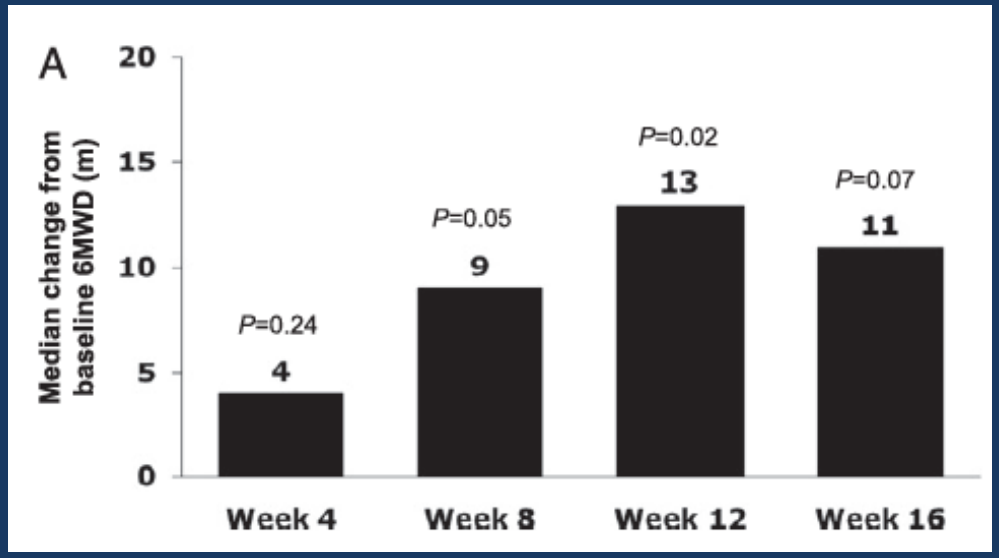

6 MWD

Composite endpoint (clinical worsening, time to clinical failure or MM)

- Key secondary endpoint
- Shift in paradigm towards event-driven trials

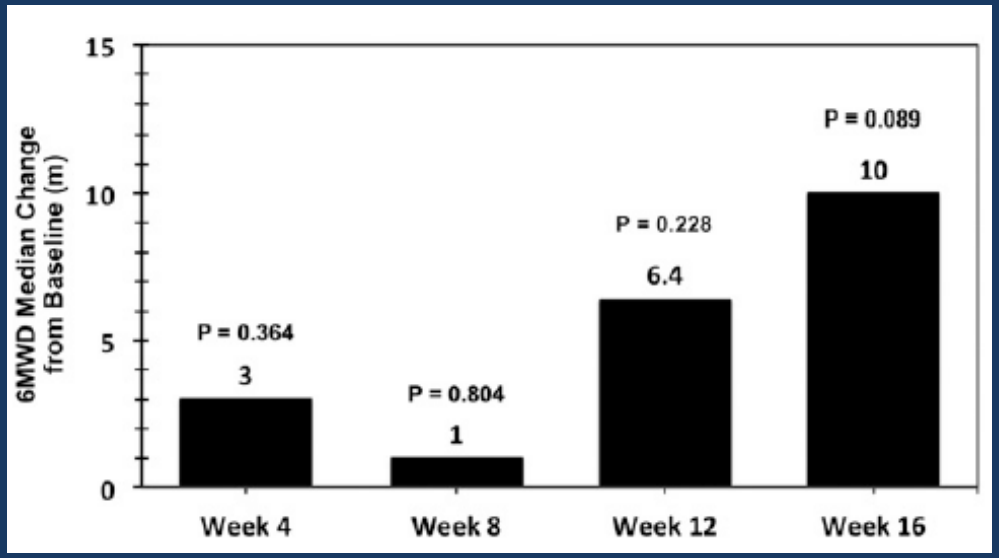
1. Tapson V. Chest 2012; 142: 1383. 2. Tapson V. Chest 2013; 142: 1363.
3. Hoeper MM. Circulation 2013;127:1128. 4. Pulido T. N Engl J Med 2013. 5. Ghofran A. N Engl J Med 2013

# No effect of oral treprostinil on 6MWD in FREEDOM C and FREEDOM C2




FREEDOM C [1]

N=350 patients with PAH
On background therapy



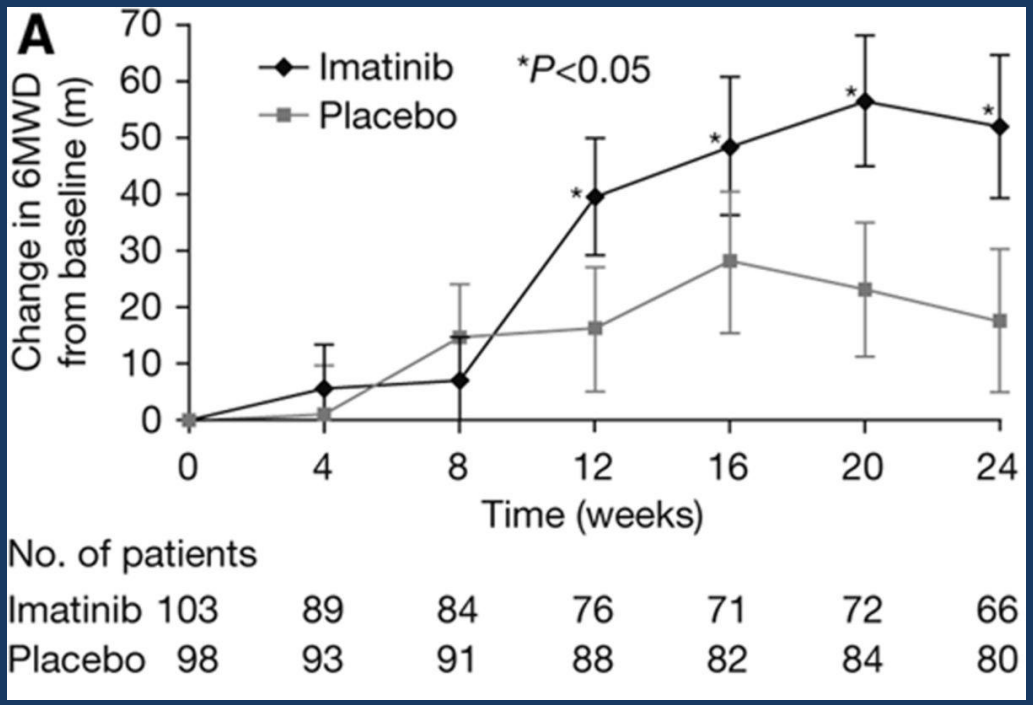

FREEDOM C2 [2]

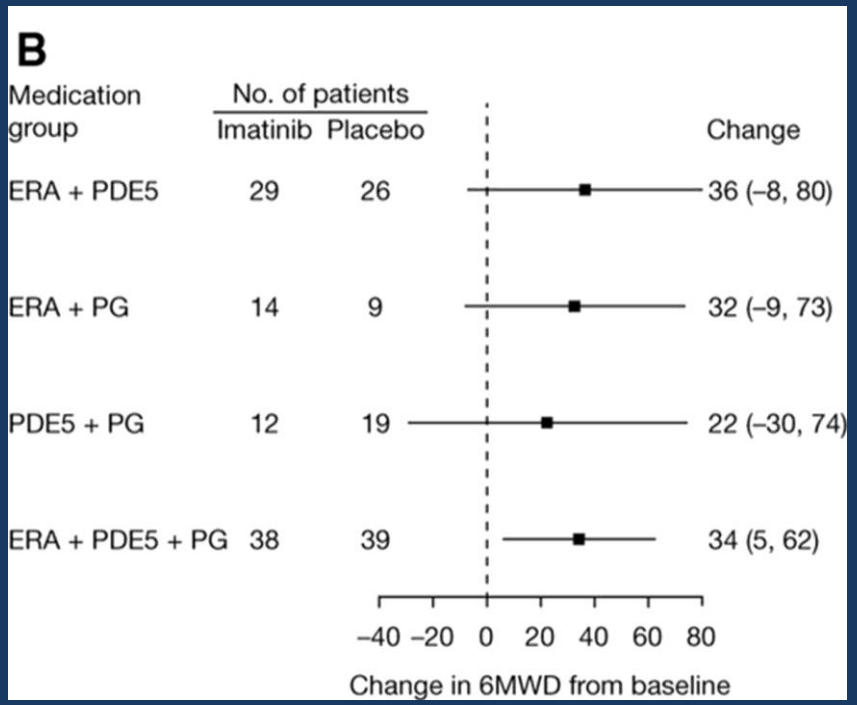
N=310 patients with PAH
On background therapy


1. Tapson V. Chest 2012; 142: 1383.
2. Tapson V. Chest 2013; 142: 1363.

# Imatinib improved 6MWD in IMPRES

- N=202 patients on background therapy



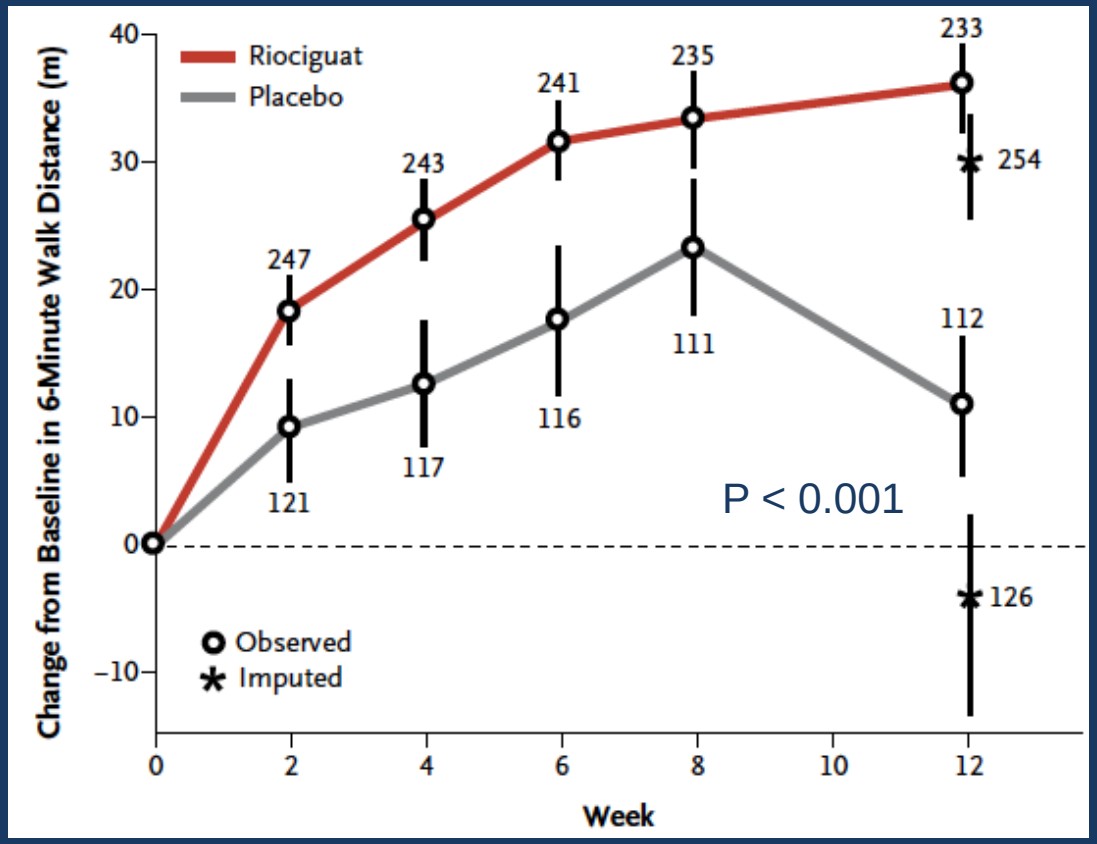




- No effect in delaying clinical worsening
- Safety issues (33% vs 18% completed, 8 subdural hematoma)
- Market approval application withdrawn

Hoeper M M et al. Circulation. 2013;127:1128-1138

# Riociguat improved 6MWD in PATENT-1

N=443 patients, both naive and on background therapy




<u>Improvement in 2ary EP in the 2.5 mg tid group:</u>

- NT Pro BNP
- WHO FC
- PVR
- Clinical worsening (n=13 events reported)

Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

# PATENT-1: Change in 6MWD for patients on background therapy (± 50%)

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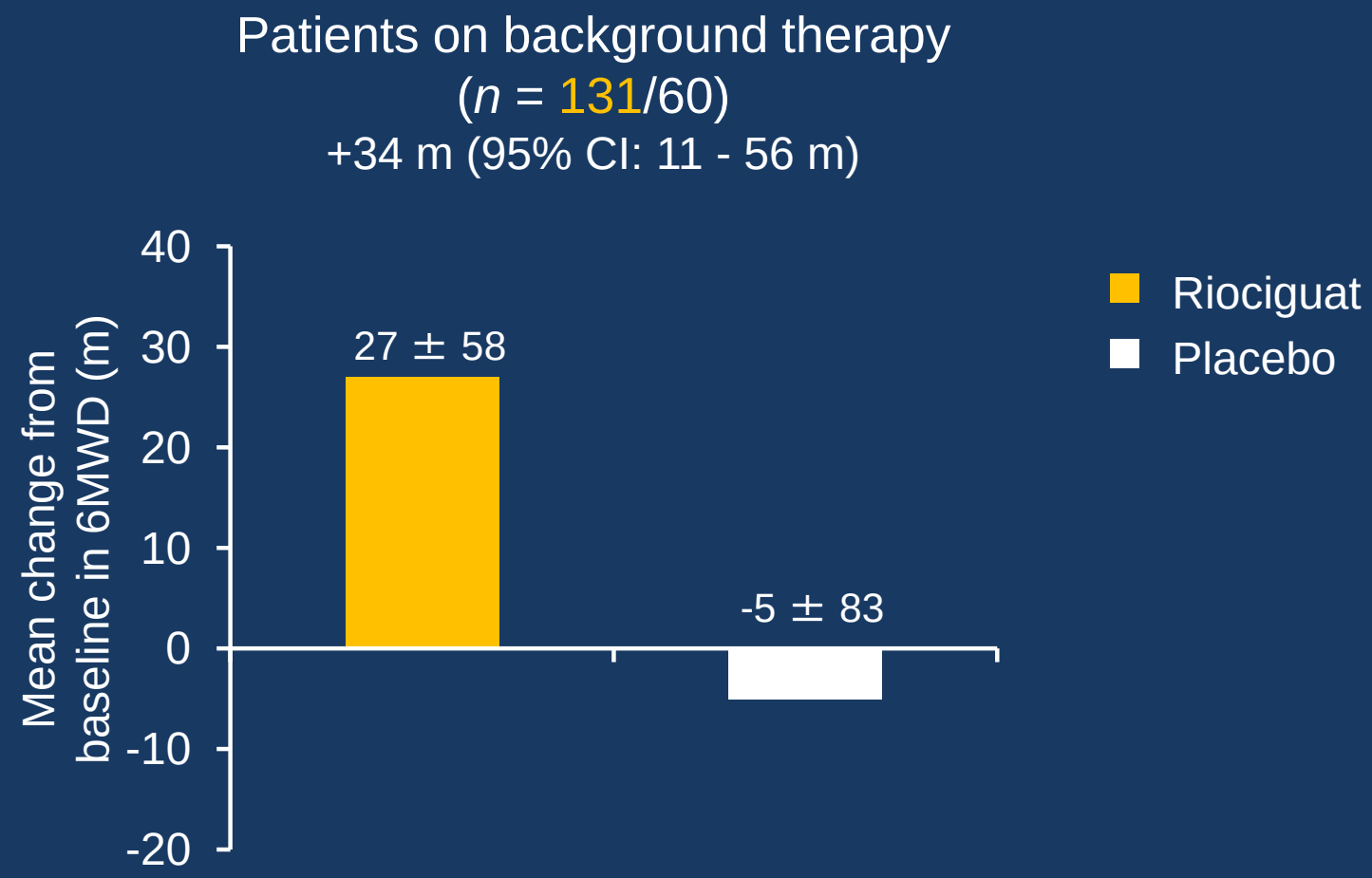
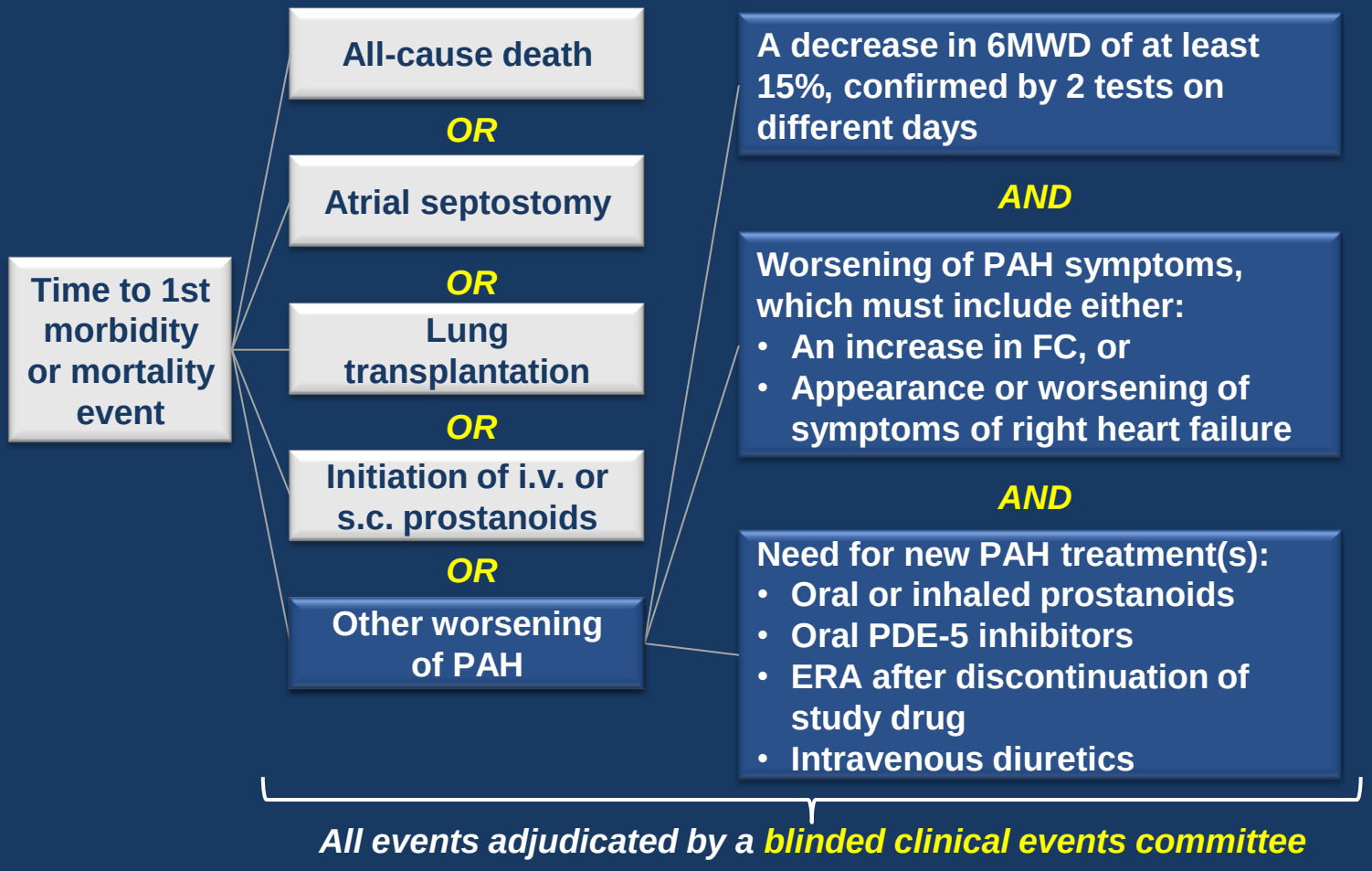



Ghofrani HA, *et al. New Engl J Med* 2013; 369:330-40.

# SERAPHIN: event-driven trial with a composite morbidity and mortality EP

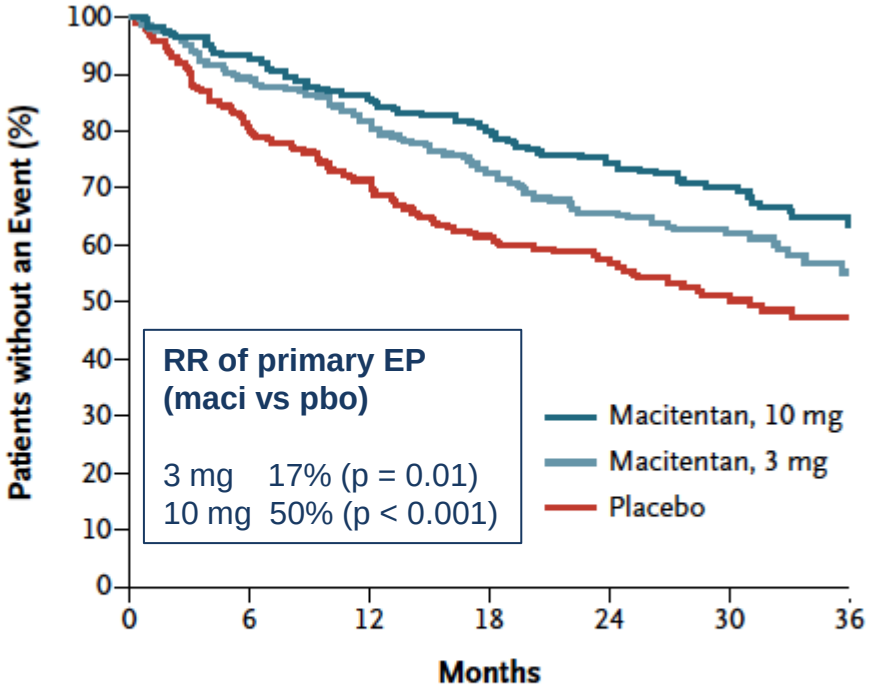



6MWD: 6-minute walk distance; ERA: endothelin receptor antagonist;
FC: functional class; PDE-5: phosphodiesterase-5

Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

# Macitentan delayed time to first event

- N=742 patients, both naive and on background therapy
- Randomisation 2:1 to macitentan (3 and 10 mg) vs PBO



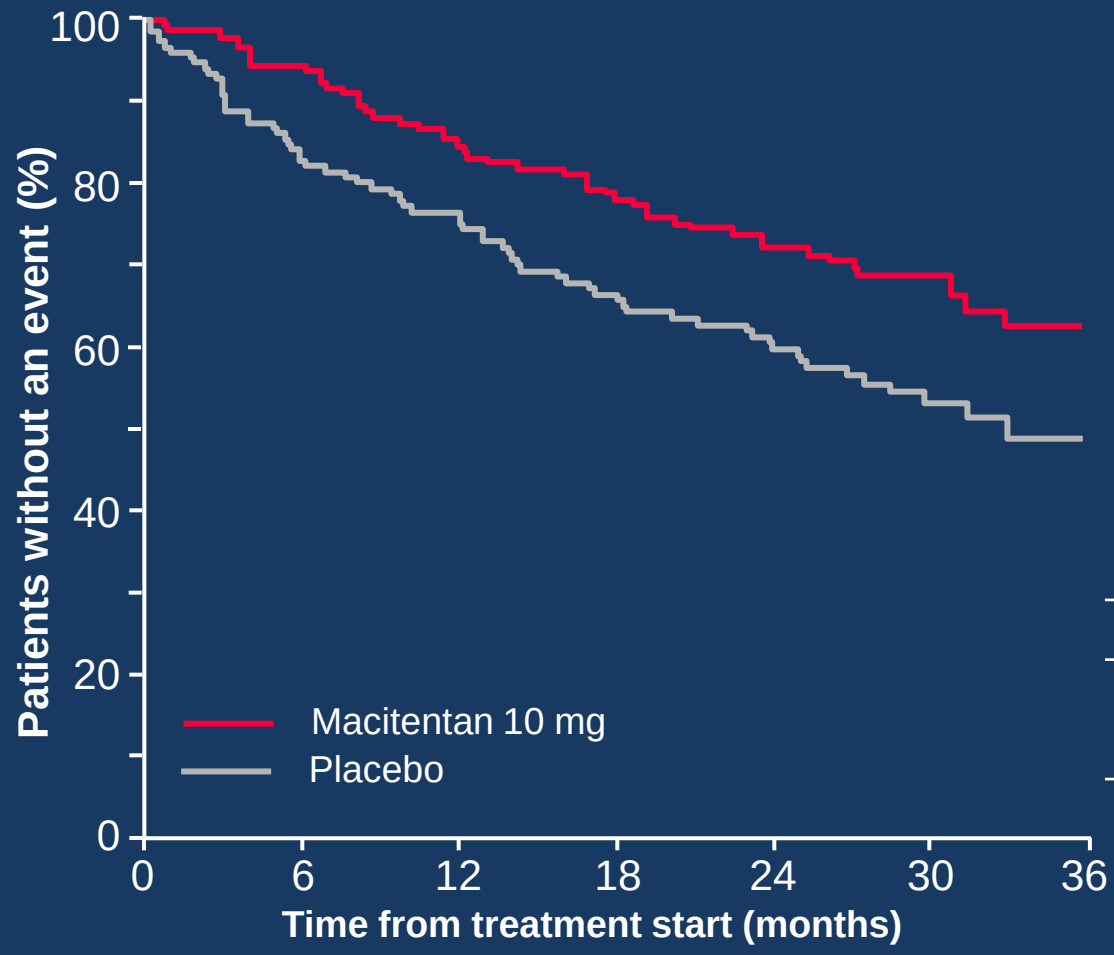

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 250 | 188 | 160 | 135 | 122 | 64 | 23 |
| Macitentan, 3 mg | 250 | 213 | 188 | 166 | 147 | 80 | 32 |
| Macitentan, 10 mg | 242 | 208 | 187 | 171 | 155 | 91 | 41 |

<u>Improvement in 2ary EP:</u>

- 6MWD
- WHO FC
- NT Pro BNP
- PVR

Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

# SERAPHIN: effect of macitentan on 1ary endpoint in patients on PAH therapy (64%)




**Risk reduction of primary endpoint event vs placebo**

Macitentan 10 mg: 38%

| Treatment difference | Macitentan 10 mg |
|---|---|
| Hazard ratio (HR) | 0.62 |
| Log-rank *p*-value | 0.009 |

Patients at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 154 | 134 | 119 | 107 | 97 | 53 | 24 | Macitentan 10 mg |
| 154 | 122 | 106 | 90 | 80 | 40 | 10 | Placebo |

Pulido T, *et al. N Engl J Med* 2013; 369: 809-18.

# NCT00323297: No additional benefit of sildenafil when added to bosentan

- N = 103 patients on background bosentan
- Primary endpoint: change in 6MWD at week 12
- Mean difference (final values) = -2.38 m
- *p*-value = 0.5802

| | Placebo | Sildenafil |
|---|---|---|
| Number of patients analysed (*n*) | 53 | 50 |
| Change from baseline in the total distance walked during 6MWT at week 12 (m), mean ± SD | | |
| Change from baseline at week 12 (*n* = 46,44) | 17.42 ± 57.270 | 14.08 ± 63.679 |
| Change from baseline at week 12 LOCF (*n* = 53,49) | 14.08 ± 57.557 | 13.62 ± 60.950 |

LOCF: last observation carried forward

NCT00323297, www.clinicaltrials.gov.

# COMPASS-2: no additional benefit of bosentan in patients on background sildenafil

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- Event-driven trial including around 350 patients on sildenafil

| Primary endpoint | Treatment effect |
|---|---|
| Time to first morbidity/mortality event | HR = 0.831 (0.582, 1.187)<br>(*p* = 0.2508) |

| Secondary endpoints | Treatment effect |
|---|---|
| Change in 6MWD to week 16 | |
| Mean (SD) | +21.8 (74) |
| Median (95% CL) | +13.0 (3.0, 23.0) |
| Change in WHO FC to week 16 | None |
| Time to death (all causes) | None |

- Issues with sample size and duration (started in 2006)
- Improvement in 6MWD similar to other recent RCTs

Actelion press release, March 2013.

# Phase III study with selexipag: GRIPHON

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- N = 1156 patients
- Naive, or on background therapy (ERA, PDE5 inhibitor or both)
- Event-driven trial (composite EP of morbidity and mortality)
- Duration of treatment up to 4.3 years

80% were on background therapy
Decrease in risk of 39% (selexipag vs placebo, p<0.0001)
Efficacy accross key subgroups

1. NCT01106014. *www.clinicaltrials.gov.*
2. Actelion press release, June 2014.

# AMBITION:
# Monotherapy vs initial combination

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**To compare 2 treatment strategies**

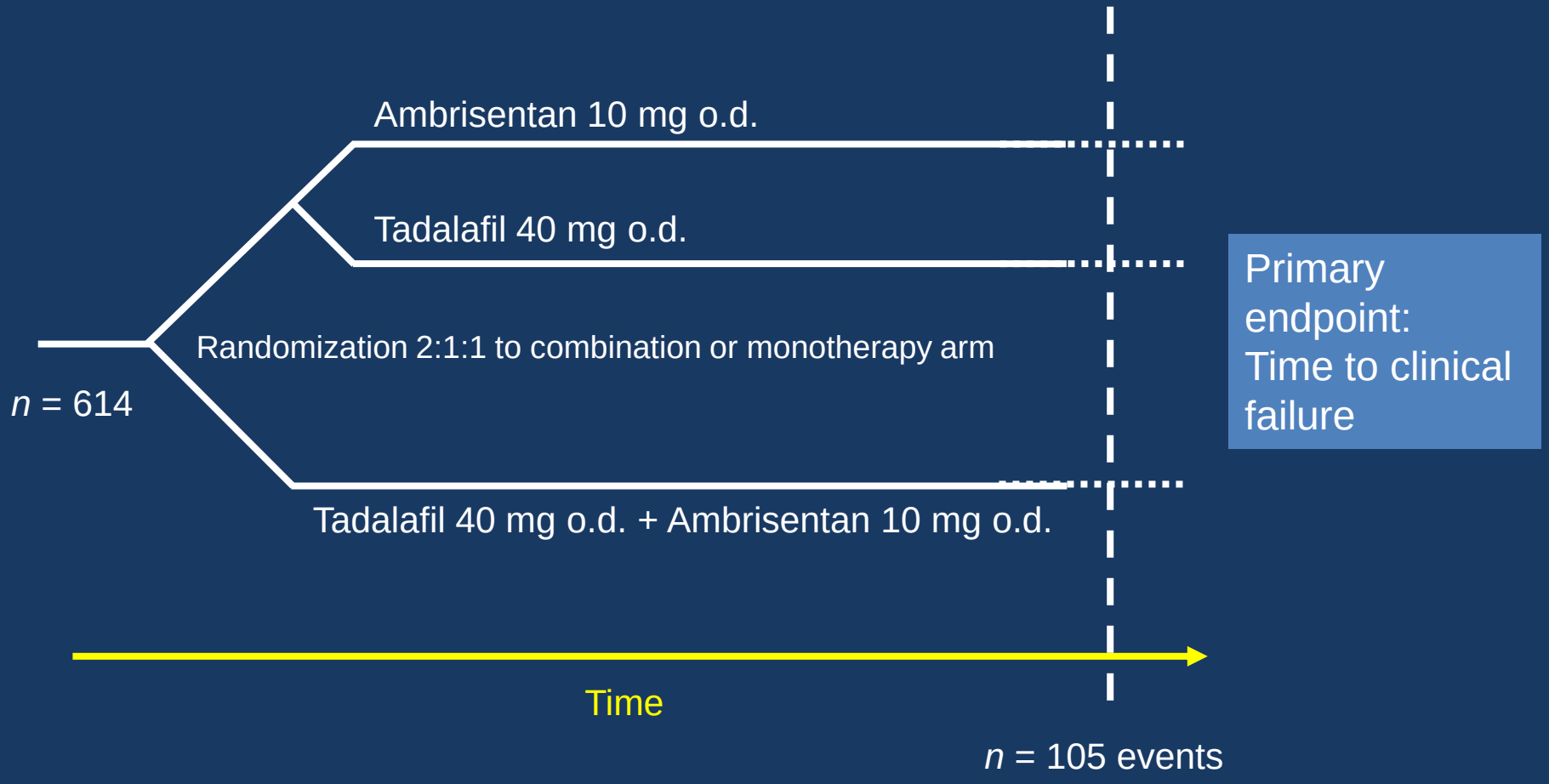
**intial combo (amb+tad) vs mono (amb or tad)**

**Event-driven trial**

- **Primary objective: time to clinical failure**

- **Secondary objectives:**
  - **compare the changes in other clinical measures**
  - **safety and tolerability**
  - **6MWD at peak and trough level**

# AMBITION study design




Primary endpoint: Time to clinical failure

A randomised, multicentre study of first-line AMBrIsentan and Tadalafil combination therapy in subjects with pulmonary arterial hypertensION

NCT01178073, *www.clinicaltrials.gov*.

# AMBITION primary endpoint: Time to first clinical failure event

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**Death (all cause)**

**Hospitalisation for worsening PAH** →
- non-elective hospitalisation (CW)
- lung transplantation
- atrial septostomy
- initiation of prostanoid therapy

**Disease progression** →
- Decrease in 6MWD >15% vs base
- With FC III-IV (2 visits >14 days)

**Unsatisfactory long-term response** → ALL →
- > 6 months on therapy
- Disease progression
- NYHA FC III-IV at 6 months

All events were adjudicated

# AMBITION:
# Primary and secondary endpoint analysis

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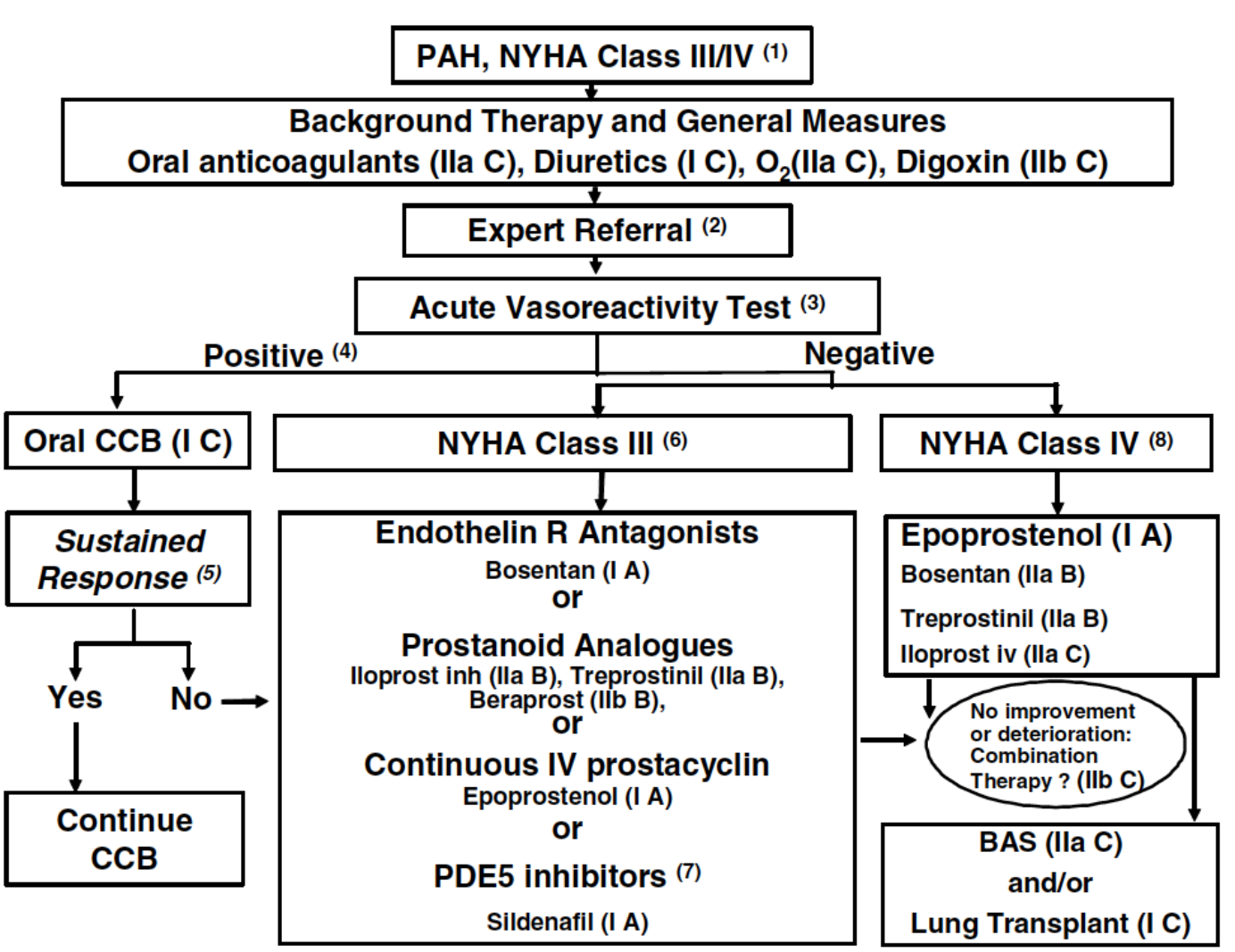
| | Combination | Monotherapy pooled |
|---|---|---|
| **Number of subjects** | 253 | 247 |
| **Number of subjects with first events (%)** | 46 (18 %) | 77 (31 %) |
| **Hazard ratio from Cox model** | | 0.502<br>95 percent CI: 0.348, 0.724 |
| **P-value** | | 0.0002 |

- All events contributed to reduce TtCF, driven by a reduction in hospitalizations (no effect on mortality)
- Initial combination improved NT Pro BNP, the % patients with satisfactory clinical response and 6MWD at W 24
- WHO FC and Borg dyspnea index were unchanged

Adapted from GSK press release - Galiè et al presented at ERS 2014 Abstract #2916 – Rubin et al presented at CHEST 2014

# ESC guidelines 2004: First treatment algorithm




Galiè N, *et al. Eur Heart J* 2004; 25:2243–78.

# 5th World Symposium on PH: Initial combination therapy for patients in FC III/IV

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| Recommendation (Evidence*) | FC II | FC III | FC IV |
|---|---|---|---|
| I (A or B) | Ambrisentan<br>Bosentan<br>***Macitentan***<br>Riociguat<br>Sildenafil<br>Tadalafil | Ambrisentan, Bosentan,<br>***Epoprostenol i.v.***,<br>Iloprost inhaled, ***Macitentan***<br>Riociguat, Sildenafil,<br>Tadalafil,<br>Treprostinil s.c., inhaled† | ***Epoprostenol i.v.*** |
| IIa (C) | | Iloprost i.v. †<br>Treprostinil i.v. | Ambrisentan, Bosentan,<br>Iloprost inhaled and i.v.†<br>***Macitentan***, Riociguat,<br>Sildenafil, Tadalafil,<br>Treprostinil s.c., i.v., inhaled† |
| IIb (B) | | Beraprost† | |
| IIb (C) | | Initial combination therapy | Initial combination therapy |

**Yellow:** Morbidity and mortality as primary endpoint in randomised controlled study or reduction in all-cause mortality (prospectively-defined)

*Level of evidence is based on the FC of the majority of the patients of the studies
†Approved only: by the FDA (treprostinil inhaled); in New Zealand (iloprost i.v.); in Japan and S. Korea (beraprost)

Adapted from Galiè N, *et al. J Am Coll Cardiol* 2013; 62:D60-72.

# Expert consensus recommendations for sequential combination therapy have improved with increasing experience

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Sequential combination therapy ***may be considered*** in patients who fail to show improvement or who deteriorate on a single drug (monotherapy)

Combination therapy ***should be considered*** in patients on monotherapy with 'inadequate clinical response'
**Evidence level: IIa-B**

In FC IV, initial combination should be considered
**Evidence level: IIa-C**

In case of inadequate clinical response, sequential therapy ***is recommended***
**Evidence level: I-A**

In FC III/IV patients initial combination therapy may be considered
**Evidence level: IIb-C**

1. Galiè N, *et al. J Am Coll Cardiol* 2004; 43:81S-88S. 2. Barst RJ, *et al. J Am Coll Cardiol* 2009; 54:S78-84. 3.Galiè N, *et al. Eur Heart J* 2009; 30:2493-537. 4. Galiè N, *et al. J Am Coll Cardiol* 2013; 62:D60-72.

# Conclusions

- There is robust evidence supporting a strategy of sequential combination therapy in PAH.
- However, not all combinations appear to be associated with a similar benefit
- It is unclear whether differences are due to the design of the RCTs, differences in populations, interaction between compound or true efficacy issues
- If timing of sequential combination remains to be better understood, initial combination may be considered as standard of care.
- The jury is out to decide whether we should move from a drug-oriented to a strategy based treatment algorithm