- EISENMENGER SYNDROME- MEDICAL MANAGEMENT & THE ROLE OF SELECTIVE VASODILATORS

가천의대 길병원 소아심장과 -최 덕영-

Medical management of Eisenmenger syndrome

- Conventional treatment
- Targeted medical therapy

Phlebotomy

- Secondary erythrocytosis – erythropoietin ↑
- Decompensated erythrocytosis – hyperviscosity symptoms, Hct(70% ↑)
- Severity of erythrocytosis (per se) – not risk factor for stroke
- Primary goal of phlebotomy – relieve temporarily moderate to severe hyperviscosity sx (with absence of volume depletion & IDA)

Rosove MH et al. Lancet 1986;2:313-5

Perloff JK et al. Circulation 1993;87:1954-9

Anticoagulation

- Remains controversial
- Thromboembolic events (pulmonary circulation) – 20% of ES patients
- Risk of fatal and life threatening bleeding complication
- Not recommend – combined use of systemic anticoagulation and platelet aggregation inhibitors

Silversides CK et al. J Am Coll Cardiol 2003;42:1982-7

Anticoagulation

To reduce the risk of bleeding

- Limitation of anticoagulation – A fib, recurrent thromboembolic events, mechanical valve
- INR : 2.0~2.5, aPTT : 1.5 times of normal
- Prompt therapy of respiratory infection

Oechslin E et al. Curr Cardiol Rev 2010;6:363-72

Oxygen therapy

- Long term oxygen supplementation – controversial
- Side effects – dryness of nasal mucosa, epistaxis, sleep disturbance, etc.
- Nocturnal oxygen therapy – no effects on exercise capacity, natural history, survival
- Not recommend – routine use of oxygen at home

Sandoval J et al. Am J Respir Crit Care Med 2001;164:1682-7

Calcium channel blockers

- Favorable effects in iPAH with responders
- The effects of CCB – not restricted pulmonary circulation
- In ES – systemic vascular resistance ↓, right to left shunt ↑, worsening cyanosis and hypotension
- Empiric CCB therapy in ES – not recommend

Sitbon O et al. Circulation 2005;111:3105-11

Depta J et al. Adv Pulm Hyperten 2008;7:222-7

Paradoxical emboli

- Wide communication between pulmonary and systemic circulation
- The risk of paradoxical emboli ↑ – Intravenous pacemaker, ICD systems
- Rec) Air filters – all intravenous lines

Khairy P et al. Circulation 2006;113:2391-7

Cerebrovascular events

- Increased risk – up to 14%
- Paradoxical emboli, microcytosis, hypertension, A fib., endothelial dysfunction
- The severity of 2’ erythrocytosis – not risk
- Microcytosis (<- iron def. <- phlebotomy) – strong predictor
- Rec) Avoid the volume depletion, Air filters, Iron supply

Ammash N et al. J Am Coll Cardiol 1996;28:768-72

Oechslin E et al. Circulation 2005;12:1106-12

Renal dysfunction

- Affects two thirds
- Functional, structural abnormality
- Multifactorial and complex causes – still a matter of debate
- Volume depletion and NSAID – fatal
- Rec) Routine assessment of renal function

Dimopoulos K et al. Circulation 2008;117:2320

Perloff J et al. Congenital heart disease in adults. 3rd. Elsevier, Saunders;2009:pp.265-89

Hemoptysis

- Life threatening Cx – near 100% reported
- Rupture of AP collaterals
- Rec) hospitalization, suppression of cough, chest X-ray and CT, stop specific medicine (aspirin, NSAID, anticoagulant), Tx of hypovolemia and anemia, transfusion, cath and selective embolization

Daliento L et al. Eur Heart J 1998;19:1845-55

Oechslin E. Diagnosis and management of adult CHD. Churchill Livingstone;2003. pp.363-77

Gout

- Hyperuricemia ← uric acid production ↑ renal clearance ↓
- Acute gouty arthritis – rare, but very painful complication, triggered by diuretics
- Colchicine, probenecid, allopurinol

Cholelithiasis

- Increased concentration of unconjugated bilirubin in the bile
- Increased turnover of heme ← erythrocytosis
- Gallstones, acute cholecystitis – serious, life threatening complication (bacteremia, endocarditis)
- Cholecystectomy must be considered

Hypertrophic osteoarthropathy

- Local cell proliferation, new osseous formation and periostitis
- Arthralgia (knees, ankles)
- Unknown etiology, associated with R-L shunt lesion bypassing the pulmonary circulation
- Factors or mediators in the systemic venous circulation (must be inactivated in the lung) – maybe causative for HOA

Perloff JK et al. Cardiol Clin 1993;11:689-99

Erwin O et al. Curr Cardiol Rev 2010;6:363-72

Pregnancy

- Systemic vascular resistance drops during pregnancy, the R-L shunt increases, $SaO_2 \downarrow$
- Patients are already functional class III, IV
- Spontaneous abortion (40%), premature delivery (50%), intrauterine growth retardation, high perinatal mortality
- Maternal mortality (30-60%) – during delivery or within 1st week
- Therapeutic termination should be rec.
- Hospitalization after 20th week – conservative management

Pregnancy

- Mode of delivery (NSVD, C-sec) – still matter of discussion
- During delivery, significant blood loss induce hypotension-increase the shunt and cyanosis – volume replacement and vasopressor
- Prevention of pregnancy and contraceptives – essential
- ET-blocker(Bosentan) ; efficacy of oral progestogens ↓

Avila WS et al. Eur Heart J 1995;16:460-4

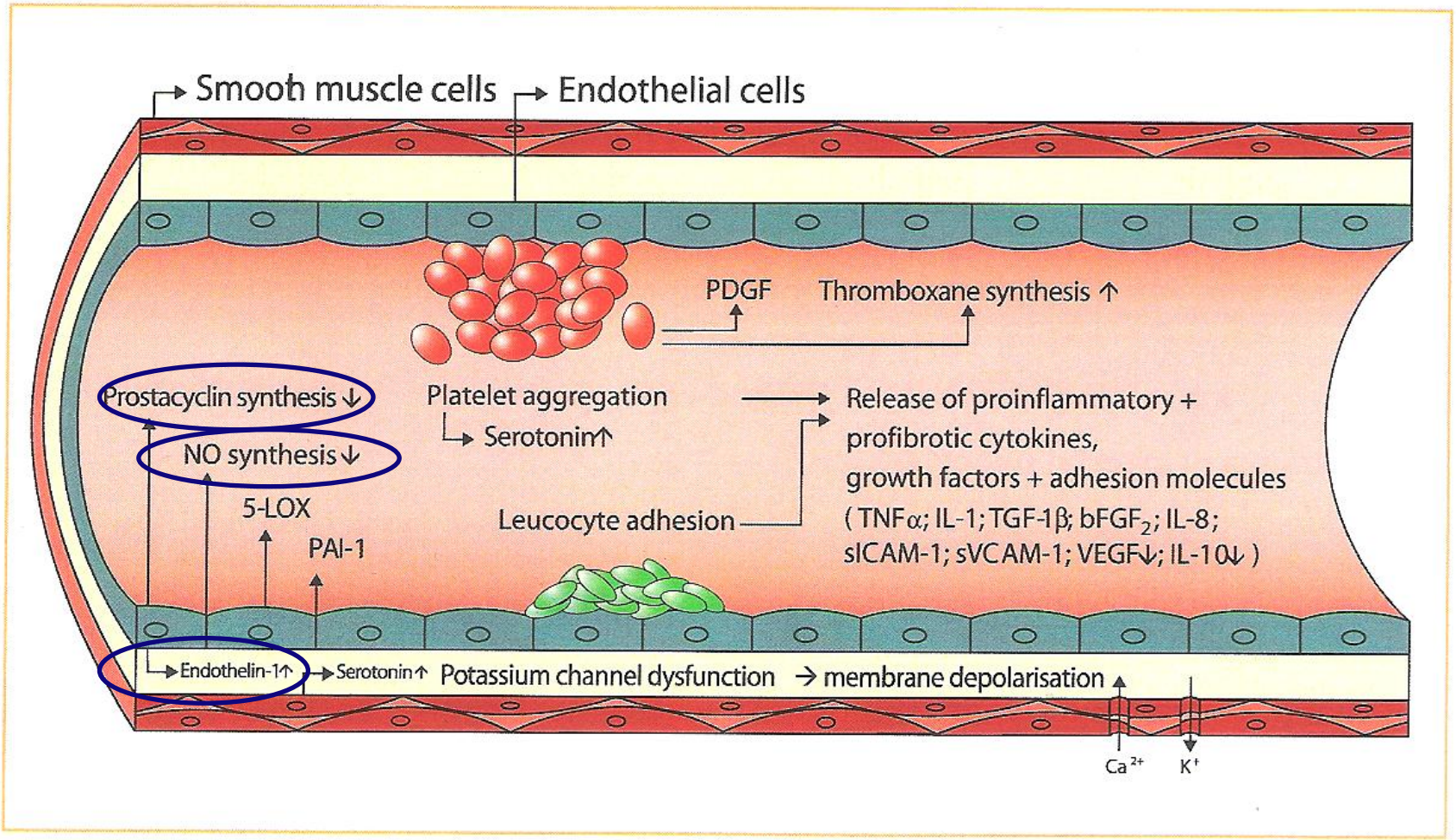
Kiely D et al. Heart disease and pregnancy.London:RCOG Press;2006 pp.211-29

Non-cardiac surgery

- ↓Rapid adaptive mechanism to any hemodynamic change caused by anesthetics, fluid shifting and surgery (high PVR state)
- Perioperative evaluation with expert team
- Local anesthesia (if possible)
- General >> epidural-spinal – symphathetic block, decrease after_preload
- Preoperative phlebotomy (↑PLT, ↓intraop. Bleeding)
- Careful monitoring (detect the R-L shunt)
- Endocarditis prophylaxis, use air filter

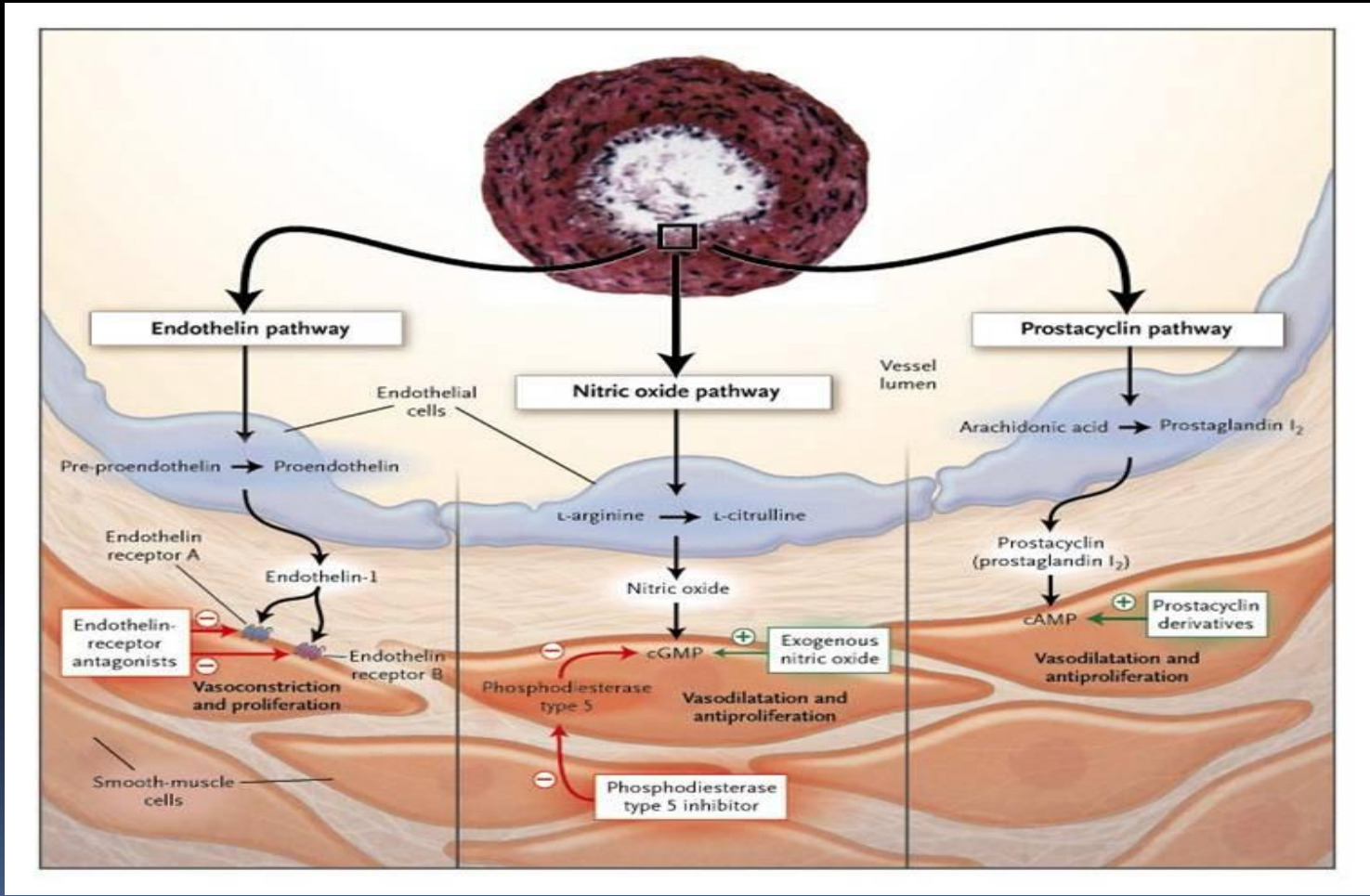
Ammash NM et al. J Am Coll Cardiol 1999;33:222-7

Endothelial dysfunction



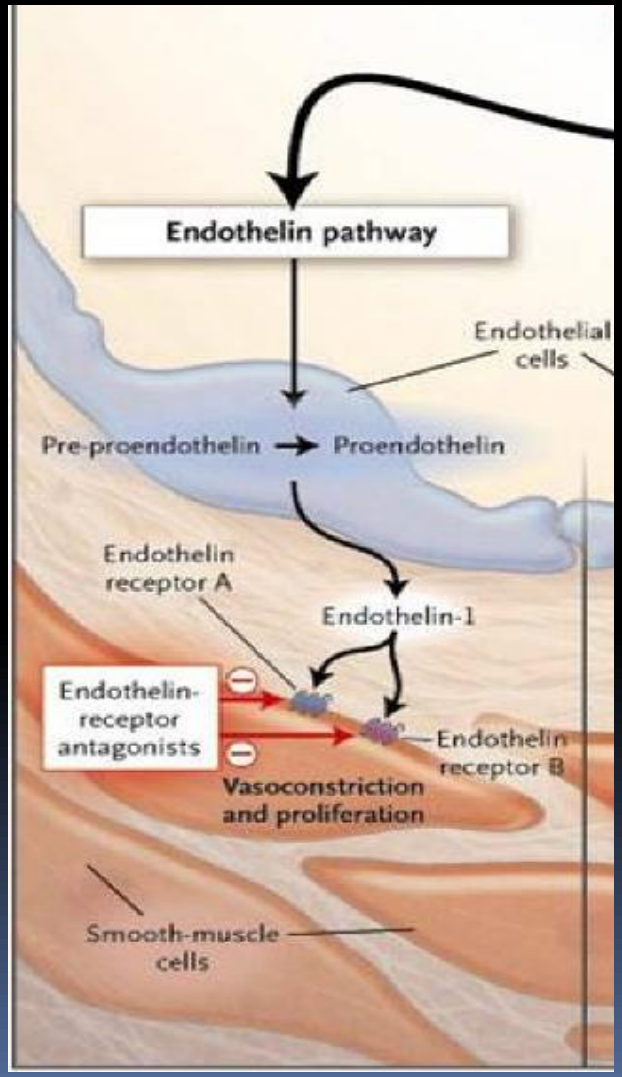
Bayer Vital GmbH, Data on file

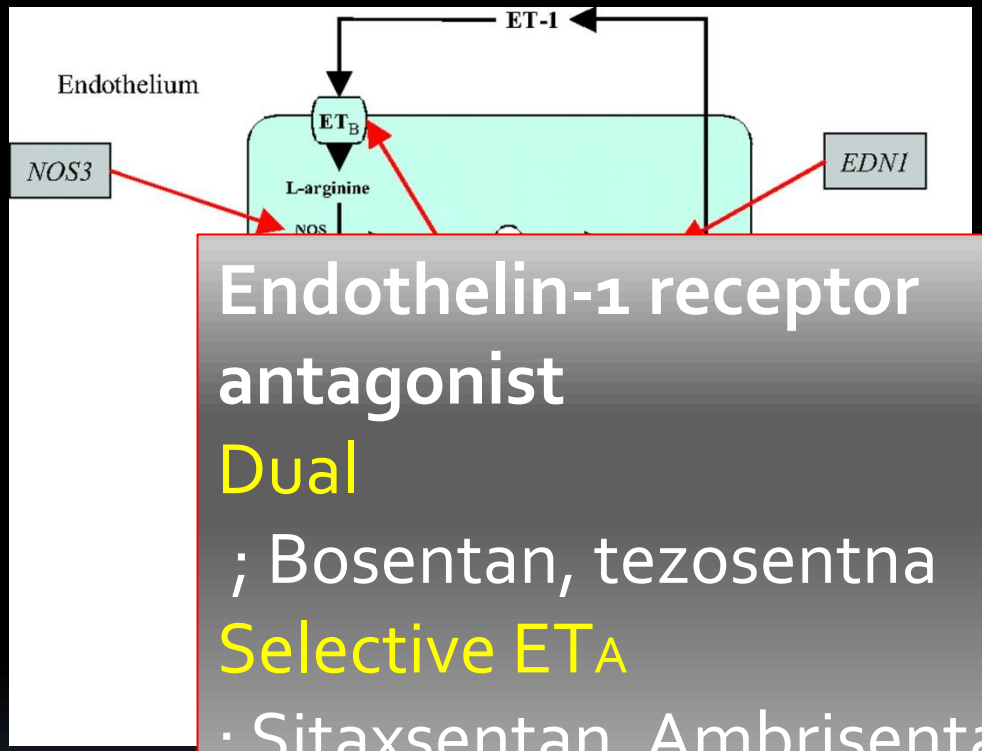
The 3 pathophysiological pathway of PAH → Targeted therapy



N EJM 2004;35:1425

Endothelin pathway





Endothelin-1 receptor antagonist

Dual

; Bosentan, tezosentna

Selective ET$_A$

; Sitaxsentan, Ambrisentan, BQ-123, zibotentan

Bosentan

- Non selective ET receptor antagonist
- Approved by the FDA, EMEA – 2002
- The only approved drug for children
- Study for ES
  - ✓ BREATHE-5 open label extension study
  - ✓ BREATHE-5 :a subgroup analysis

  → improvement in exercise capacity and cardiopulmonary hemodynamics

Gatzoulis MA et al. Int J Cardiol 2008;127:27
Berger RM et al. Int J Cardiol 2010;144:373

- Dose dependent liver disease

GOT/GPT	recommend
3xULN < level ≤ 5x ULN	Decrease the 1 day dose or recheck 2wks after, if enzyme recover – continue the tx
5xULN < level ≤ 8x ULN	Stop medication, recheck every 2 wks , if enzyme recover – continue the tx
> 8xULN (upper limit of normal)	Stop medication, never restart

- Edema, systemic hypotension
- Caution ; interfere the action of contraceptive

Sitaxsentan

- Potent & highly selective ET_A receptor antagonist, half life-upto 7hrs (once daily)
- Predominantly focused on iPAH
- Lower incidence of hepatic toxicity than bosentan
- Only 1 report – related with ES

  (safe, improvement in hemodynamics and 6MWD, but limited data)

Rosenzweig E et al. Circulation 2007;116:II457(abstr)

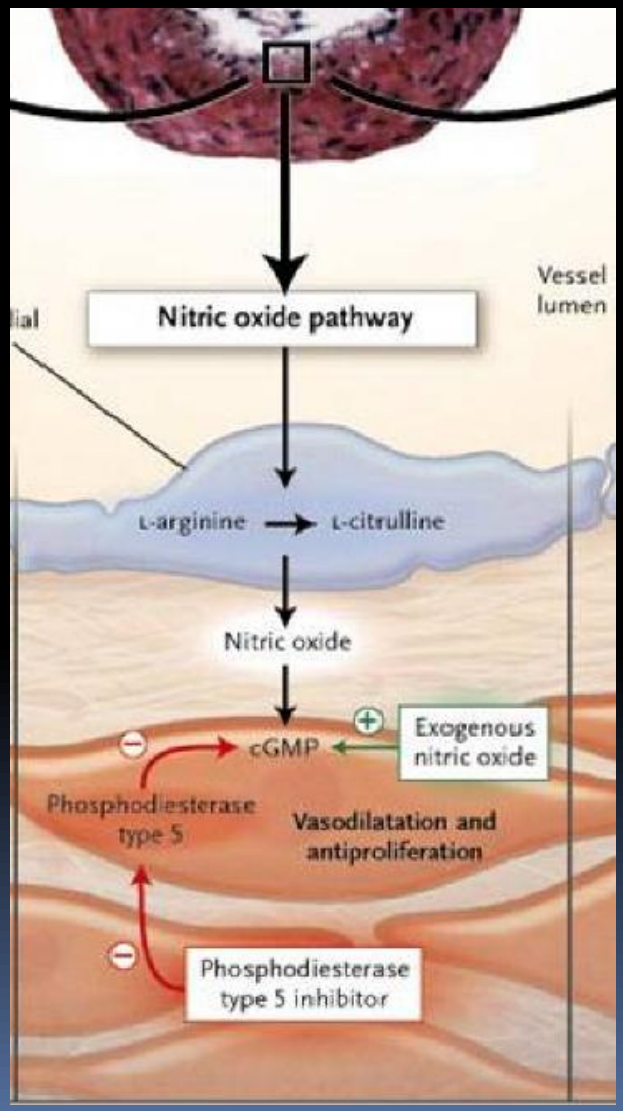
Ambrisentan

- Another selective ET_A receptor antagonist, recently approved for WHO class II, III
- 17 patients, with ES, 2007.1.1 ~ 2008.8.1 , improvement of exercise capacity and functional class

Zuckerman WA et al. Am J Cardio 2011;107:1381

NO pathway

PDE-5 receptors ; located predominantly in the penile and pulmonary vasculature



-Exogenous NO
-PDE-5 inhibitors ; sildenafil
tadalafil
vardenafil
udenafil
avanafil

Phosphodiesterase-5 inhibotor

PDE-5 Inhibitors in Patients with PAH [34]

	Sildenafil	Vardenafil	Tadalafil
T_{max} [min]	60	40 - 45	75- 90
$T_{½}$ [h]	~ 3,5	~ 3,5	17,5
PVR/SVR	Decrease	---	Decrease
paO_2	significant improvement	---	---

Abbreviations: T max; time to peak hemodynamic effects, T ½; mean half-life, PVR/SVR; pulmonary to systemic vascular resistance ratio, paO_2; arterial oxygenation

Similar results (improvement of exercise capacity, oxygen saturation, functional class) in ES patients

Wort SJ. Int J Cardiol 2007;120:314
Mukhopadhyay S et al. Circulation 2006;114:1807

10-year analysis of adverse event reports to the FDA for PDE-5 inhibitors

- Department of Urology – Ohio state, Virginia University
- Sildenafil ; 14818 AEs, 1824(12.3%) deaths
- Tadalafil ; 5548 AEs, 236 deaths
- Vardenafil ; 6085 AEs, 121 deaths
- Most deaths – related c cardiovascular events

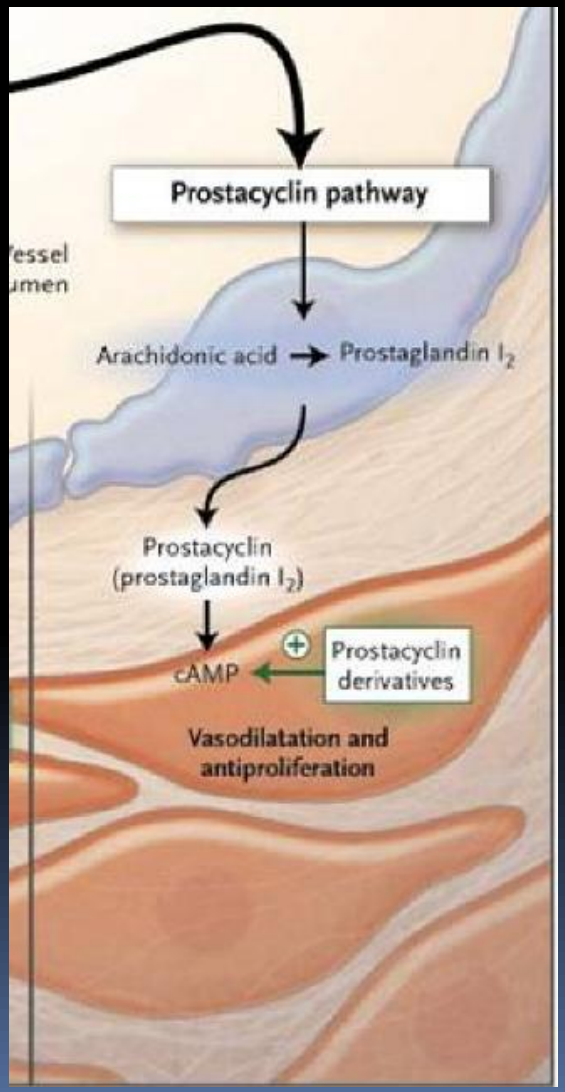
Lowe G, Costabile RA. J Sex Med 2011 Oct 24(Epub)

Prostacyclin pathway

- ✓Intravenous or subcutaneous infusion ; epoprostenol, treprostinil
- ✓Inhalation ; iloprost
- ✓Oral ; beraprost, selexipag

Active profile with vasodilatory, antiproliferative , anti-inflammatory, anticoaculant effects

For patients with NYHA class III, IV – particularly in right heart failure



Targeted Medical therapy (AT = advanced therapy) in Eisenmenger syndrome

- Epoprostenol (continuous infusion) ; improved FC, O2 sat., exercise capacity

Fernandes SM. Am J Cardiol 2003;91:632-5

- Bosentan (BREATHE-5) ; significantly improved hemodynamics, exercise capacity

Galie N. Circulation 2006;114:48-54

- Sildenafil ; improve FC, hemodynamic parameters

Chau EM. Int J Cardiol 2007;120:301-5

Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension

- Total 229 patients (aged 34.5±12.6)
- Eisenmenger physiology
- 53.7% - NYHA class ≥ III
- Resting O2 sat ; 84.3% (mean)
- 68 patients (29.7%) – AT(advanced therapy)
- 4.0 years median F/U
- Patients on AT : significantly low risk of death

Dimopoulos K, Inuzuka R, et al. Circulation 2010;121:20-5

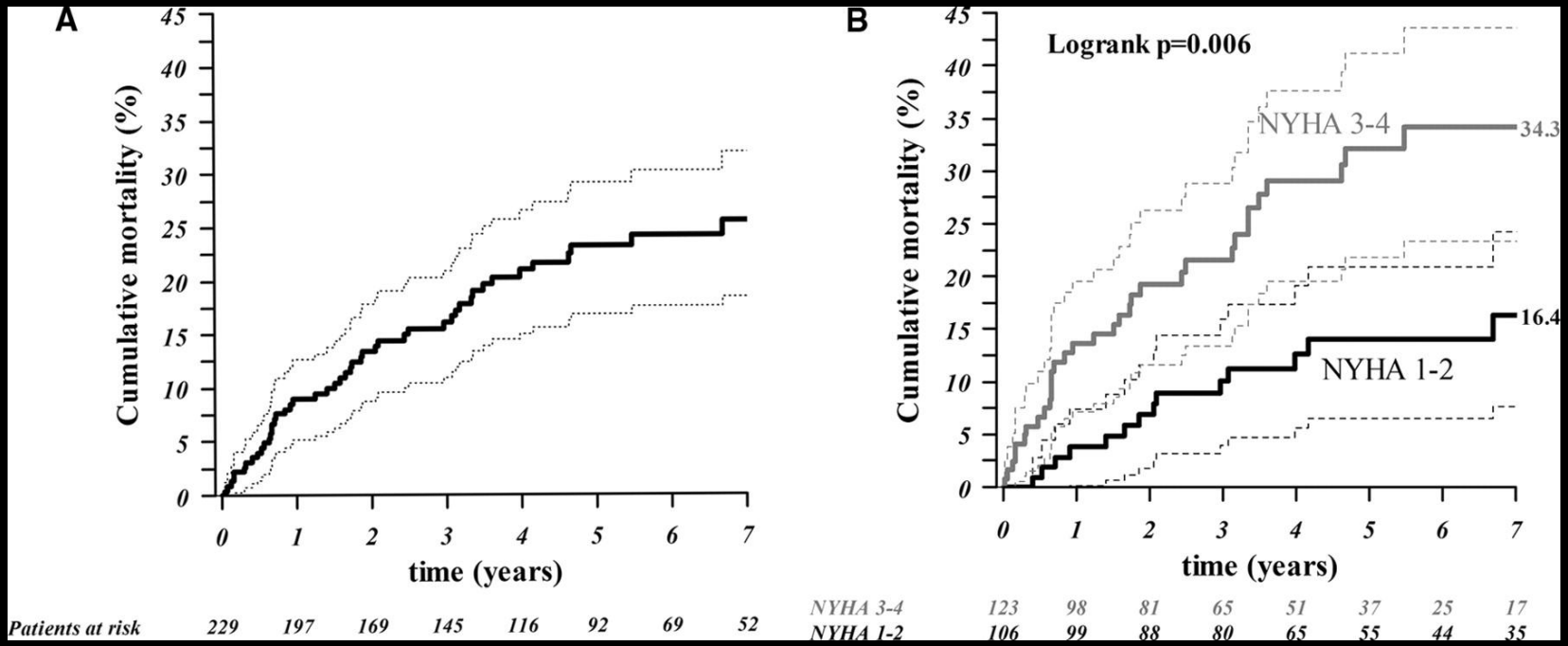
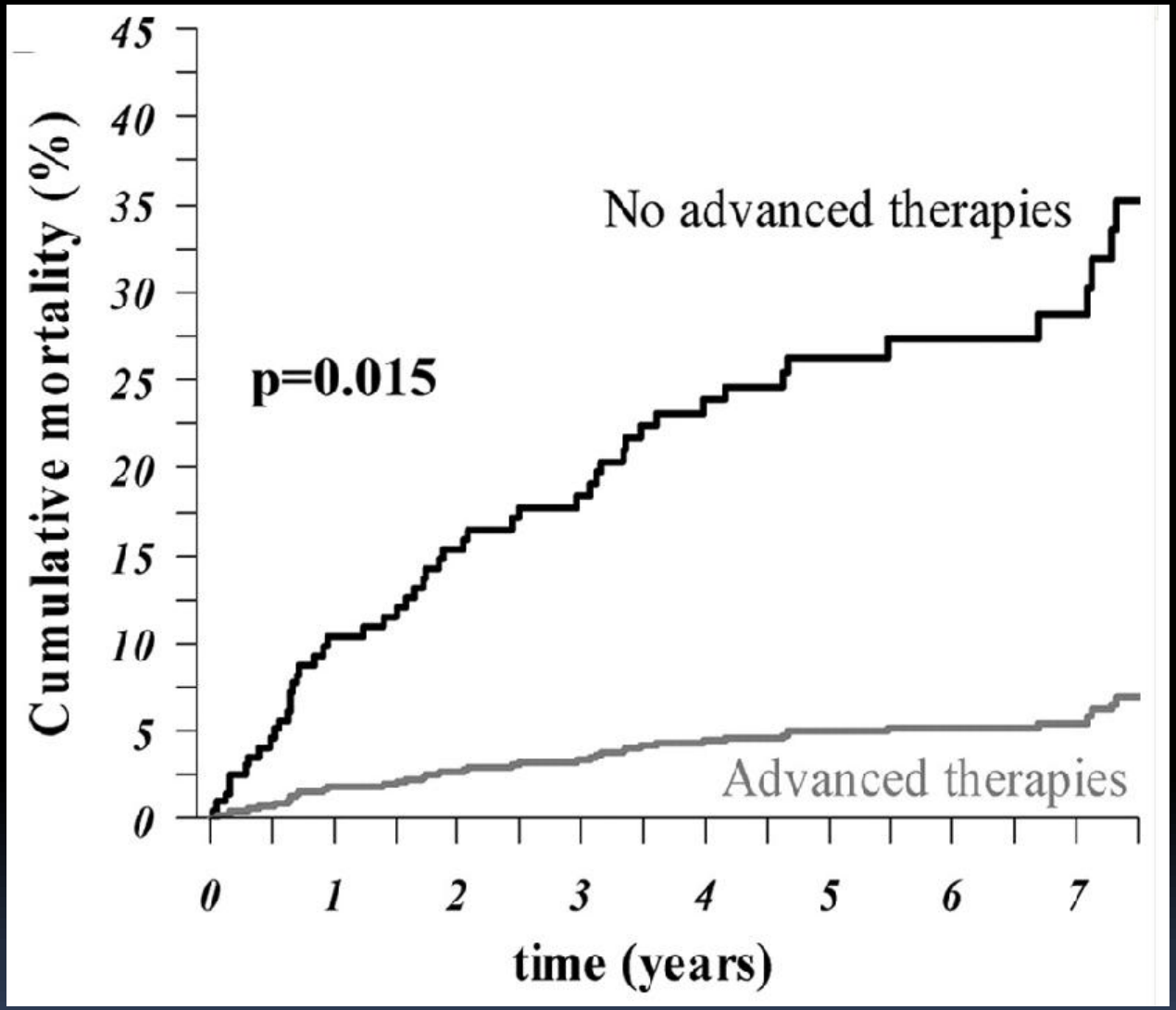


Figure 2. A, Cumulative mortality rate curve (with 95% CIs) in the overall population (n=229). B, Cumulative mortality rate curves (with 95% CIs) according to functional class (n=229).

Dimopoulos K et al. Circulation 2010;121:20-25



Dimopoulos K et al. Circulation 2010;121:20-25

American Heart Association
Learn and Live

Combination therapy

- May have synergic effects – interaction of different pathobiological pathways
- Considered for symptomatic patients who failed to improve with 1st line, monodrug tx
- A case report (68yr, female, iloprost + sildenafil for 2yrs)

OkyayK et al. Cardiol Rev 2005;13:312

- Open-label, prospective study(11 patients, CHD-4, bosentan + sildenafil, safe & effective)

Lunze K et al. Eur J Clin Invest 2006;36:32

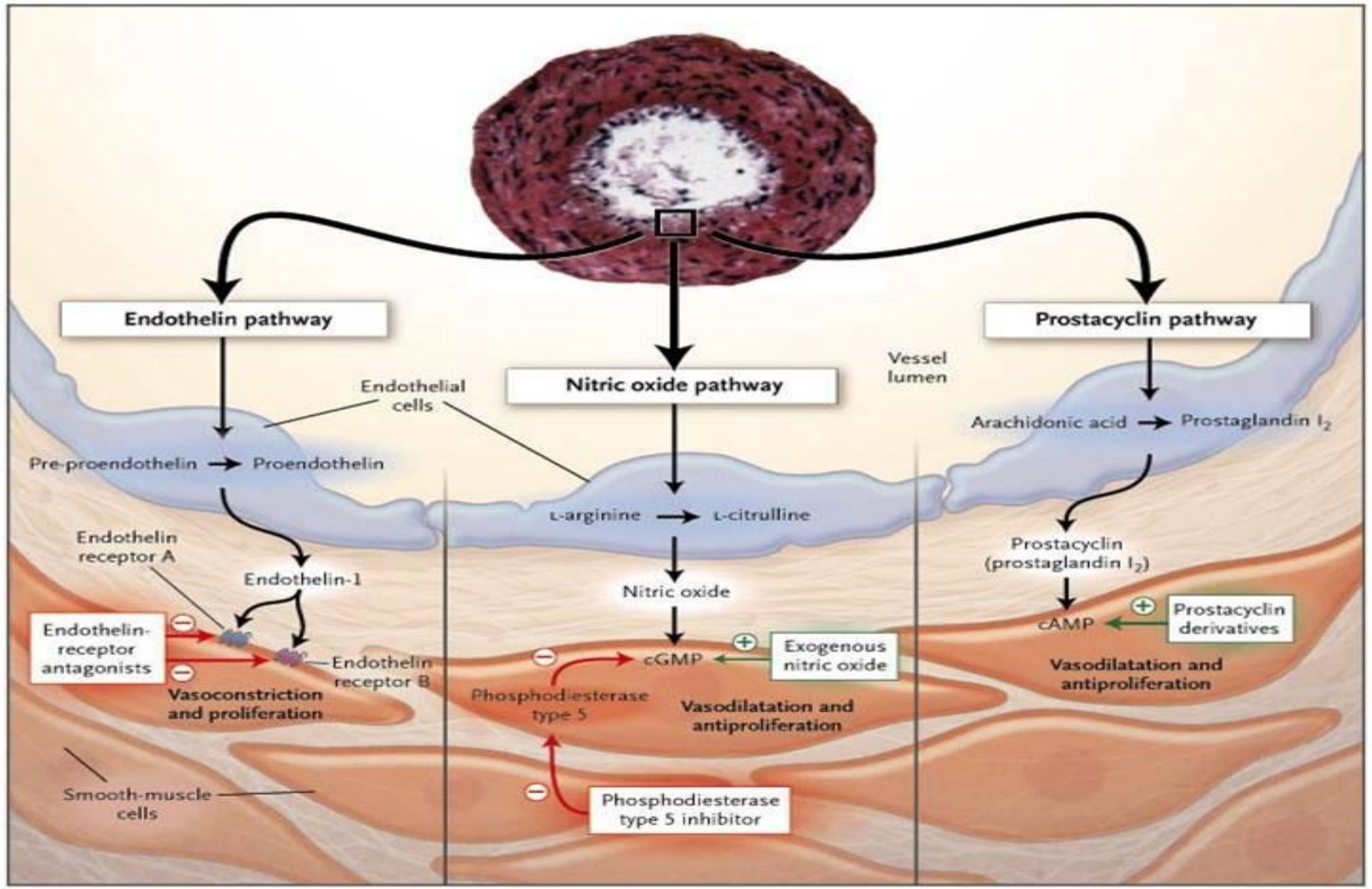
TABLE 1 Summary of combination therapy studies in pulmonary arterial hypertension (PAH) involving small numbers of patients and case reports

Combination by background therapy	Patients n	Study duration	Aetiology of PAH	Key findings: combination *versus* baseline therapy alone/placebo	Ref.
Prostanoids					
Epoprostenol + iloprost	8	Single dose	IPAH	Significant improvements in mean P_{pa}, CI, S_{v,O_2}, and P_{a,O_2}	[23]
Beraprost + iloprost	23	12 months	PAH-CHD	Improvement in 6MWD and RVSP	[24]
Beraprost/iloprost + bosentan	20	16 months	IPAH	Improvement in 6MWD	[25]
	16	13.5 months	IPAH, thromboembolic	Significant improvement in 6MWD and Tei index	[26]
Epoprostenol + bosentan	8	1 yr	IPAH	Reduction in epoprostenol dose and side-effects Discontinuation of epoprostenol and stabilisation of haemodynamics for ⩽1 yr in three patients	[27]
	8	1 yr	IPAH	Significant decrease in mean P_{pa} Delay in disease progression	[28]
Iloprost + bosentan	9	12 weeks	Not given	Significant improvement in exercise capacity	[29]
Treprostinil + bosentan	19	~3 yrs	Not given	Significant additional improvement in P_{pa}, 6MWD and Borg dyspnoea scale	[30]
Epoprostenol + sildenafil	5	3 months	IPAH	Improvement in mean P_{ra} and WHO functional class	[31]
	3	5 months	IPAH, PAH-CHD	Reduced mean P_{pa} and PVR Increased 6MWD	[32]
	3	2 h	IPAH	Significant decrease in mean P_{pa} and PVR	[33]
Iloprost + sildenafil	30	3 h	IPAH, CTEPH	Increased vasodilation	[34]
	14	9–12 months	PAH unresponsive to iloprost	Improved 6MWD, haemodynamics and WHO functional class	[35]
Prostanoids + sildenafil	20	2 yrs	Not given	Significant improvement in WHO functional class and signs of right heart failure Increase in 6MWD after 1- and 2-yr follow-up	[36]
	4	Not given	IPAH, PAH-CTD	Improvements in 6MWD, P_{pa} and dyspnoea	[37]
Bosentan + sildenafil	9	12 months	IPAH	Improvements in 6MWD and CPET	[38]
	3	⩽24 months	IPAH	Improvement in functional capacity, BNP	[39]
	11	1.1 yrs	IPAH, PAH-CTD	Improvement in WHO functional class, 6MWD and mean P_{pa}	[40]
	25	3 months	IPAH, PAH-SSc	Improved WHO functional class and 6MWD in IPAH but not in PAH-SSc	[41]
	10	6 months	IPAH, PAH-CTD	Increase in 6MWD	[42]
Bosentan + prostanoids	35	3 months	IPAH	Improvements in 6MWD, CI, mean P_{pa} and WHO functional class	[43]
Bosentan + iloprost	40	12 weeks	IPAH	No effect on 6MWD	[44]
	67	12 weeks	IPAH, APAH	Significant increase in 6MWD and WHO functional class Delay in time to clinical worsening Improvements in mean P_{pa} and PVR	[16]
Sildenafil + beraprost	1	1 month	PAH-SSc	Decrease in P_{pa} and PVR Improvements in 6MWD and WHO functional class	[45]

IPAH: idiopathic PAH; P_{pa}: pulmonary arterial pressure; CI: cardiac index; S_{v,O_2}: mixed venous oxygen saturation; P_{a,O_2}: arterial oxygen tension; CHD: congenital heart disease; 6MWD: 6-min walk distance; RVSP: right ventricular systolic pressure; P_{ra}: right arterial pressure; WHO: World Health Organization; PVR: pulmonary vascular resistance; CTEPH: chronic thromboembolic pulmonary hypertension; CTD: connective tissue disease; CPET: cardiopulmonary exercise testing; BNP: brain natriuretic peptide; SSc: systemic sclerosis; APAH: associated PAH.

Galie N et al.
Eur Respir Rev
2009;18:113

Triple therapy?



N EJM 2004;35:1425

American Thoracic Society 2011 International Conference, May 13-18, 2011. Denver, Colorado

Upfront Triple Combination Therapy Of I.v. Epoprostenol With Oral Bosentan And Sildenafil In Idiopathic And Heritable Pulmonary Arterial Hypertension

O. Sitbon[1], X. Jais[2], L. Savale[2], C. Dauphin[3], D. Natali[2], D. O'Callaghan[2], D. Montani[4], M. Humbert[4], G. Simonneau[4]

[1]Hopital Antoine Béclère, CLAMART, France, [2]Hopital Antoine Beclere, Clamart, France, [3]CHU, Clermont-Ferrand, France, [4]Hôpital Antoine Béclère, clamart, France

Corresponding author's email: olivier.sitbon@abc.aphp.fr

Background: Recent guidelines have proposed first-line combination therapy as a potential strategy for the treatment of NYHA functional class (FC) IV pulmonary arterial hypertension (PAH). However, the potential merit of an upfront triple combination therapeutic approach that simultaneously targets the prostacyclin, endothelin and nitric oxide pathways in naive PAH patients has not been explored.
Patients and Methods: Prospective observational analysis of the efficacy and safety of upfront triple combination therapy of i.v. epoprostenol with oral bosentan and sildenafil in consecutive newly diagnosed patients with severe idiopathic or heritable PAH. Inclusion criteria: NYHA FC III or IV with severe haemodynamic impairment (cardiac index < 2.0 L.min^{-1}.m^{-2} or pulmonary vascular resistance (PVR) > 1000 dyn.s.cm^{-5}).
Results: 10 patients (8 females) with idiopathic (n=5) or heritable PAH were treated with upfront combination epoprostenol, bosentan and sildenafil. Mean age was 40.5±13.4 yrs. Baseline clinical characteristics and haemodynamics are summarized in the Table. Acute vasoreactivity testing with inhaled nitric oxide was negative in all patients. Median exposure to the combination regimen was 18.5 months (range: 1-36). A marked functional and hemodynamic improvement was observed among the seven patients in whom four-month follow-up data were available. All patients improved to FC I or II and showed a mean fall in PVR of 71% relative to baseline (Table). One patient underwent urgent heart-lung transplantation due to lack of improvement; the remaining two patients await reassessment. The mean dose of epoprostenol was 16 ng.kg^{-1}.min^{-1} and all patients received the recommended doses of bosentan (125 mg bid) and sildenafil (20 mg tid). These improvements were maintained long-term in the 5 patients who have been reassessed after 12-28 months ("Last visit" in the Table).

Am J Respir Crit Care Med 2011;183:A5901

	Baseline (n=10)	4-month (n=7)	Last visit (n=5)
NYHA FC I-II:III:IV, n	0:4:6	7:0:0	5:0:0
6-min walk distance, m	290±146	454±67*	511±59*
Right atrial pressure, mmHg	13±6	6±7	6±5
Mean pulmonary artery pressure, mmHg	68±17	45±13*	48±10*
Pulmonary capillary wedge pressure, mmHg	8±3	7±3	7±4
Cardiac Index, $L.min^{-1}.m^{-2}$	1.6±0.4	3.7±0.4#	3.2±0.4#
Pulmonary vascular resistance, $dyn.s.cm^{-5}$	1798±713	461±134#	563±188#
Heart rate, bpm	92±13	85±13	84±10
Mean blood pressure, mmHg	90±14	79±10	97±27
Mixed venous O_2 saturation, %	48±10	70±3#	74±4#

* $p<0.01$, # $p<0.001$ (ANOVA)

Tolerance of the triple combination therapy was similar to that observed with each drug when taken as monotherapy. In particular, there were no dose-limiting hypotensive episodes while epoprostenol doses were increased.

Conclusion: Upfront triple combination therapy with epoprostenol, bosentan and sildenafil in patients with severe PAH is associated with substantial improvements in important outcomes such as FC, exercise capacity and pulmonary hemodynamics. Further evaluation of this approach in a large multicenter randomized controlled study is warranted.

Am J Respir Crit Care Med 2011;183:A5901

cGMP signalling

- Impaired NO bioavailability, guanylate cyclase inactivation and enhanced cGMP degradation by PDEs (cGMP ↓)
  - NO donors
  - Endothelial NO synthase augmentaion
  - Soluble Guanylate cyclase activators (Riociguat – phase III trial)
  - Natriuretic peptides
  - PDE 1, 3 inhibitors

Anti-proliferatives

- PAH – shift of proliferative/apoptotic balance and enhanced glycolytic metabolism
- Platelet derived growth factor(PDGF), fibroblast growth factor 2, epidermal growth factor, vascular endothelial growth factor (VEGF), non-canonical WNT pathway → abnormal proliferation in PH
- Developed for cancer therapy

Izikki M et al. J Clin Invest 2009;119:512

Hassoun PM. Semin Respir Crit Care Med 2009;30:429

Anti-proliferatives

- Tyrosin kinase inhibitors (Imatinib=Gleevac)
- Rho kinase inhibitors

- Bone morphogenetic protein signalling pathway – BMPR2 targetted therapy
- 5-HT(serotonin) blockers
- Angiotensin-converting enzyme 2
- Statins
- K_{ATP} channel activators(iptakalim)
- Beta-blocker

✓ Carvedilol, metoprolol – RV reverse remodeling, improve RV function in PH rat

Bogaard HJ et al. Am J Respir Crit Care Med 2010;182:652