Management of Pulmonary Hypertension in 2017

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Disclosures

- Consulting/Speaking: Bayer, Actelion, United Therapeutics, Gilead

Outline

- Clinical Features
- Prognosis
- Medical therapies
- Advanced therapies

Prognosis

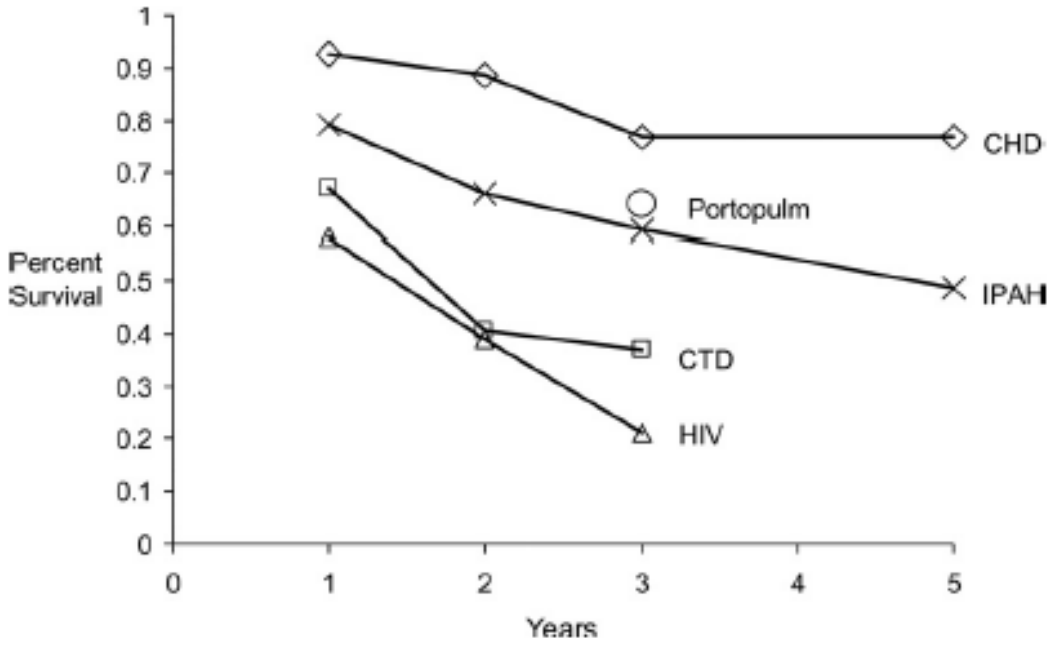


Figure 2. Mean Survival of Patients With PAH Based on Etiology

CHD indicates congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus related; IPAH, idiopathic pulmonary arterial hypertension; and Portopulm, portopulmonary hypertension. Adapted from McLaughlin et al. (69).

McLaughlin, et al. JACC 2009.

Important Clinical Factors

- Functional Class
- Exercise Tolerance
- Hemodynamics
- Echocardiography
- MRI
- Biomarkers

McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126:78S–92S.

Functional Class

- NIH Cohort Study: 1981-1985, approximately 200 patients with iPAH
- NYHA functional class I-II vs. III vs. IV
- Median survival: 6 yrs vs. 2.5 yrs vs. 0.5 yrs
- If start at functional class III/VI but improve to functional class I-II (on epoprostenol) – survival improved

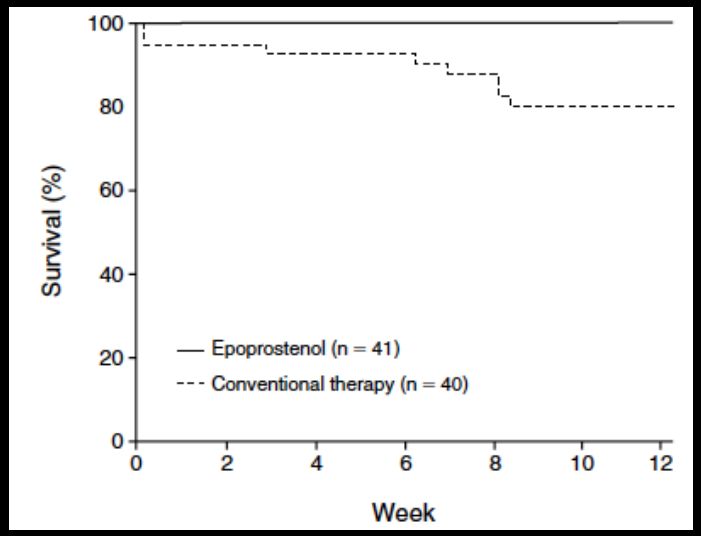
D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with PPH. Results from a national prospective registry. Ann Intern Med. 1991;115:343-9.

McLaughlin VV, et al. Survival in PPH: Epoprostenol. Circulation 2002; 106:1477-82.

Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol in PPH. JACC. 2002;40:780-8.

Exercise Tolerance (6MW)

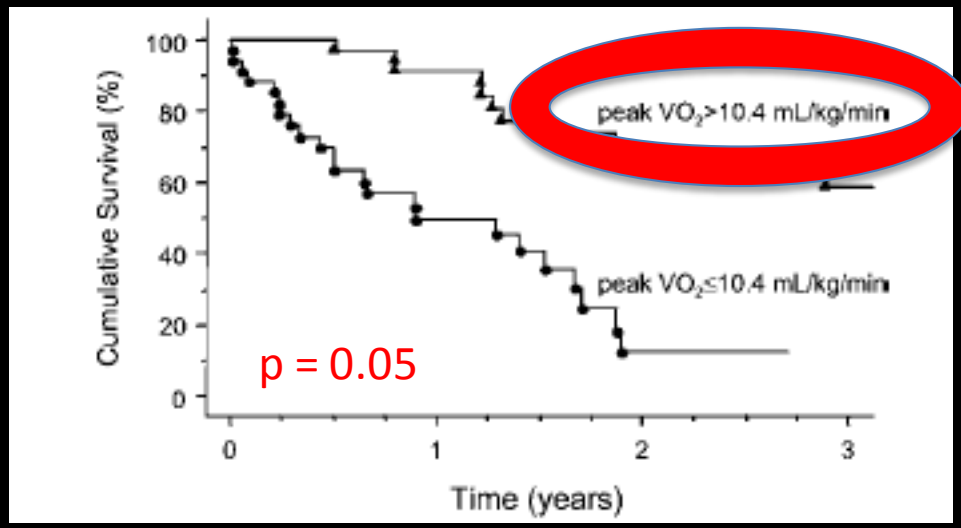
- Initially discouraged
- Epoprostenol trial: 12 wks, multicenter, placebo-controlled
- 6MW distance was an independent predictor of survival (+31 vs -20 meters, p<0.002)
- 100% (41/41) vs. 80% (32/40) survival (p=0.003)

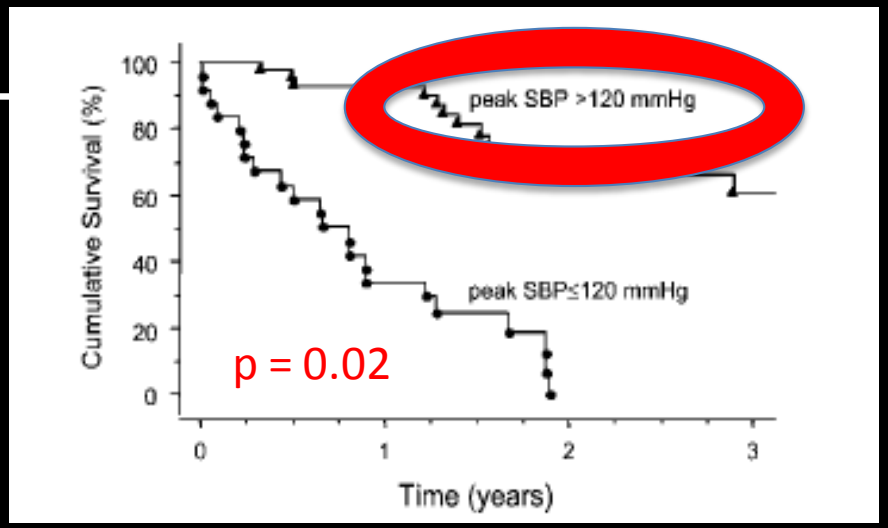


Barst RJ, Rubin LJ, Long WA, et al. Epoprostenol for PPH. PPH Study Group. NEJM 1996;334:296-3022.

Exercise Tolerance (CPET)

- Cycle ergometry predicted survival at one year
- 86 patients between 1996-2001





Wensel R, et al. Assessment of survival in PPH: importance of CPET. Circulation 2002;106:319-24.

Hemodynamics

- NIH Registry
- 32 centers, 194 patients, follow-up 1980s
- Not pre-treatment, but after treatment (epoprostenol data)
- Biggest predictors of survival:

  mPAP, RAP, CI

D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with PPH. Results from a national prospective registry. Ann Intern Med. 1991;115:343-9

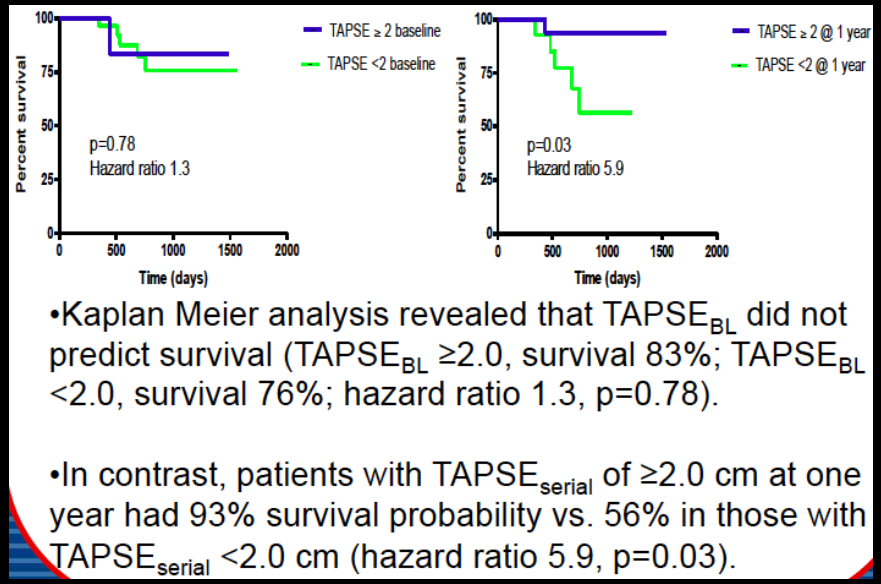
Vasodilator Challenge

- 3 agents:
  - iNO, iv epoprostenol, iv adenosine
- Responders – controversial definition based on predictive value of various parameter cutoffs
  - Decrease mPAP by 10, to <40, without drop in CO
- Prognostic – most helpful in iPAH
  - 95% survival at 5 years
- Response to CCBs (Diltiazem, Nifedipine, Amlodipine) – avoid Verapamil

Rich, S, et al. CCBs on Survival in PPH. NEJM 1992;327:76-81.

Echocardiography

- RV size/function, septal position, pericardial effusion, Tei index have been studied
- PAH – baseline echo and at one year, groups defined by TAPSE cut-off 2.0 cm



•Kaplan Meier analysis revealed that $TAPSE_{BL}$ did not predict survival ($TAPSE_{BL}$ ≥2.0, survival 83%; $TAPSE_{BL}$ <2.0, survival 76%; hazard ratio 1.3, p=0.78).

•In contrast, patients with $TAPSE_{serial}$ of ≥2.0 cm at one year had 93% survival probability vs. 56% in those with $TAPSE_{serial}$ <2.0 cm (hazard ratio 5.9, p=0.03).

Vaidya, et al. TAPSE at 1 year, not baseline, predicts mortality in PAH. CHEST. 2011.

Cardiac MRI

- RV size & function – predict mortality, treatment failure in study of 64 pts
  - RV Stroke volume ≤ 25 ml/m^2
  - RV End diastolic volume ≥ 84 ml/m^2
  - LV End diastolic volume ≤ 40 ml/m^2
- PA Stiffness – predict survival in 86 PAH pts
  - Cross sectional area change < 16%

Van Wolferen, et al. RV mass, volume, and fxn in iPAH. Eur Heart J. 2007;28:1250-7.

Gan CT, et al. PA Stiffness predicts mortality in PAH. Chest. 2007;132:1906-12

Biomarkers

- Uric Acid (impaired oxidative metabolism)
  - Functional class and hemodynamics in iPAH
- Troponin-T
- BNP and NT-ProBNP

Fijalkowska A, et al. NT-ProBNP in PH. Chest. 2006;129:1313-21.
Nagaya N, et al. Uric acid & mortality in PPH. Am J Respi Crit Car Med. 1999;160:487-92.
Torbicki A, et al. Troponin T poor prognosis in precapillary PH. Circulation 2003;108:844-8.

PAH: Determinants of Prognosis

Clinical Feature	Lower Risk	Higher Risk
Clinical RV Failure	No	Yes
Symptom onset	Gradual	Rapid
WHO Class	II, III	IV
6MW distance	> 400m	< 300m
CPET (VO2)	> 10.4 ml/kg/min	< 10.4 ml/kg/min
Echocardiography	Minimal RV dysfxn	Sig RV dysfxn, enalrgement, RAE, Pericardial effusion
Hemodynamics	RAP <10, CI > 2.5	RAP > 20, CI < 2.0
BNP elevation	Minimal	Significant

McLaughlin VV, McGoon MD. PAH. Circulation. 2006;114:1417-31.

General Treatment

- Na < 2400 mg/day
- Influenza, Pneumovax vaccinations
- Contraception (30-50% maternal mortality)
- Low level exercise (walking)

General Treatment

- Anticoagulation – iPAH
  - 1.5-2.5
  - Not PoPH, scleroderma
- O2 (baseline – flying) – Sat > 90%
- Diuresis
- Rhythm Control
- Digoxin

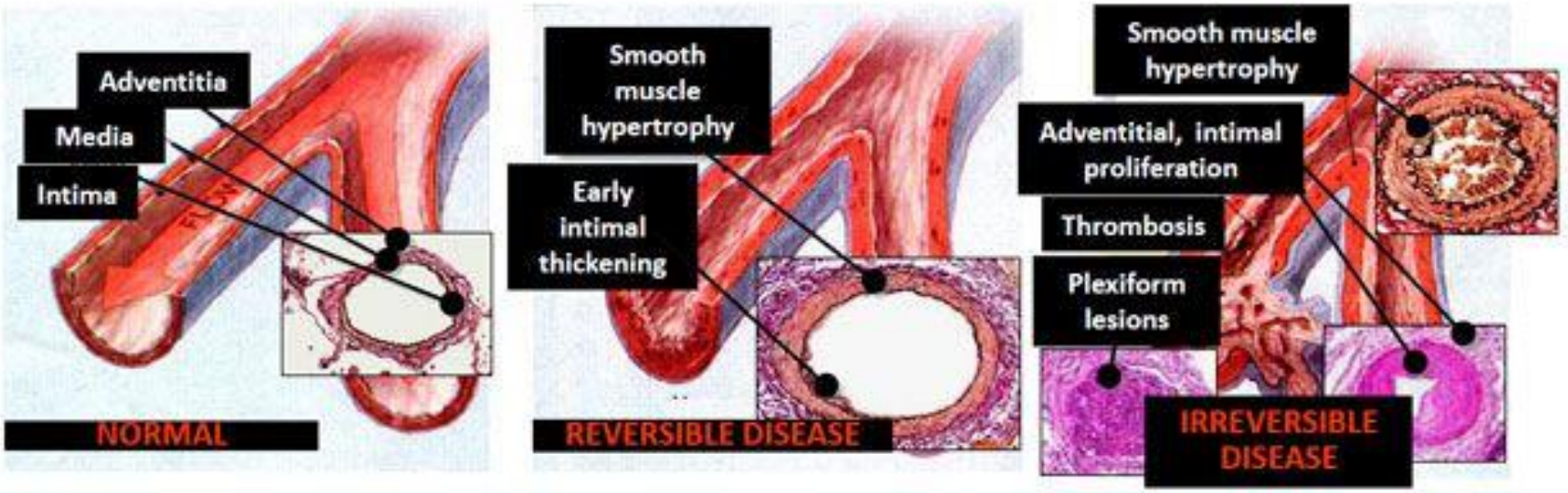
Pathogenesis of PAH

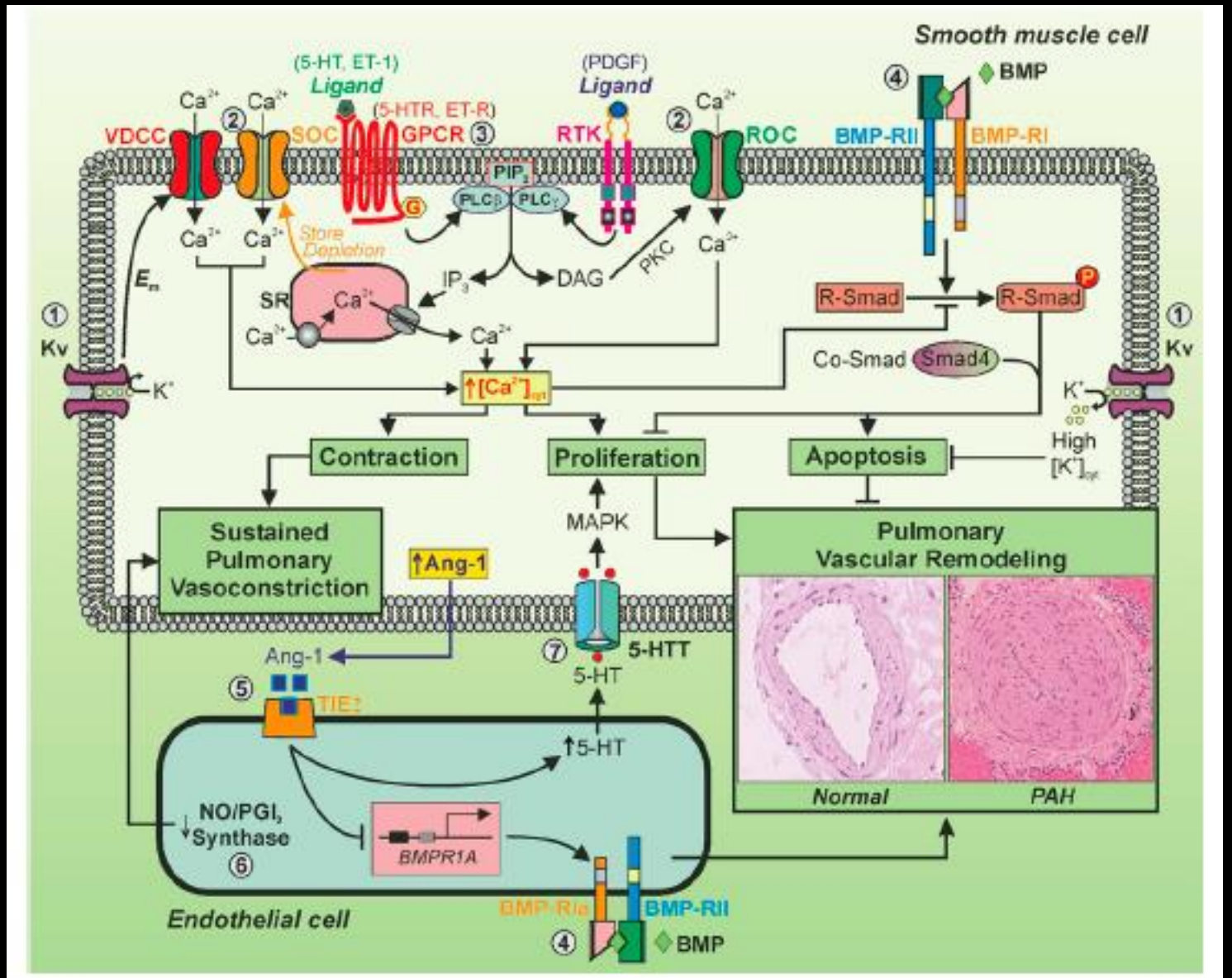
1. **Risk Factors and Associated Conditions**
   - Collagen vascular disease
   - Congenital heart disease
   - Portal hypertension
   - HIV infection
   - Drugs and toxins
   - Pregnancy

Susceptibility
- Abnormal *BMPR2* gene
- Other genetic factors

2. **Vascular injury**
   - Endothelial dysfunction
     - ↓ Nitric oxide synthase
     - ↓ Prostacyclin production
     - ↑ Thromboxane production
     - ↑ Endothelin 1 production
   - Vascular smooth muscle dysfunction
     - Impaired voltage-gated potassium channel ($K_{V1.5}$)

3. **Disease progression**
   - Loss of response to short-acting vasodilator trial



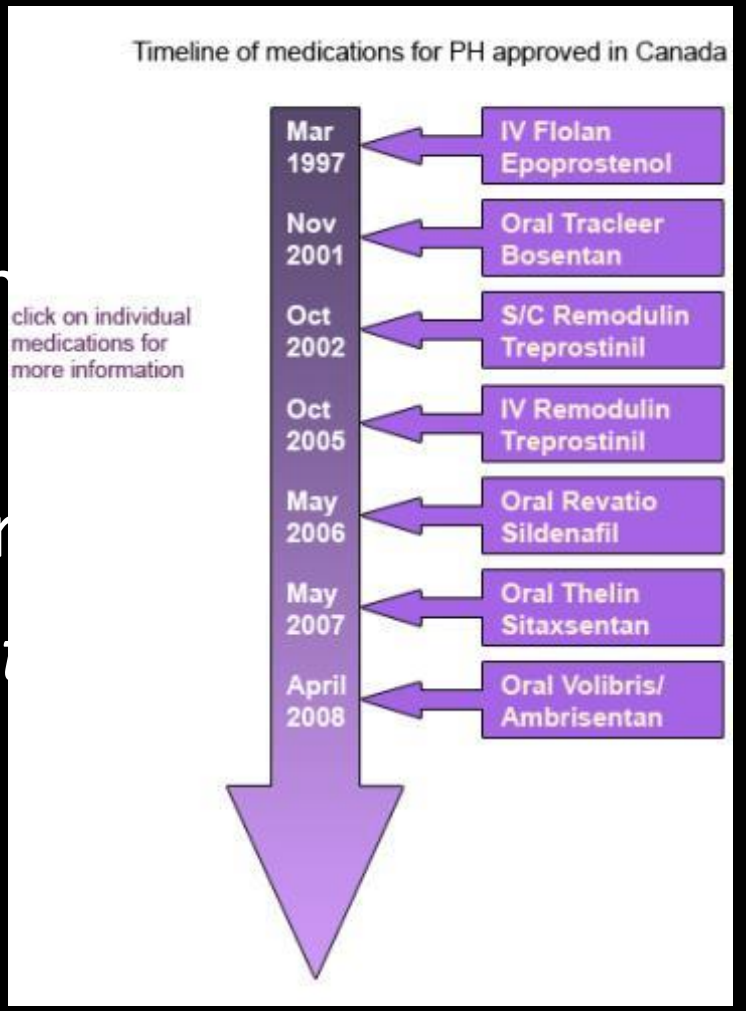


Relevant Pathways in the Pathogenesis of Pulmonary Arterial Hypertension

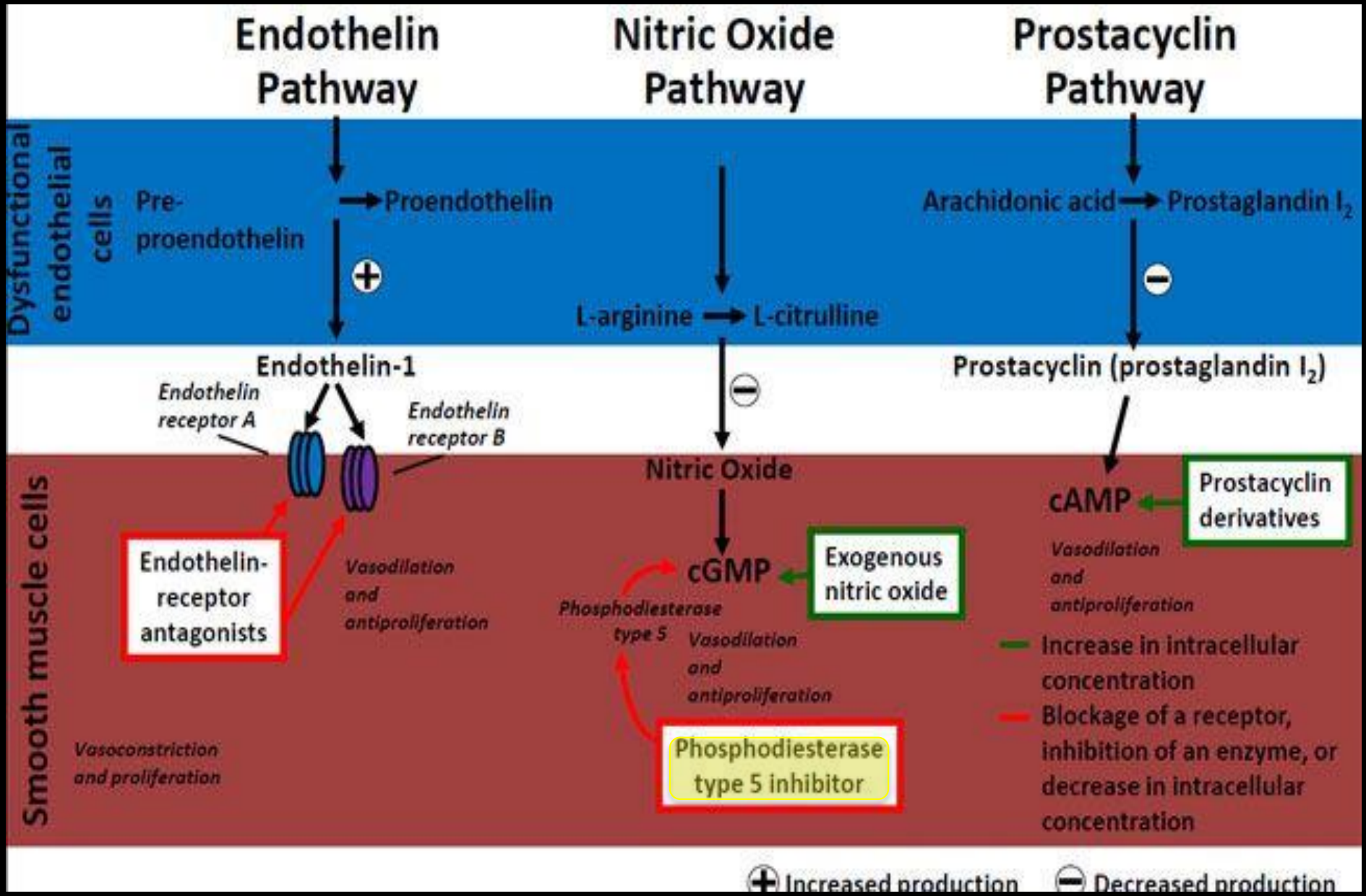
McLaughlin, et al. JACC 2009.

PH: Therapy

- PDE-5 inhibitors
- Endothelin receptor antagon
- Prostacyclin therapy
- Guanylate cyclase stimulator
- *Prostacyclin receptor agonist*



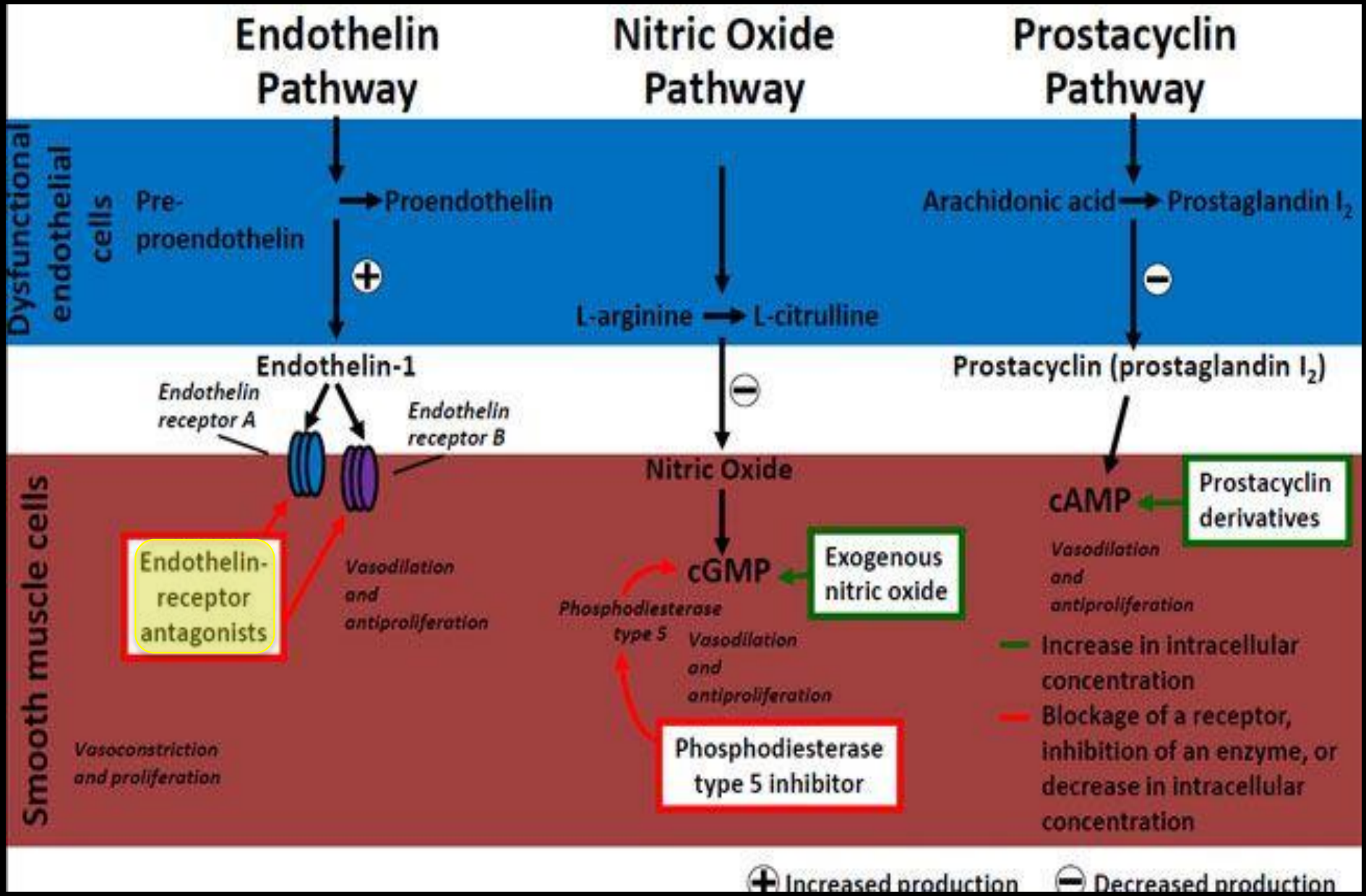
Drug Pathways in PAH



PDE-5 Inhibitors

- Sildenafil (Revatio)
  - Three times daily
- Tadalafil (Adcirca)
  - One time daily

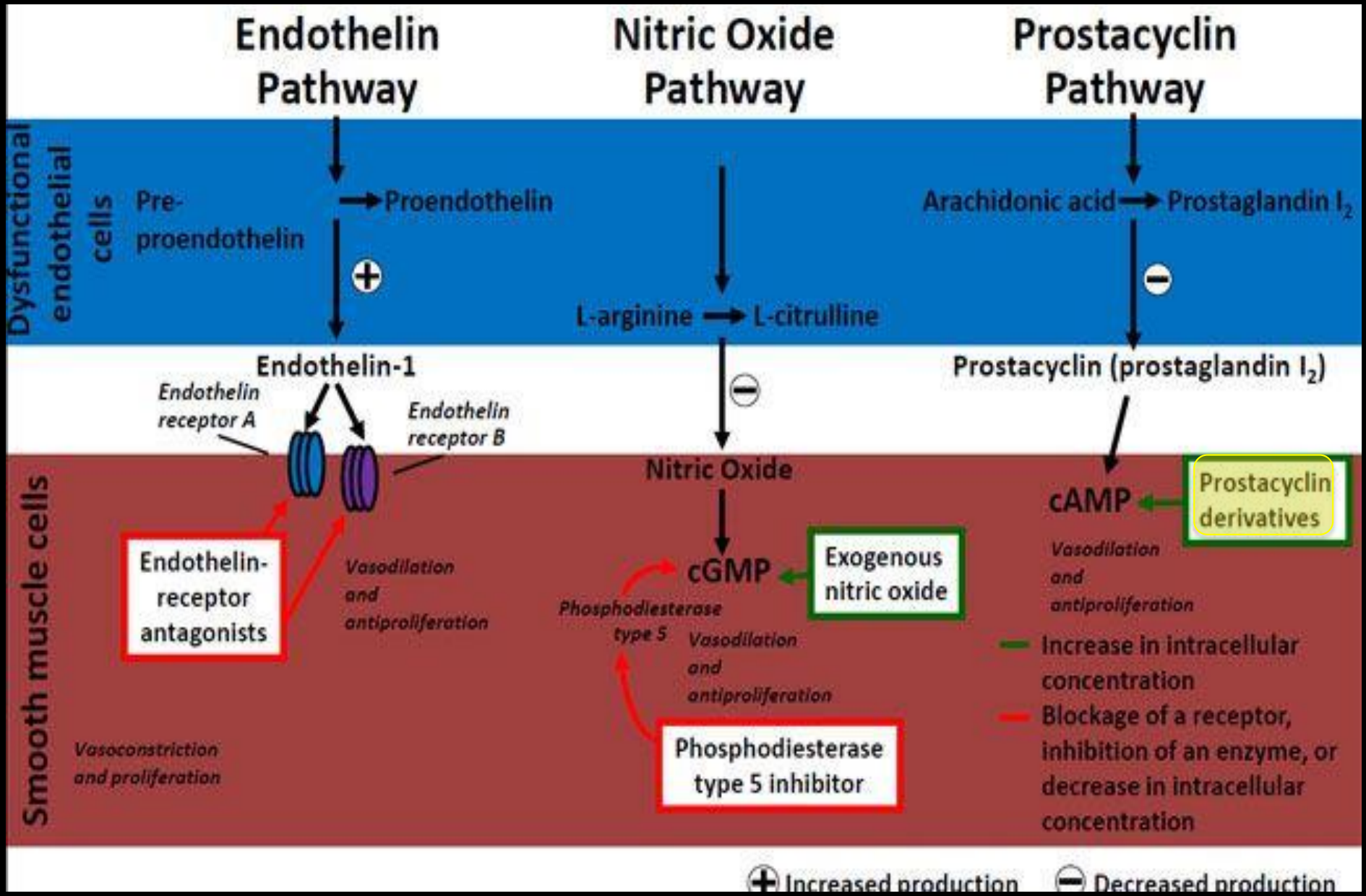
Drug Pathways in PAH



Endothelin Receptor Antagonists

- Bosentan (Tracleer) – ETA&B
  - Twice daily
  - LFT monitoring
- Ambrisentan (Letairis) – ETA
  - Once daily
  - No LFT monitoring
- Macitentan (Opsumit) – ETA&B
  - SERAPHIN STUDY – 742 patients worlwide
  - Once daily (no LFT abnormality, no edema, ↓Hgb)

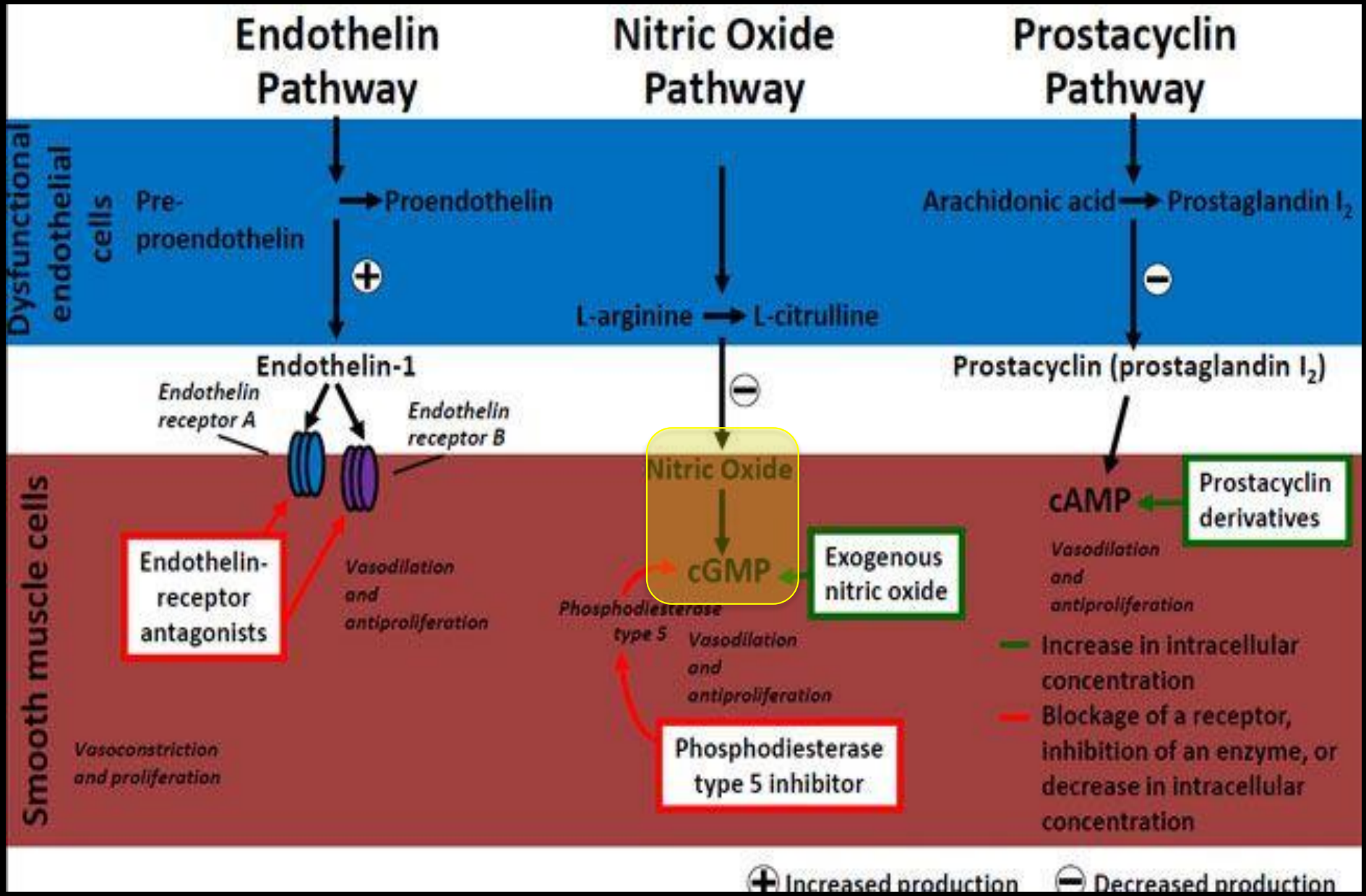
Drug Pathways in PAH



Prostacyclin

- Inhaled
  - Iloprost - Ventavis
  - Treprostinil - Tyvaso
- Parenteral
  - Treprostinil – Remodulin (SC or IV)
  - Epoprostenol – Flolan/Valetri (IV)
- Oral
  - Treprostinil – Orenitram (2014…)

Drug Pathways in PAH

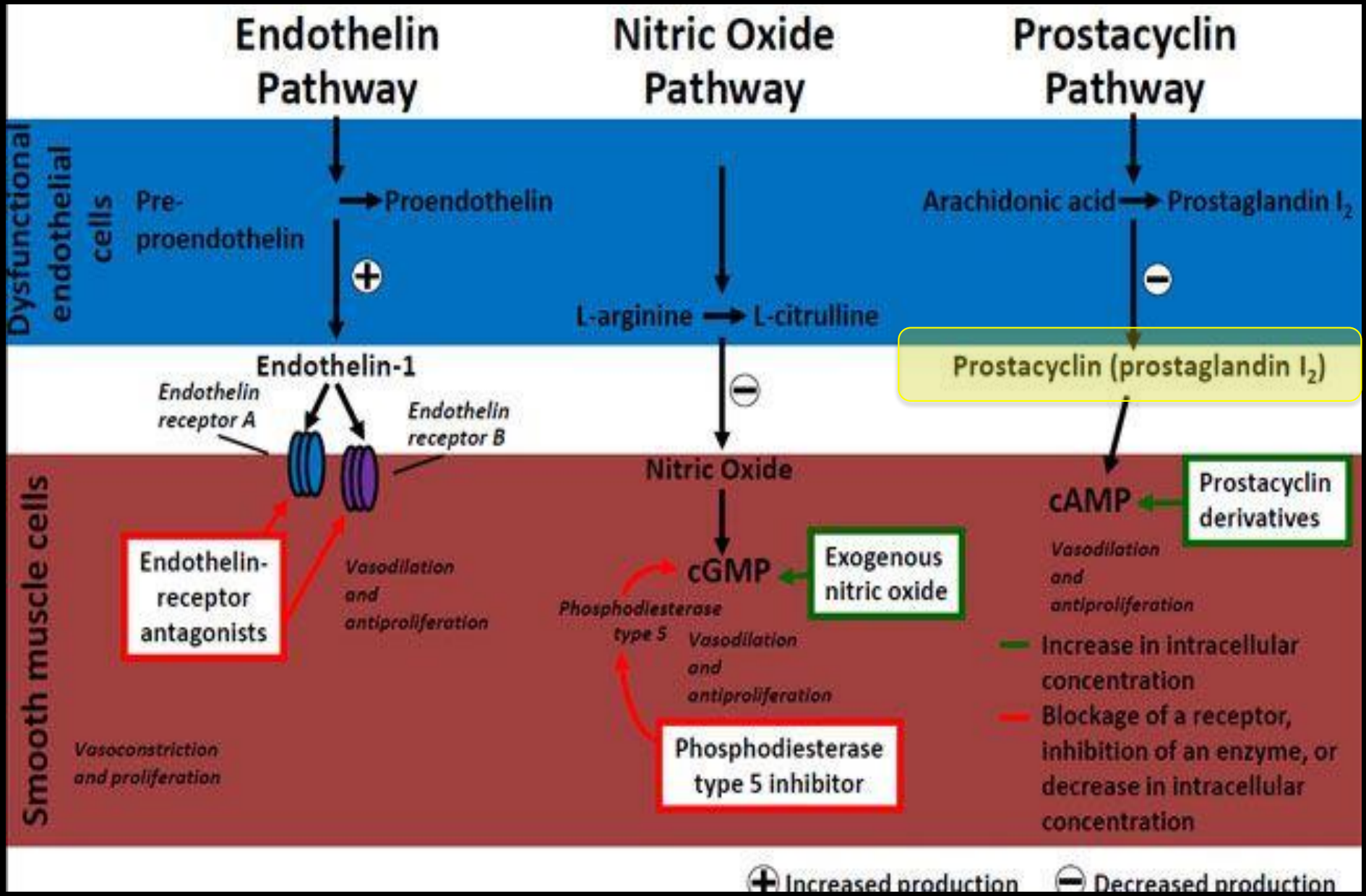


Guanylate-Cyclase Stimulator

- Riociguat (soluble – works via cGMP, NO)
- PAH and CTEPH: Two Randomized, Double-Blind, Placebo-Controlled Studies
- Follow-up for 16 (CTEPH) and 12 (PAH) weeks
- Significant improvements were observed in 6MWD, PVR, NT-proBNP, and WHO FC in both populations

N Engl J Med 2013; 369:330-340.

Drug Pathways in PAH



Prostacyclin (PGI_2) Receptor Agonist

- Selexipag (GRIPHON – 1,100 PAH pts)
- Oral pro-drug
- After 17 wks: 30% reduction in combined morbidity/mortality, improved 6MWD
- Well-tolerated, good safety profile thus far
- Final results expected mid-2014

Advanced Therapies

- Surgical
  - Lung transplant
  - PTE
- PA Denervation
- Atrial septostomy
- Potts


IT'S QUITE SERIOUS
TAKE THIS MEDICINE
WHEN IT'S AVAILABLE..
WHENEVER YOU CAN
AFFORD IT
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Thank You!