Introduction to Pulmonary arterial hypertension

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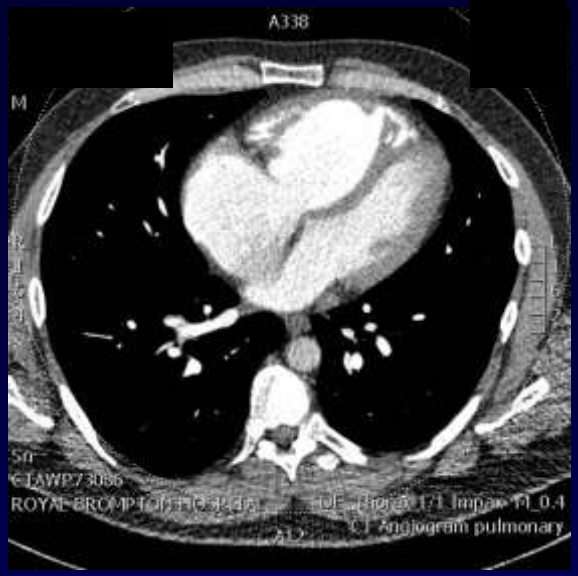
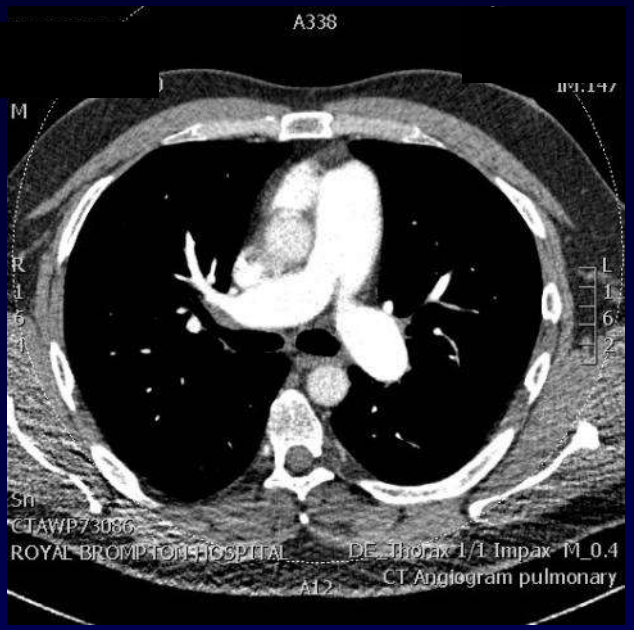
Outline and objectives

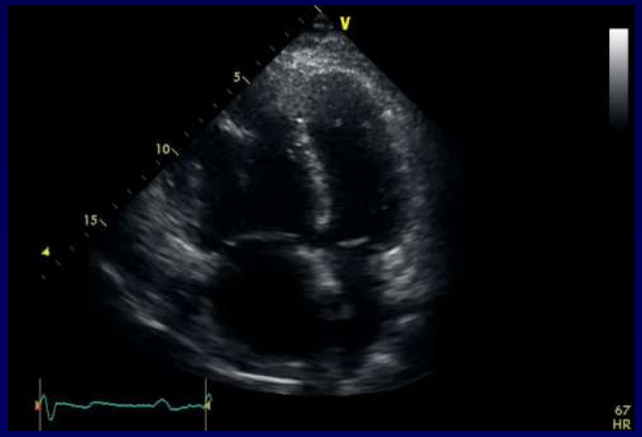
- **PAH is a** devastating disease **which in the absence of effective treatment progresses rapidly to death**
- Early diagnosis**: difficult due to low prevalence and non-specific symptoms**
- **There are 9 PH specialist centres within the UK and they offer important benefits e.g. resources to aid an accurate and timely diagnosis and access to advanced therapies**

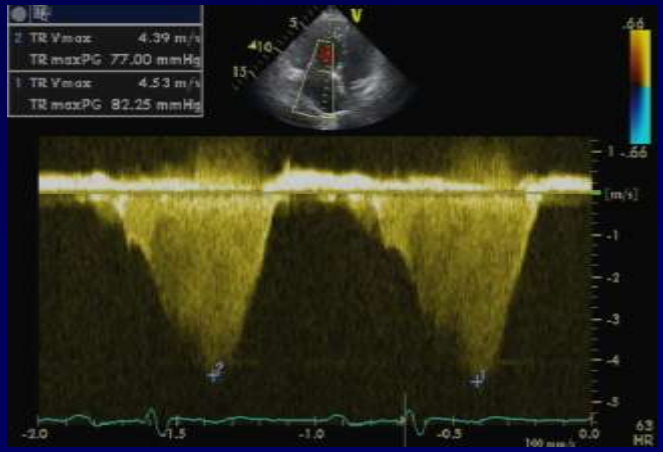
- 40y old
- Progressive SOB over last 2 years
- Now can manage less than 50m on flat
- Ankle swelling, abdominal swelling
- Mother, grandmother died in their 30s-40s

IHD? DCM/Heart failure? Lungs?.....

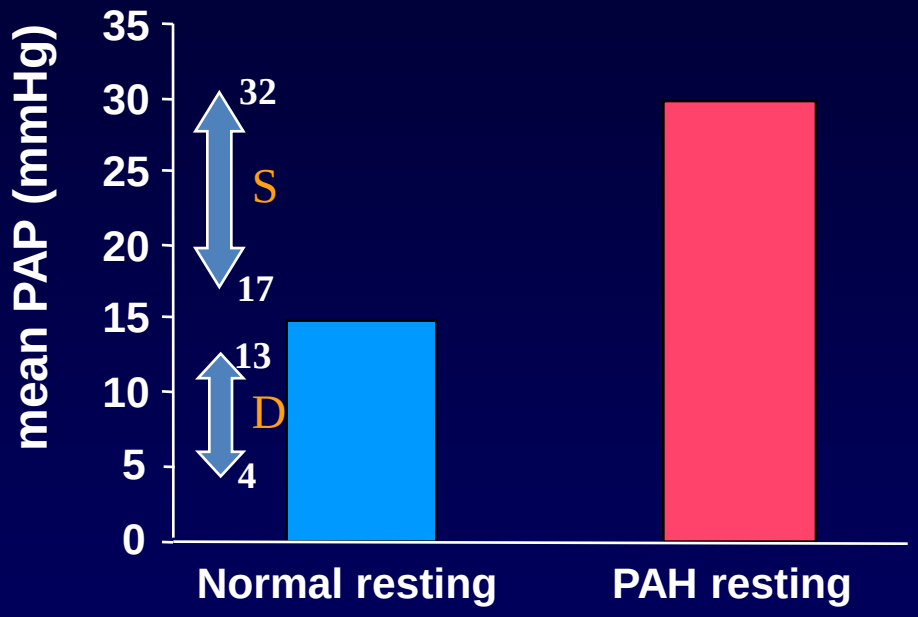

A338
M
CTAWP73086
CT Angiogram pulmonary


A338
M
CTAWP73086
ROYAL BROMPTON HOSPITAL
DE_Thorax 1/1 Impax M_0.4
CT Angiogram pulmonary


V
67
HR


TR Vmax 4.39 m/s
TR maxPG 77.00 mmHg
TR Vmax 4.53 m/s
TR maxPG 82.25 mmHg
V
[m/s]
63
HR

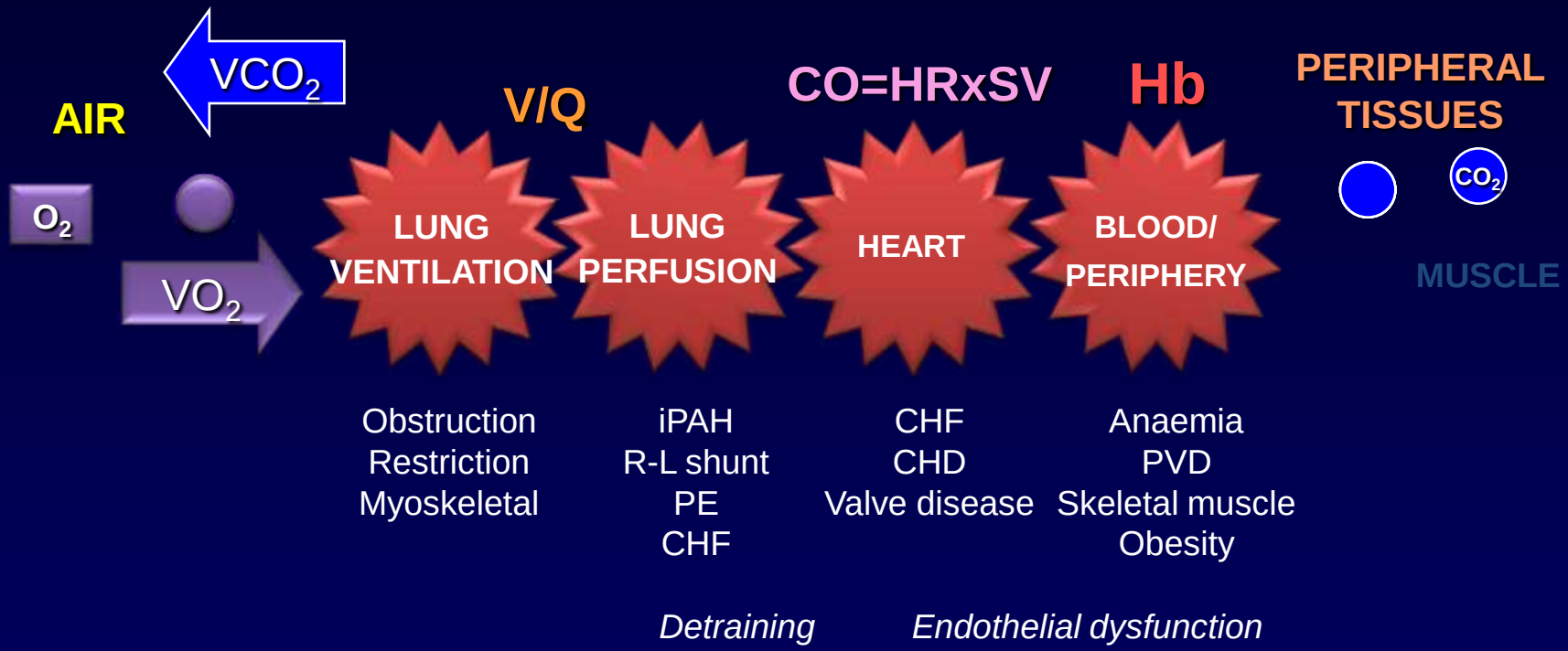
Definition of PH



- PH definition: mPAP>25 mmHg at rest

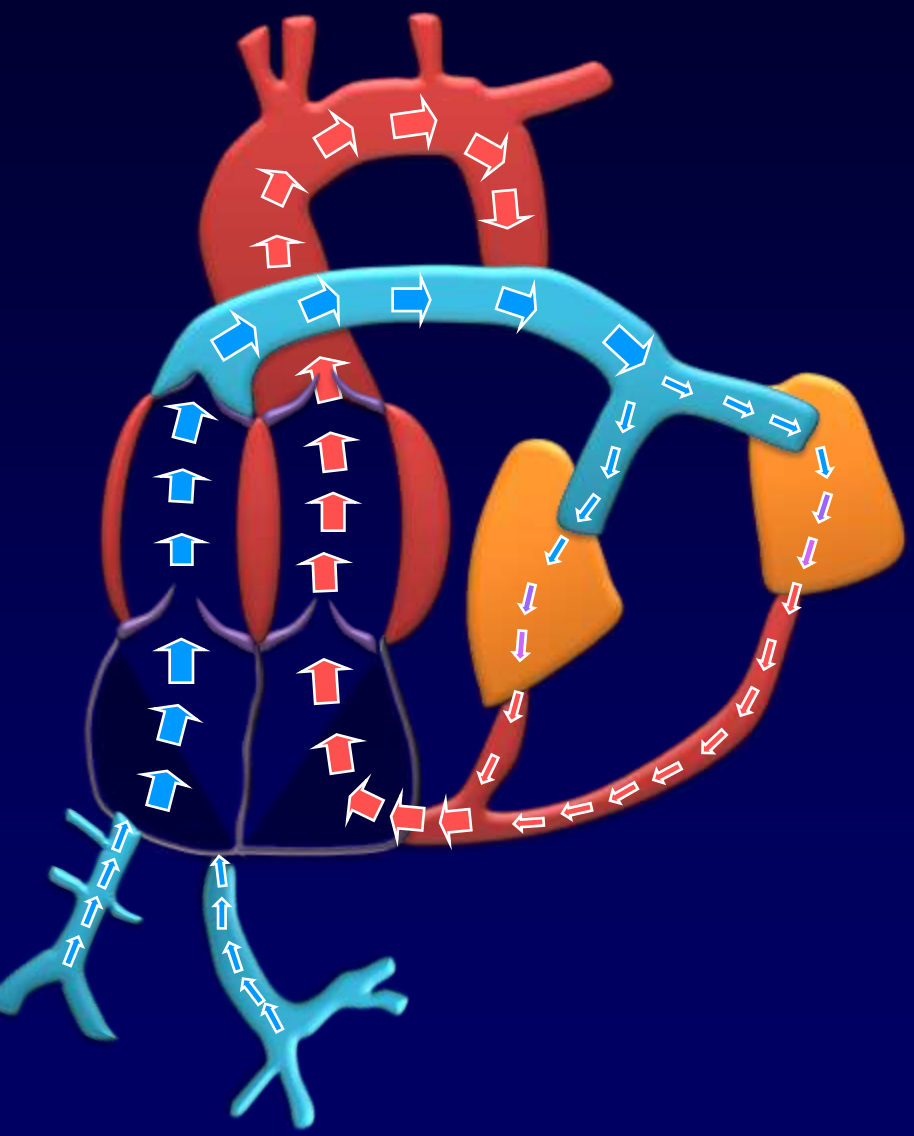
Galiè N, *et al. Eur Heart J* 2009; 30:2493-2357.

Cardiopulmonary Physiology

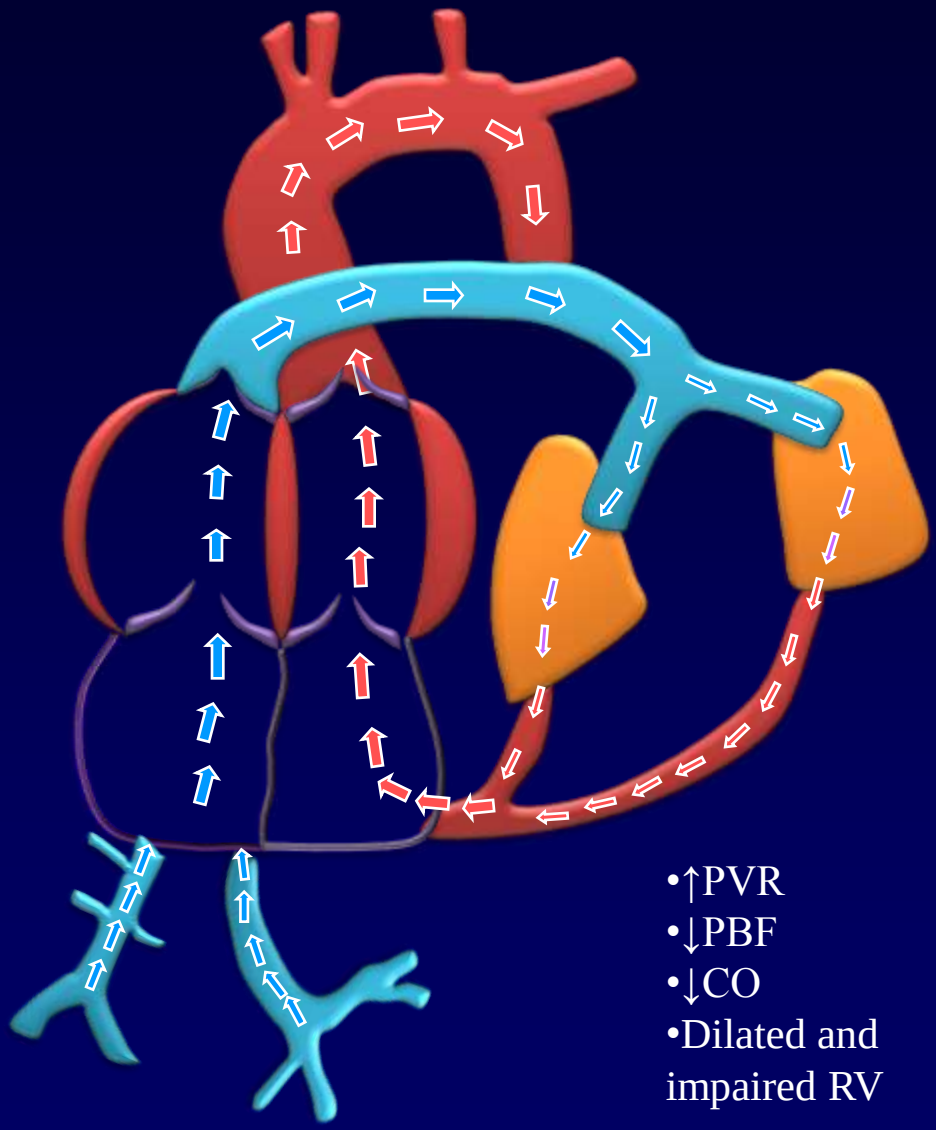


The CPET allows the simultaneous study of the responses of the cellular, cardiovascular and ventilatory systems to a known exercise stress through the *measurement of the gas exchange at the airway*

Normal



iPAH



- ↑PVR
- ↓PBF
- ↓CO
- Dilated and impaired RV

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics	Clinical group(s)
Pulmonary hypertension (PH)	Mean PAP ≥ 25 mmHg	All
Pre-capillary PH	Mean PAP ≥ 25 mmHg PWP ≤15 mmHg CO normal or reduced	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥ 25 mmHg PWP ≥ 15 mmHg CO normal or reduced	2. PH due to left heart disease
Passive	TPG ≤ 12 mmHg	
Reactive (out of proportion)	TPG > 12 mmHg	

WITHIN THE LUNGS?

COMING FROM THE LEFT HEART?

www.escardio.org/guidelines

European Heart Journal 2009;30:2493-2537

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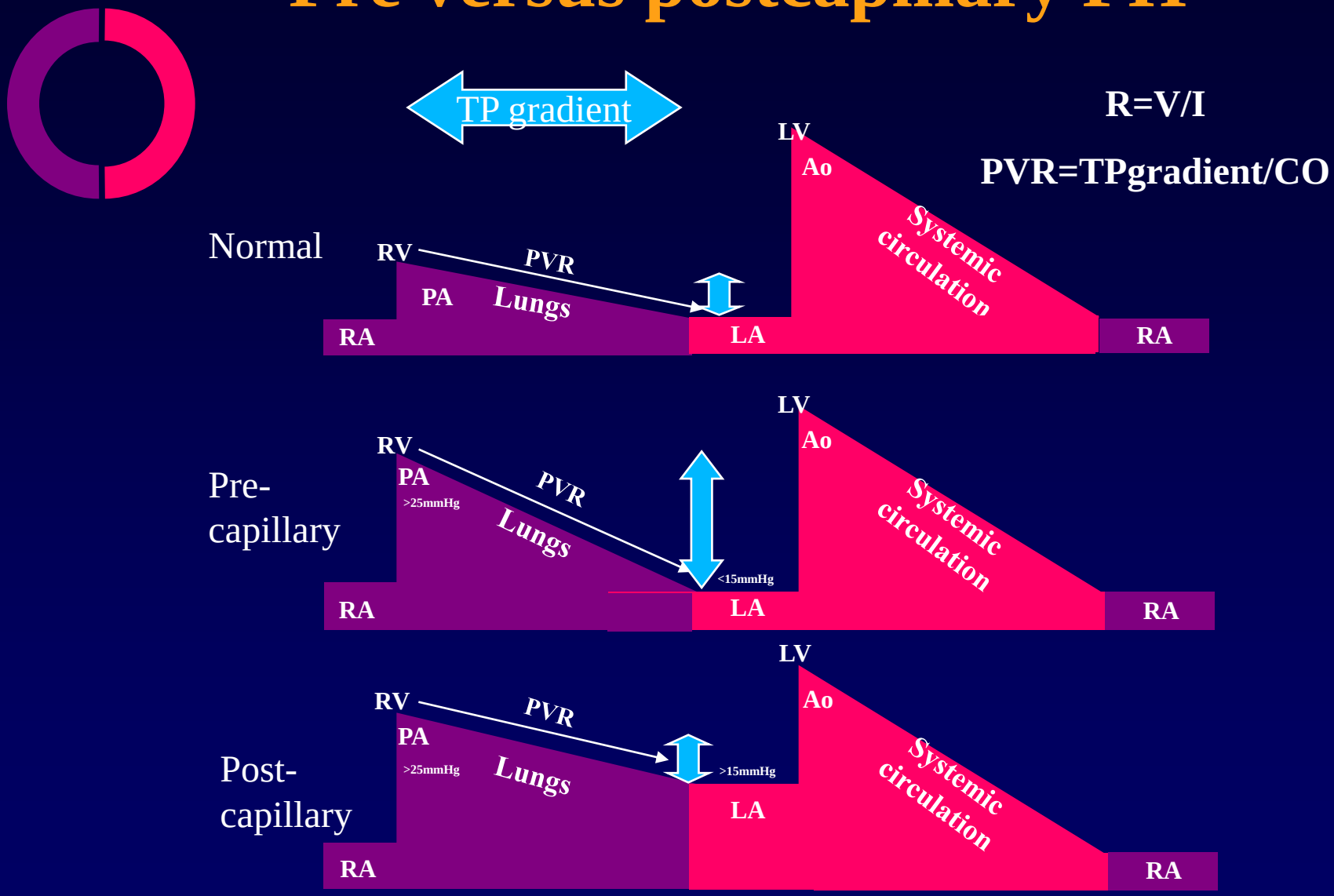
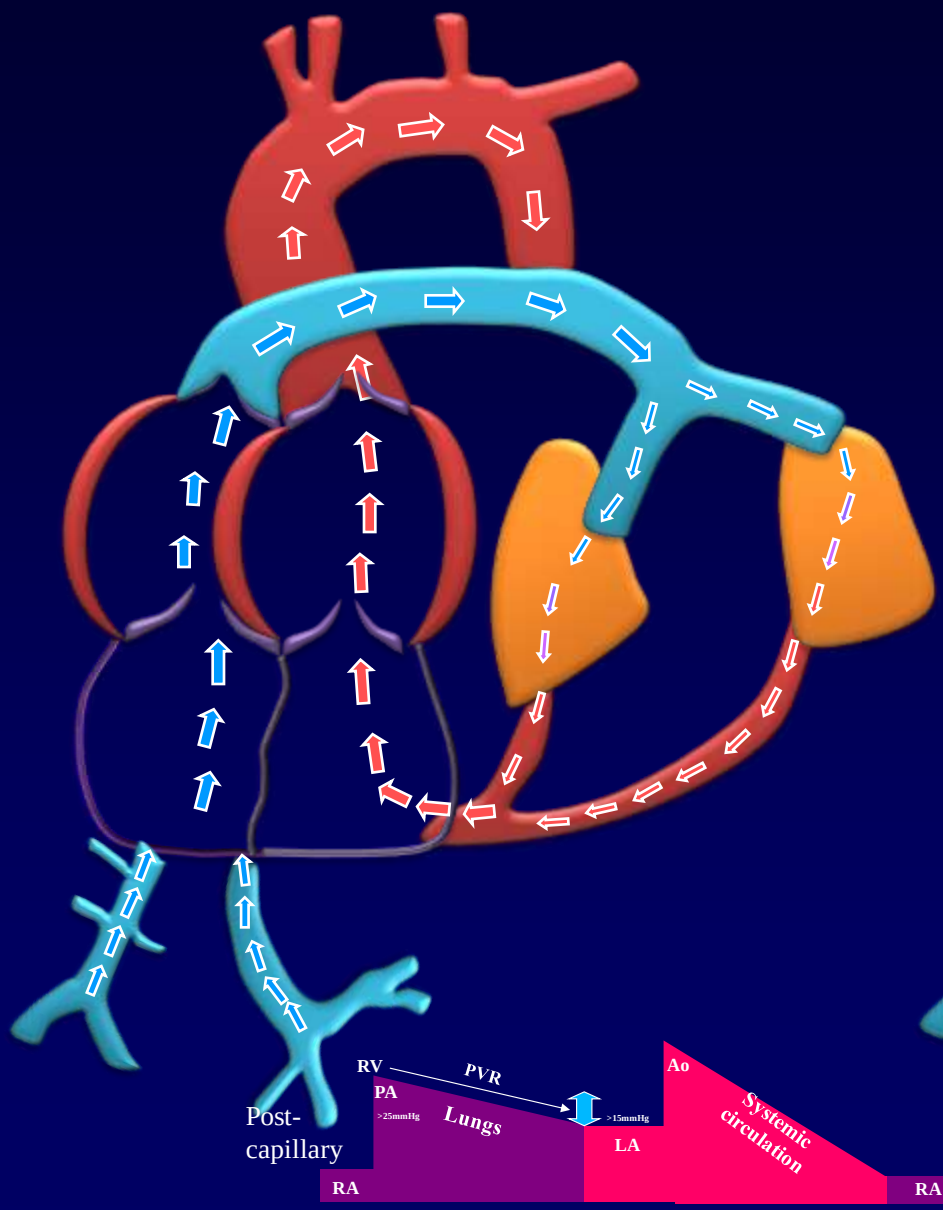
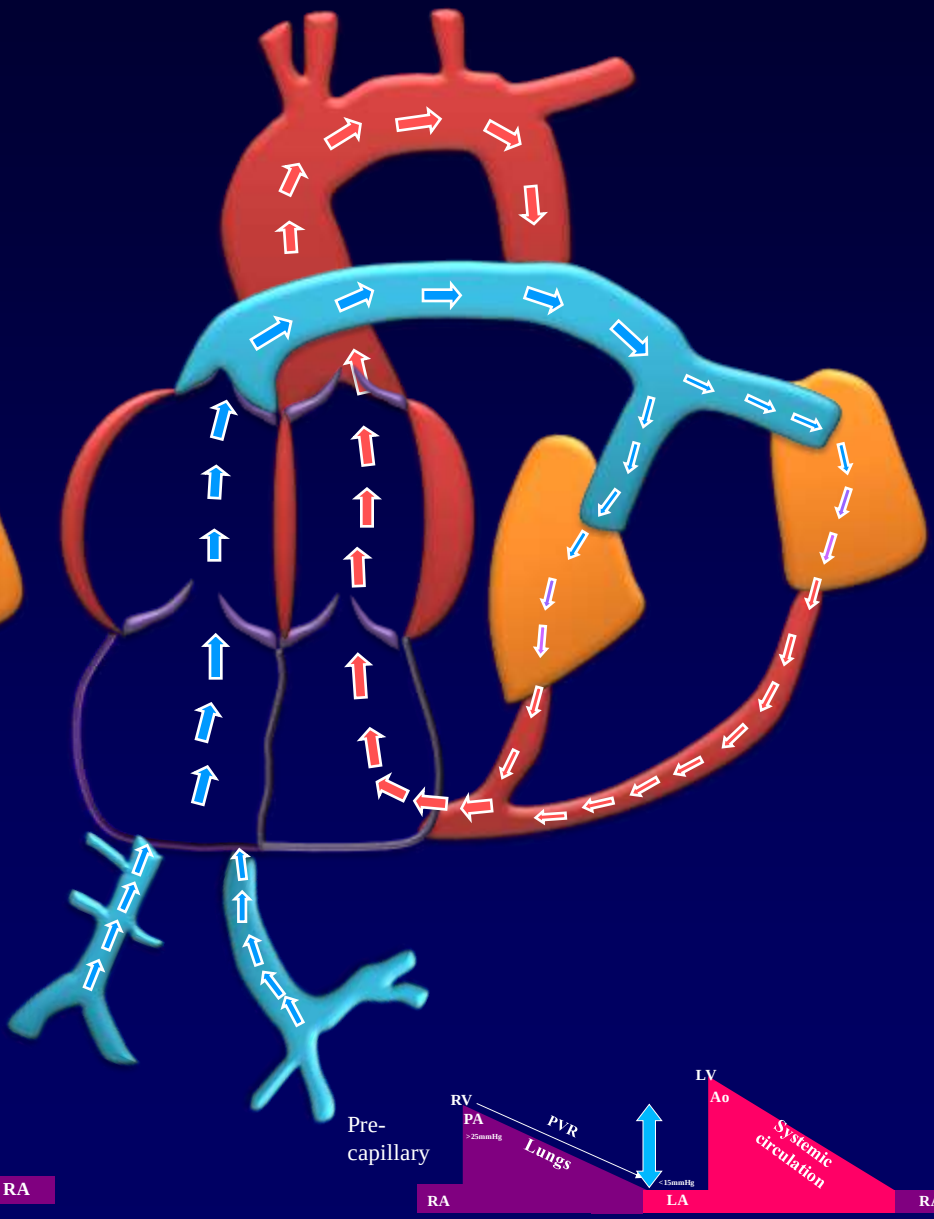
Pre versus postcapillary PH



DCM

iPAH


Post-
capillary
RV
PVR
PA
>25mmHg
Lungs
>15mmHg
LA
Ao
Systemic
circulation
RA
RA


Pre-
capillary
RV
PVR
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WITHIN THE LUNGS?

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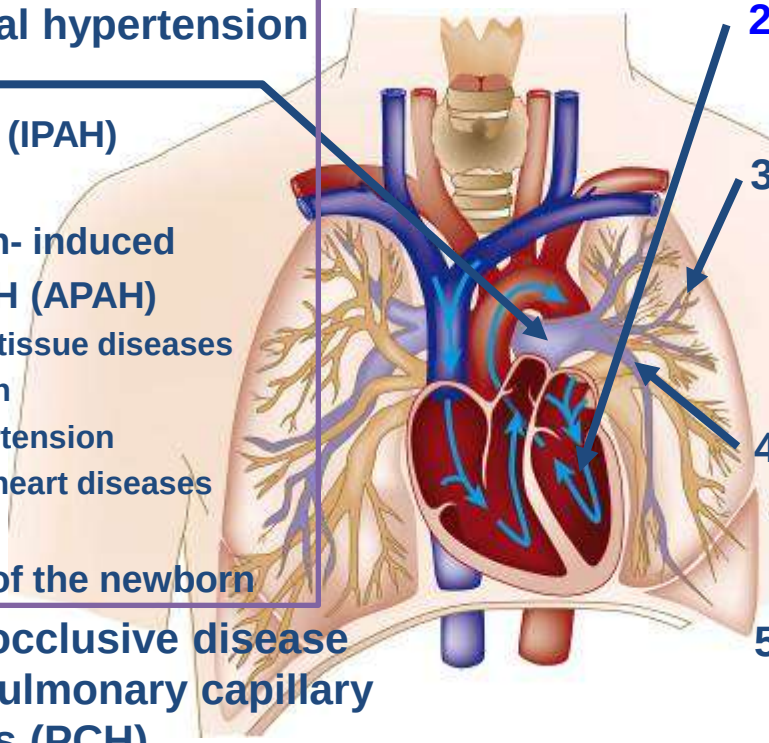
Clinical classification of PH

1. Pulmonary arterial hypertension (PAH)
   - Idiopathic PAH (IPAH)
   - Heritable PAH
   - Drug- and toxin- induced
   - Associated PAH (APAH)
     - Connective tissue diseases
     - HIV infection
     - Portal hypertension
     - Congenital heart diseases
     - Others
   - Persistent PH of the newborn

1' Pulmonary veno-occlusive disease (PVOD) and /or pulmonary capillary hemangiomatosis (PCH)



2. PH owing to left heart disease= POSTCAPILLARY

3. PH owing to lung diseases and/or hypoxia
   - COPD
   - Interstitial lung disease

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. PH with unclear multifactorial mechanisms
   - Sarcoidosis

Galiè N, *et al. Eur Heart J* 2009; 30:2493-2357.

Definitions

- **Pulmonary hypertension (PH)** is a *haemodynamic and pathophysiological condition* defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization. PH can be found in multiple clinical conditions.
- The definition of PH on exercise as a mean PAP > 30 mmHg as assessed by right heart catheterization is not supported by published data.
- **Pulmonary arterial hypertension** (PAH, group 1) is *a clinical condition* characterised by the presence of precapillary PH in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thrombo-embolic PH or other rare diseases. PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.

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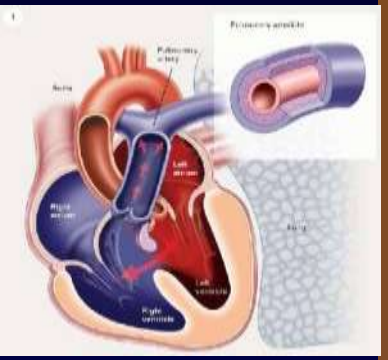
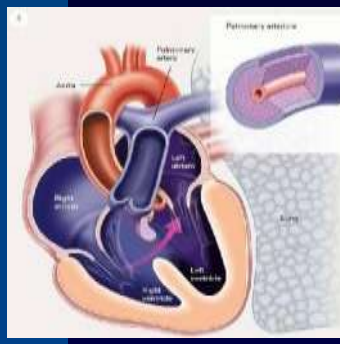
PAH associated with L-R shunt

Eisenmenger syndrome





Shunt

L-R

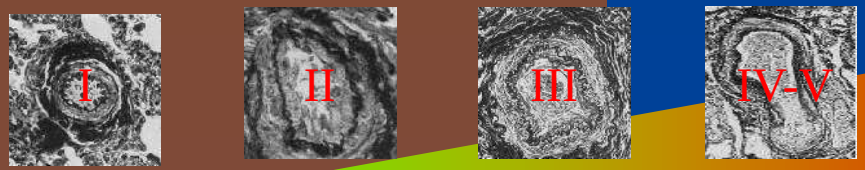
Bidirectional/RL shunt

R-L

Endothelial dysfunction

Shear stress & stretch Vascular Remodeling

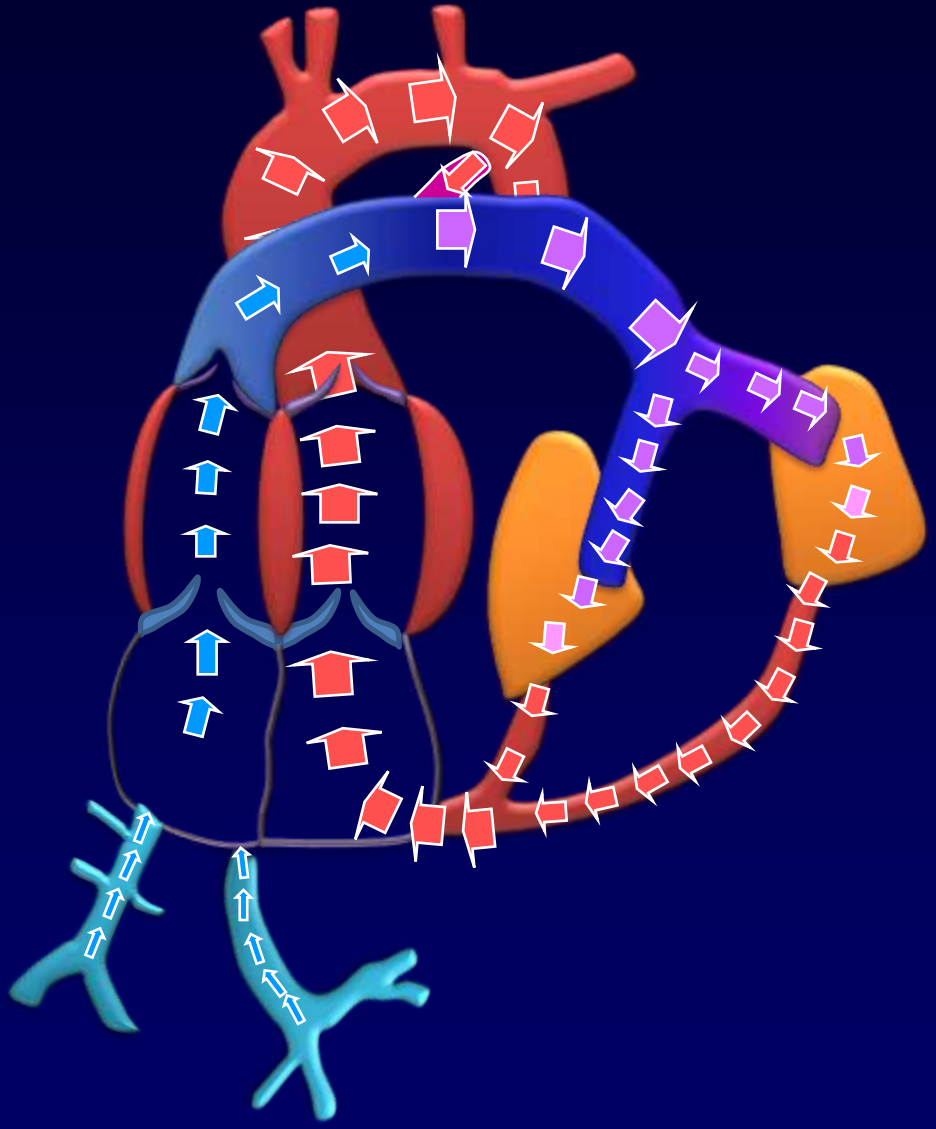
Histology

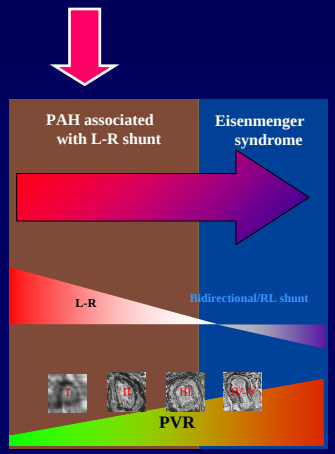


PVR

PVR

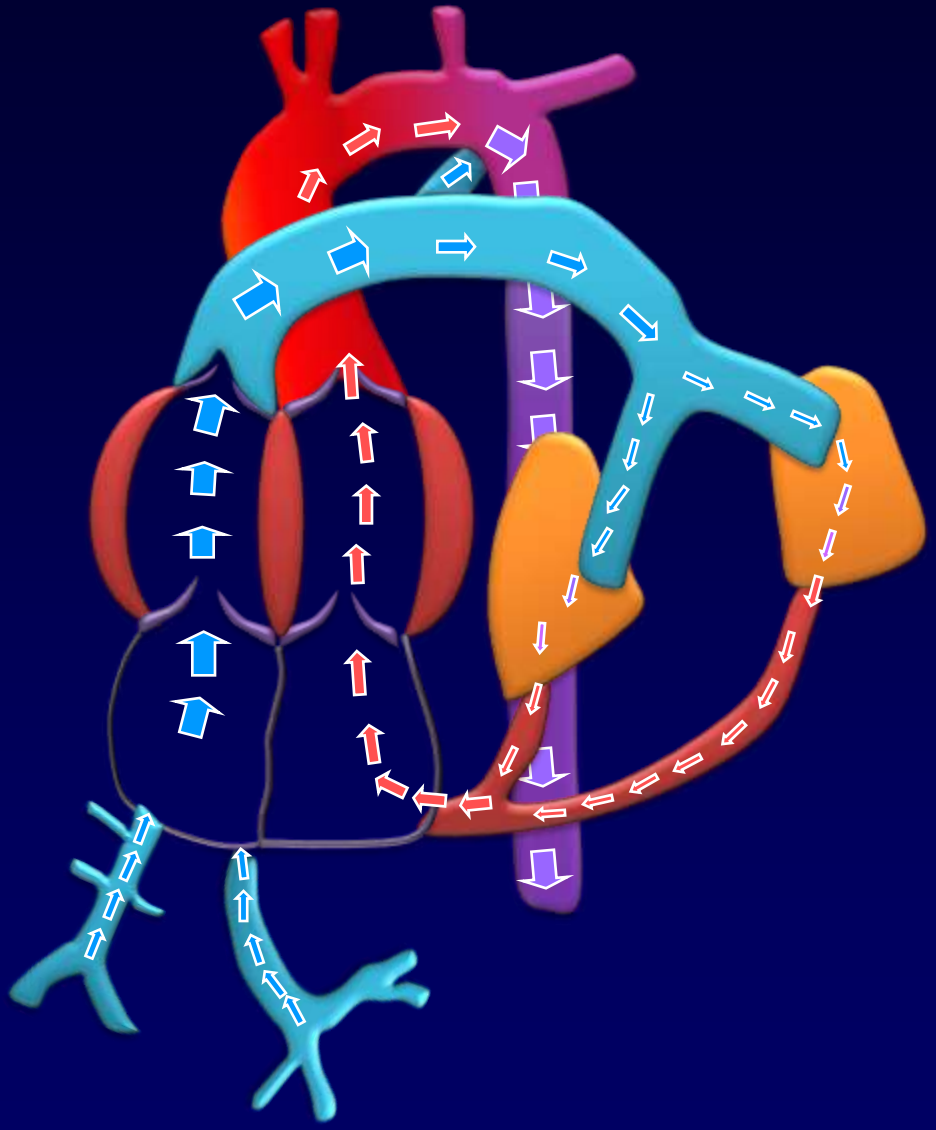
Patent Ductus Arteriosus
Infant

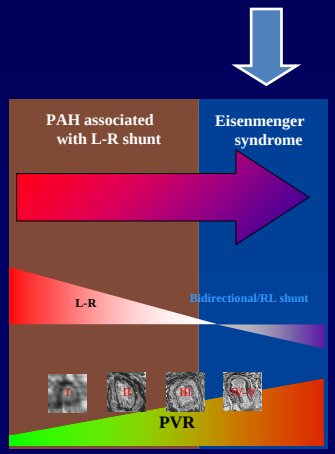




Patent Ductus Arteriosus
Severe PAH

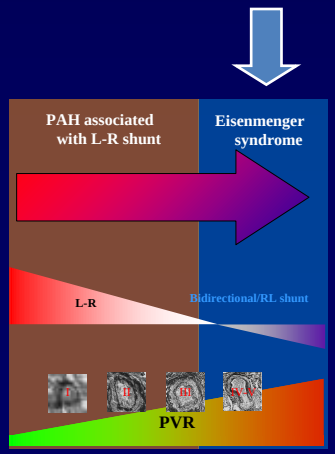
- **Shunt: Bidirectional/R-L**
- **PBF: Reduced**
- **CO: Normal/reduced**
- **Cyanosis: ++ differential**





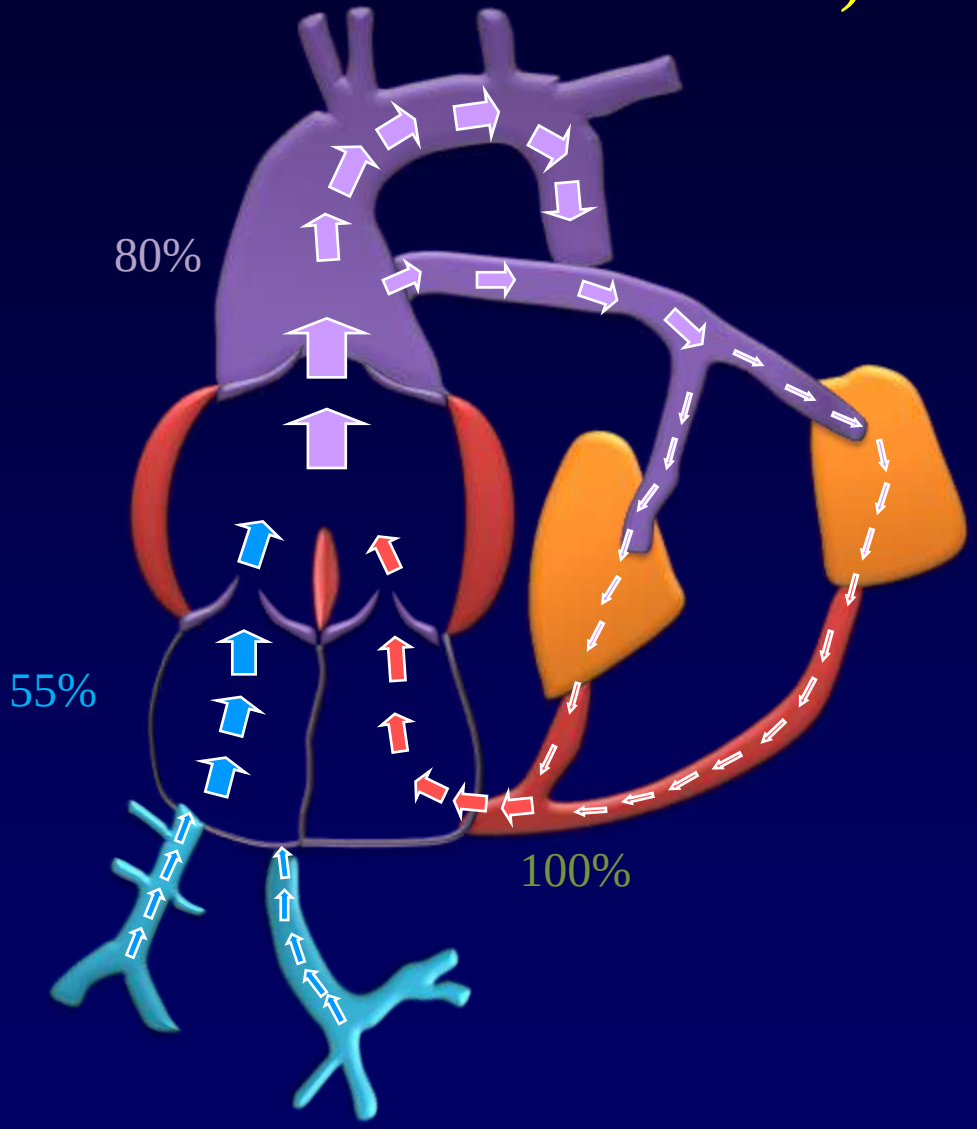
Ventricular septal defect
(large, >1cm)

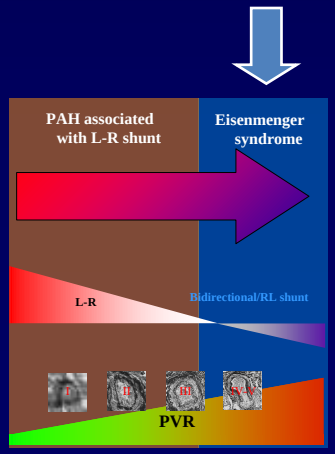
- **Shunt: Bidirectional/R-L**
- **PBF: Reduced**
- **CO: Normal/reduced**
- **Cyanosis: ++**



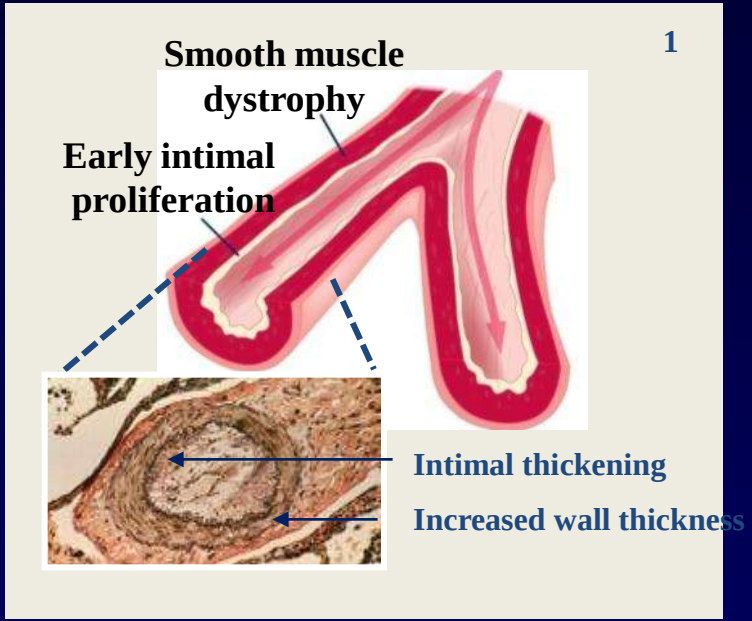
Truncus arteriosus
(common arterial trunk+VSD)

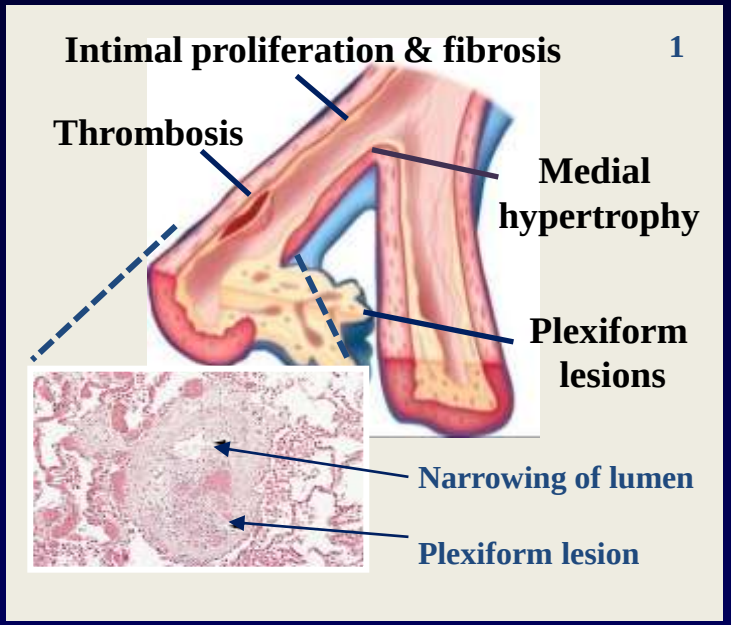
- **Shunt: complete mixing**
- **PBF: Reduced (PH/PS)**
- **CO: Normal/reduced**
- **Cyanosis: +++**





The malignant nature of PAH



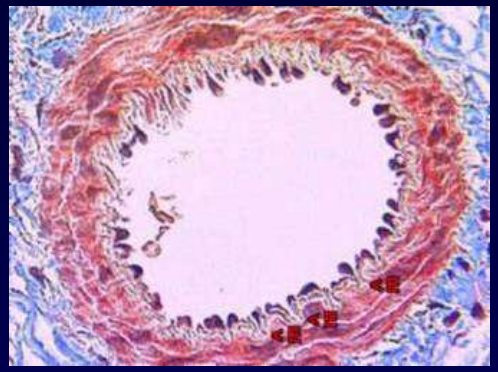


- Angiogenesis & evasion of apoptosis[2]
- Self-sufficient in growth signals & insensitivity to anti-growth signals[2]
- Tissue invasion and limitless replicative potential[2]

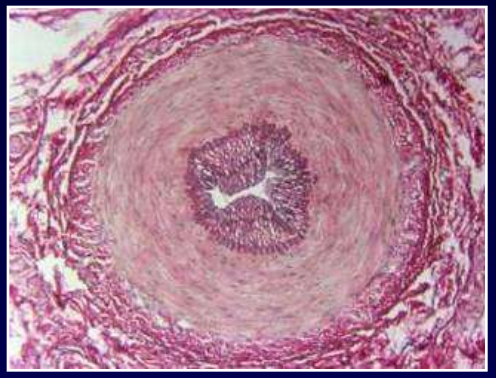
Hallmarks shared with cancer

1. Gaine S. *JAMA* 2000; 284:3160-8.
2. Rai PR, *et al. Am J Respir Crit Care Med* 2008; 178:558-64.

Pathogenesis of PAH



Normal



Abnormal

- Increased pulmonary vascular resistance and raised pulmonary artery pressure:
  - Vascular proliferation and remodelling
  - Distal muscularisation of normally non-muscular arteries
  - Increased muscularisation of muscular pulmonary arteries
  - Neointima formation
  - Formation of plexiform lesions

Jeffery T, Morrell N. *Prog Cardiovasc Dis* 2003;45:173–202

Back to RCT slide

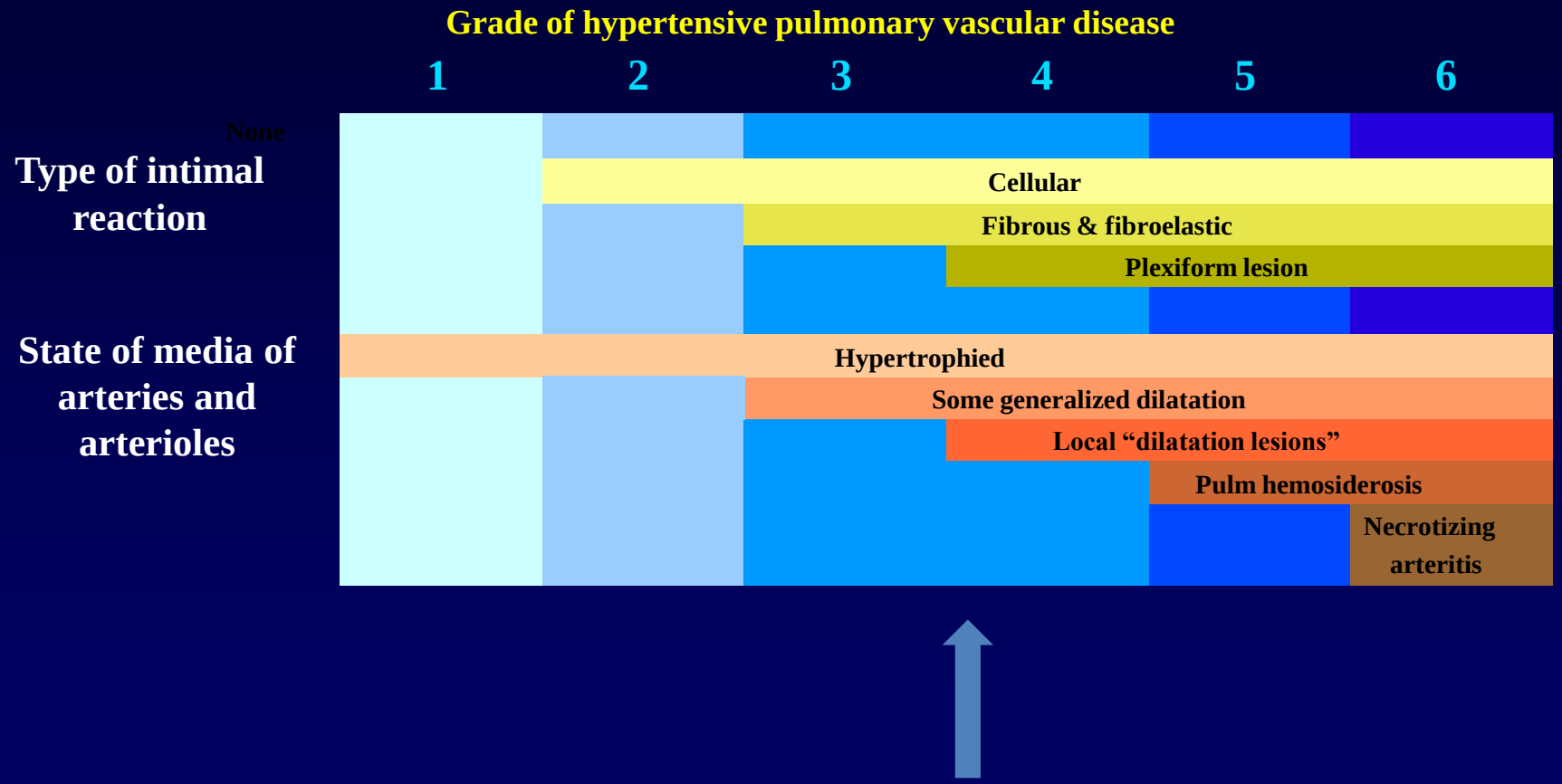
PAH is more than just vasoconstriction

Disease progression

- Narrowing of the small pulmonary arteries occurs[1]
- Increased pulmonary vascular resistance and right ventricle afterload leads to right-ventricular failure[2]
- Vascular proliferation and remodelling are the main contributing factors to PAH pathogenesis[1,2]

1. Farber HW et al. *N Engl J Med* 2004;351:1655–65
2. Humbert M et al. *J Am Coll Cardiol* 2004;43:13S–24S

Basis of grades of hypertensive PVD found in association with large VSDs and functionally related diseases

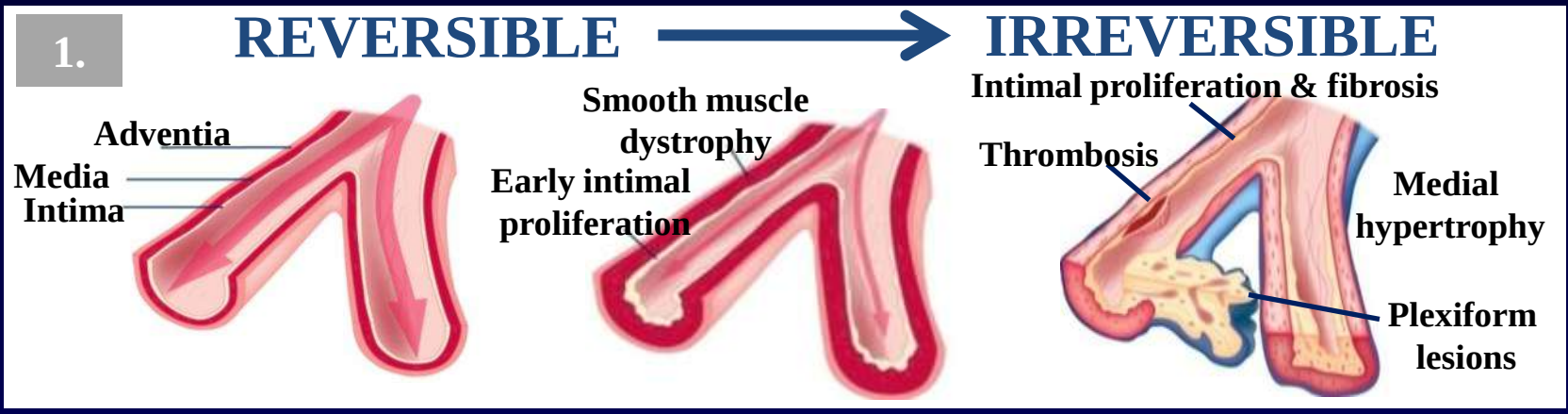


Heath, Edwards. Circulation 1958

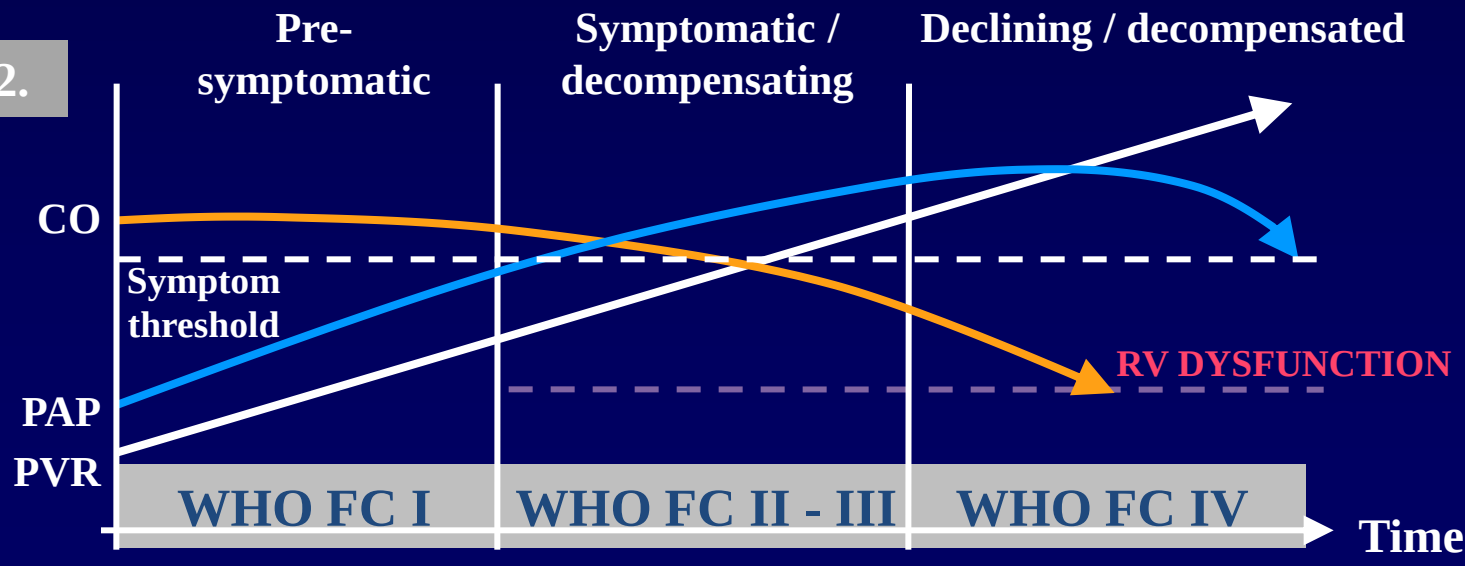
The rapidly progressive nature of PAH

Disease is often advanced before it is apparent

1.

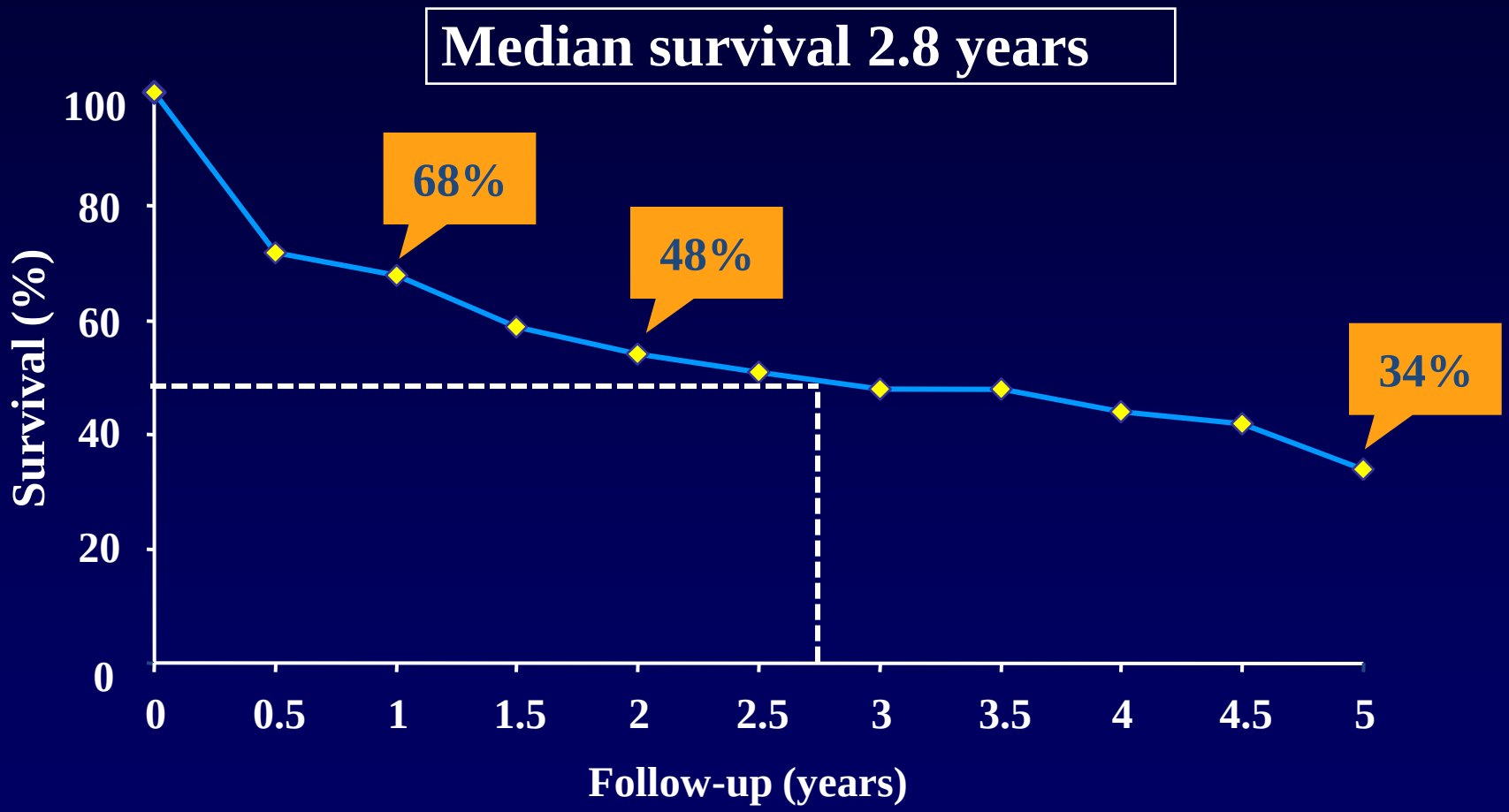


2.



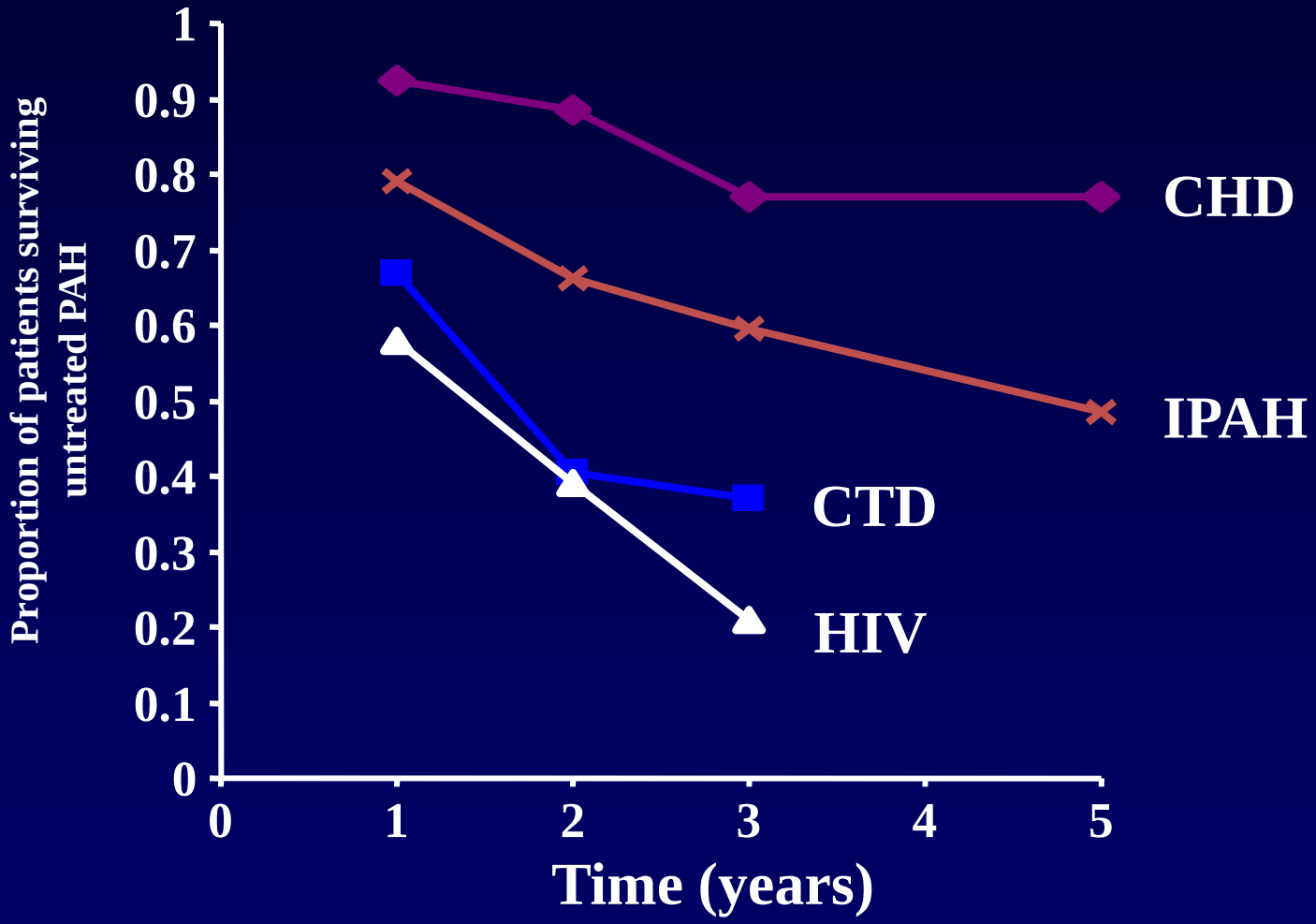
1. Gaine S. *JAMA* 2000; 284:3160-8.
2. Domenighetti G, *et al. Swiss Med Wkly* 2007; 137:331-6.

Prognosis is extremely poor in PAH



D'Alonzo GE, et al. *Ann Internal Med* 1991; 115:343-9.

Survival in patients with untreated PAH of different aetiologies



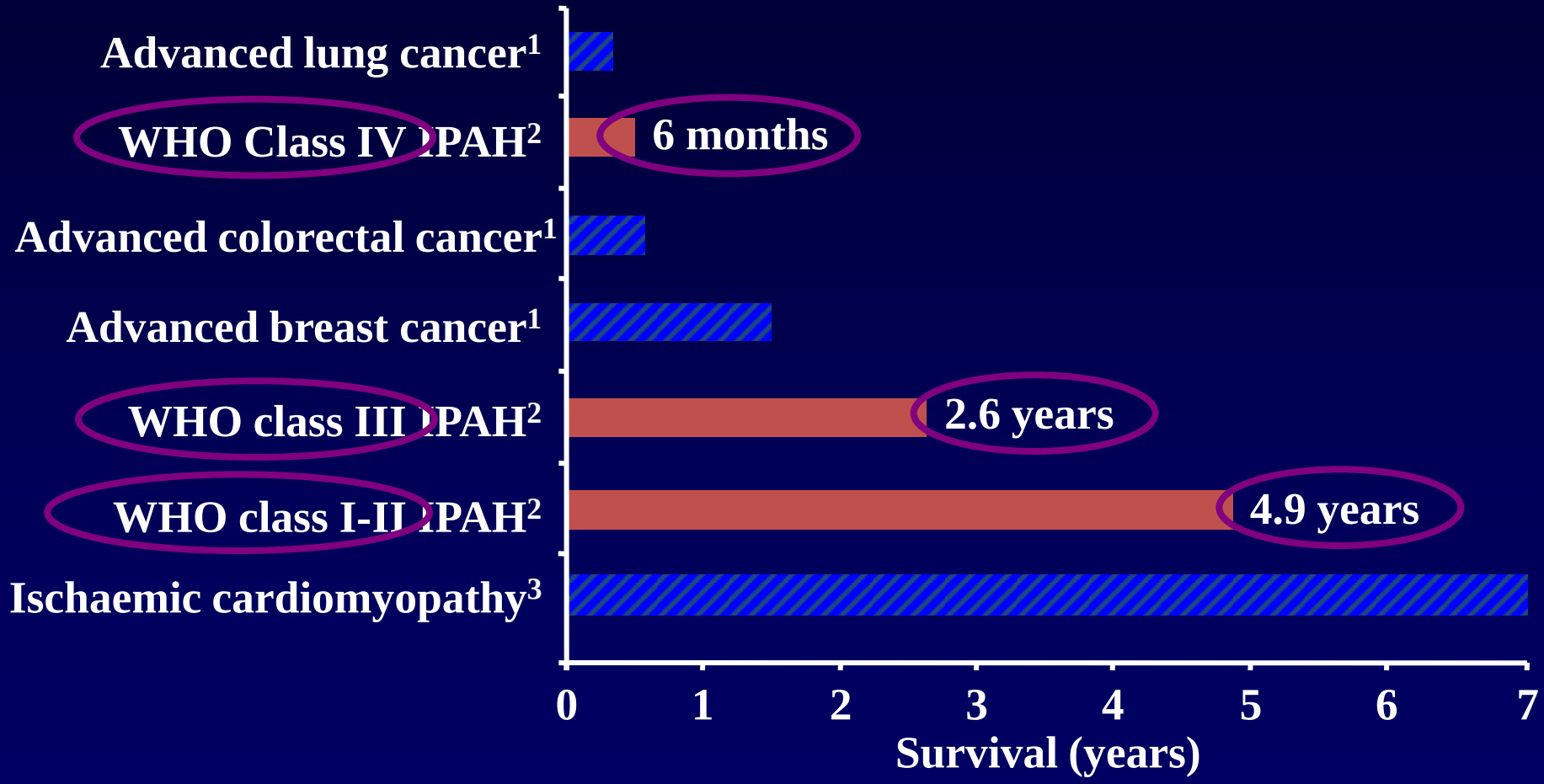
McLaughlin VV, *et al. Chest* 2004; 126:78S-91S.

Severity and classification of PAH
WHO functional classification

I	No limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea, fatigue, chest pain or near dyspnoea	ASYMPTOMATIC
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes dyspnoea, fatigue, chest pain or near syncope	MILDLY SYMPTOMATIC NON-SPECIFIC
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes dyspnoea, fatigue, chest pain or near syncope	SYMPTOMATIC SPECIFIC
IV	Inability to carry out any physical activity without symptoms. Signs of right-heart failure. Dyspnoea and fatigue may even be present at rest. Discomfort increased by any physical activity	

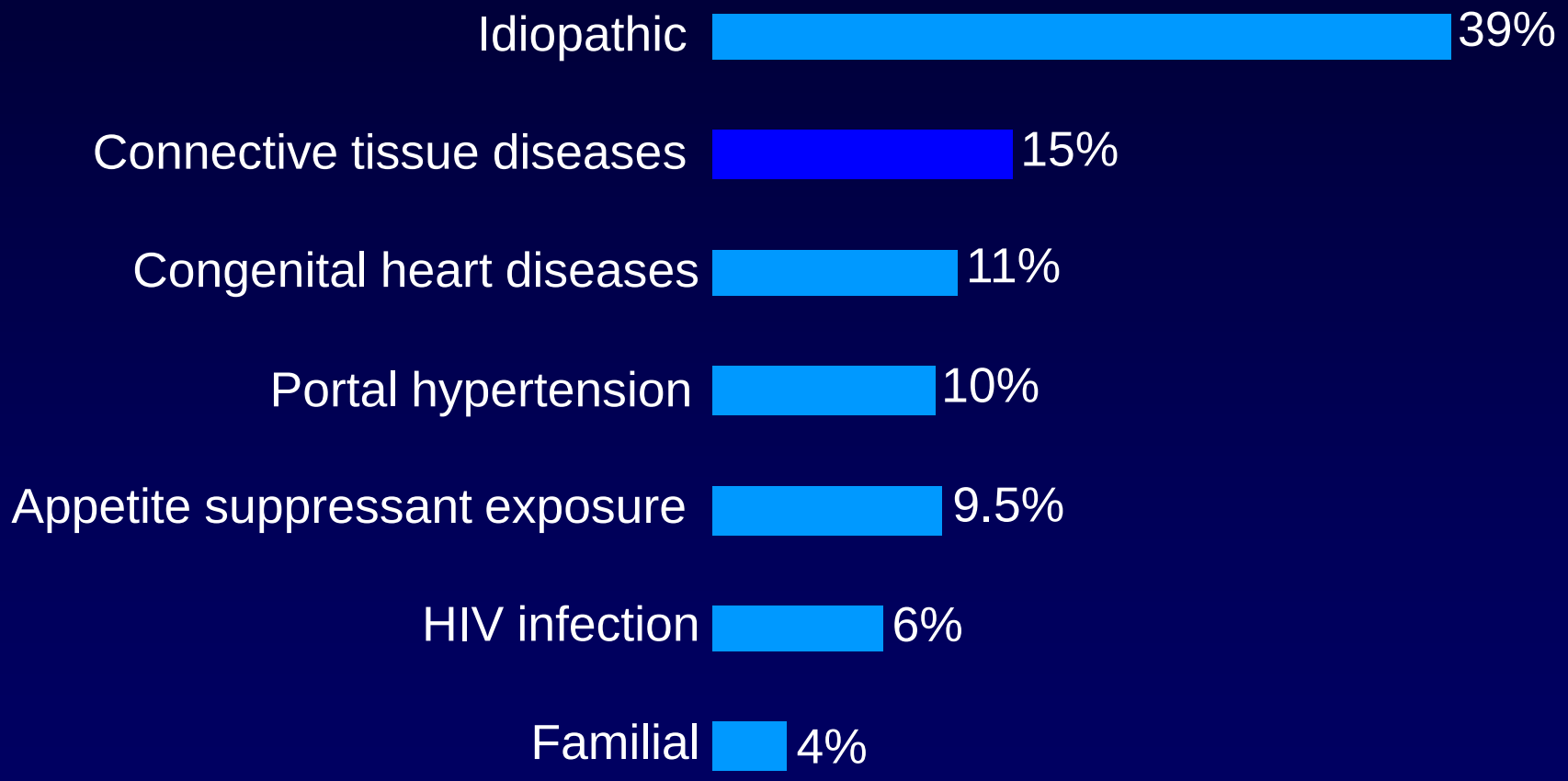
Galiè N, *et al. Eur Heart J* 2009; 30:2493-2357.

A small delay in diagnosis has a dramatic impact on prognosis



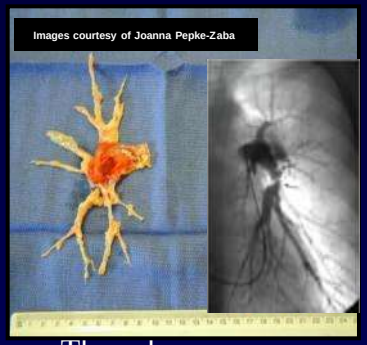
1. Kato I, *et al. Cancer* 2001; 92:2211-9.
2. D'Alonzo GE, *et al. Ann Intern Med* 1991; 115:343-9.
3. Felker GM, *et al. N Engl J Med* 2000; 342:1077-84.

FRENCH REGISTRY: CTD and CHD ARE THE LEADING CONDITIONS ASSOCIATED WITH PAH



2 RISK FACTORS 4%

Humbert M, *et al. AJRCMM* 2006; 173:1023–30.



Thrombo-
Endo-
Arterectomy

Lung Transplantation

PH and CTD
treatment, aggressive

PH and HIV treatment, effective

Symptoms / signs / history suggestive of PH

Non invasive assessment compatible with PH?

Search for Other causes And/or Re-check

No

Yes

Consider common causes of PAH

Group 2
Left heart disease?

History, Symptoms, Signs ECG, Chest X Ray TTE,PHT,HRCT

Group 3
Lung diseases and/or hypoxia

Group 2 or 3: diagnosis confirmed

Yes
PH 'proportionate' to severity

No

Yes 'out of proportion' PH

Treat underlying disease & check for progression

Perform V/Q scan

Continue'd

Segmental perfusion defects

Search for other causes

Consider Group 4 CTEPH

No

No

Yes

Consider other uncommon causes

Consider PVOD/PCH

Perform RHC (PAH probability)

mPAP ≥ 25 mmHg
PWP ≤ 15 mmHg

Yes

Specific tests

PVOD PCH

Clinical signs HRCT,ANA

History

Physical Laboratory Analysis

Schisttosomiasis Other group 5

CDT

HIV test

Physical US, LFT

TTE, TEE, CMR

Chronic Haemolysis

Drugs Toxins

HIV

CHD

Porto Pulmonary

Idiopathic or heritable PAH

BMPR2, ALK1, Endoglin (HHT) Family history

Pulmonary Arterial Hypertension (group 1)

Symptoms, Risk factors, Associated conditions

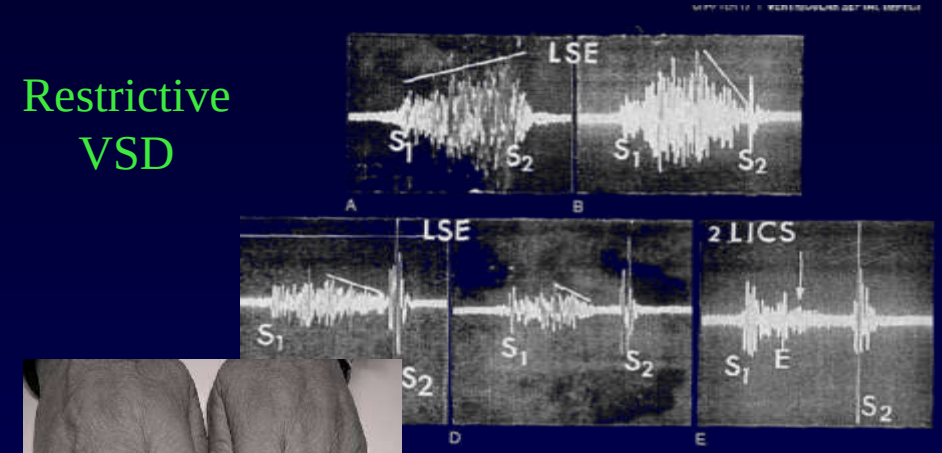
Symptoms	Risk factors	Associated conditions
Dyspnea **Fatigue** **Syncope** ...	**Definite** Aminorex Fenfluramine Dexfenfluramine Toxic rapessed oil Benfluorex **Likely** Amphetamines L-tryptophan Methamphetamines	**Drugs and toxins induced associated with (APAH)** – Connective tissue dis. – HIV infection – Portal hypertension – Congenital heart dis. – Schistosomiasis – Chronic haemolytic anaemia

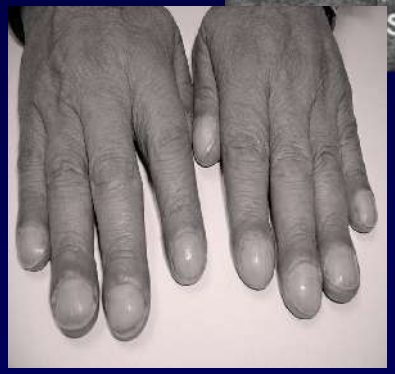
European Heart Journal 2009;30:2493-2537

Examination

- **Peripheral oedema, JVP**
- **Right ventricular heave**
- **Accentuated P2**
- **Abdominal tenderness**

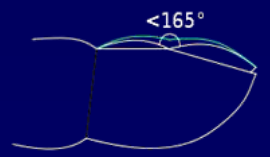
Restrictive VSD





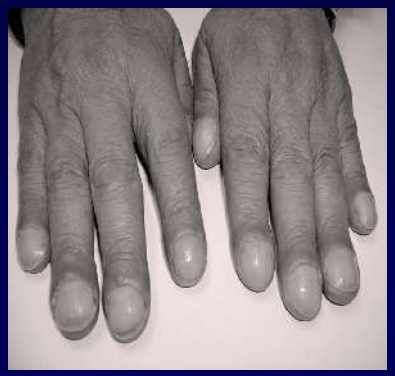
Eisenmenger

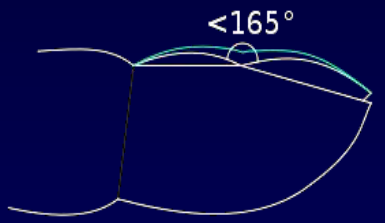
- Central cyanosis
- Clubbing
- **Murmurs: valvar regurgitation (tricuspid or pulmonary)**
- NO MURMUR DUE TO SHUNT.
- Relating to underlying CHD



cuticle/nail angle

Thrombocytopenia-clubbing: Megakaryocytes

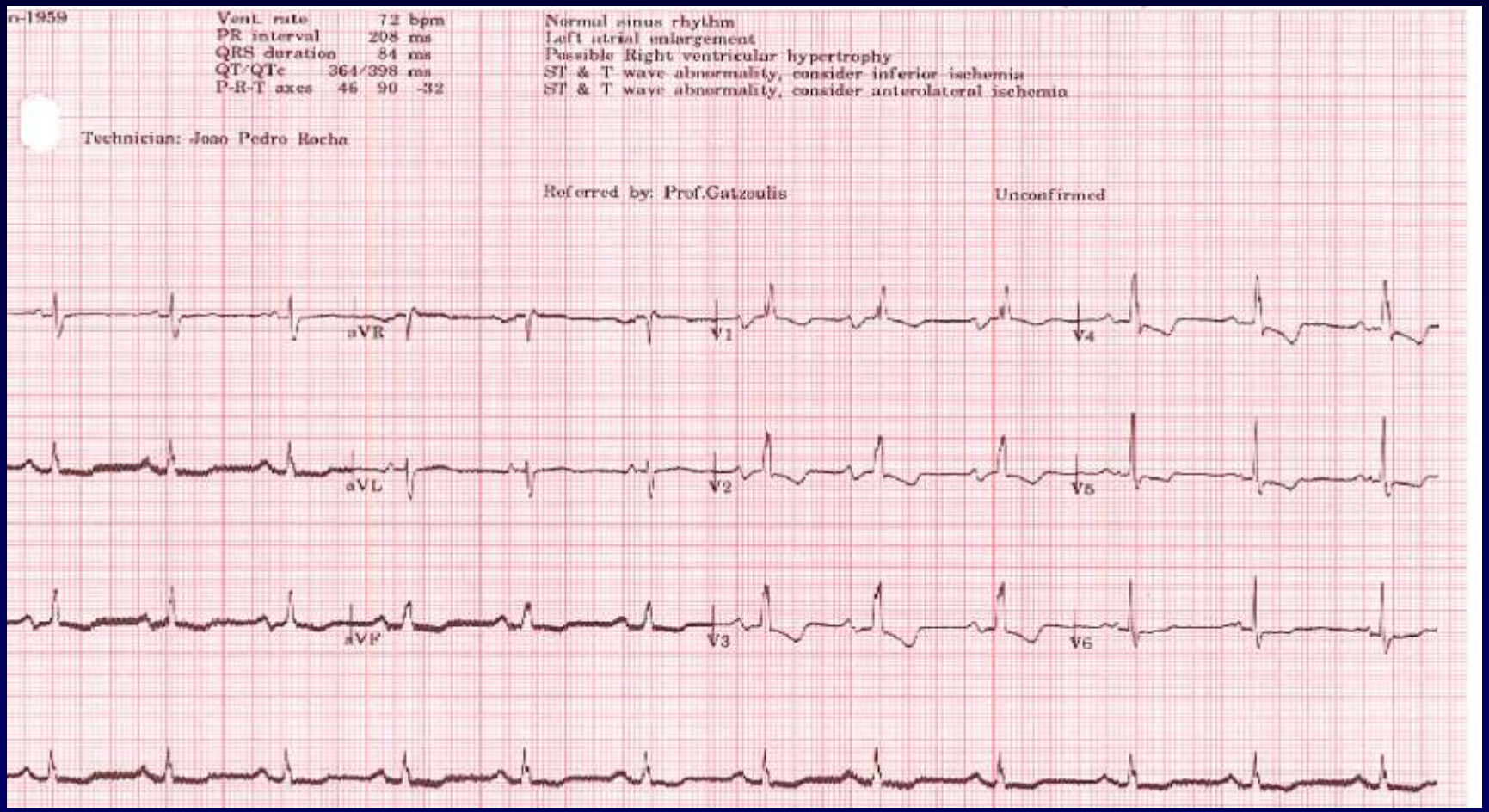




cuticle/nail angle

plt-derived growth factor and transforming growth factor beta enhance cell proliferation, connective tissue formation and deposition

Investigations

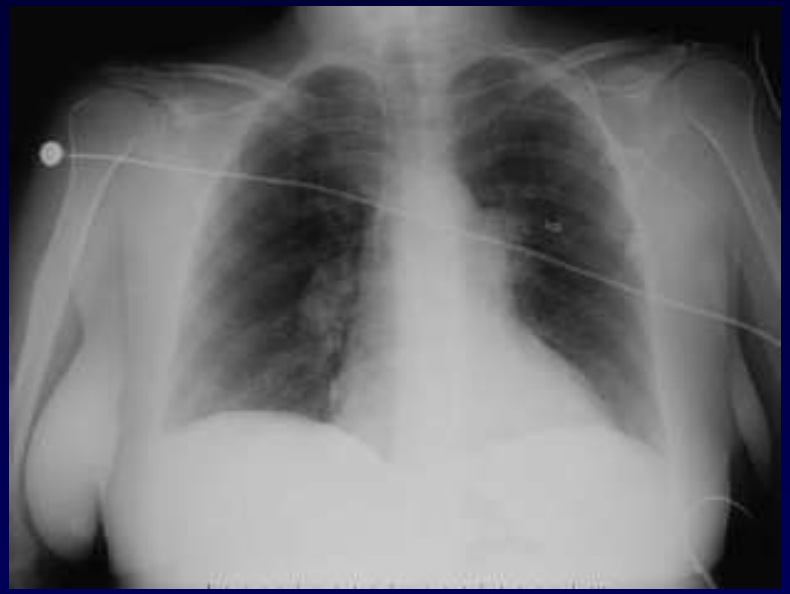


Back to RCT slide

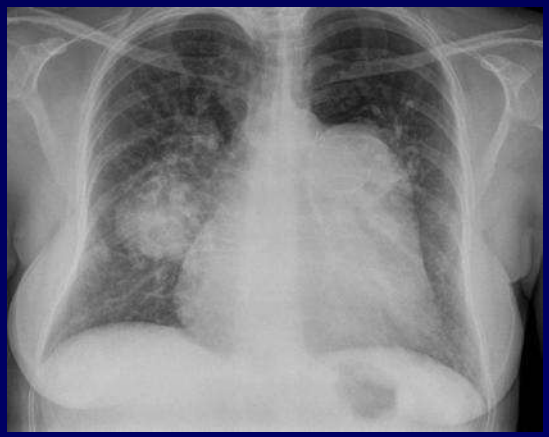
Diagnosis of PAH – initial investigations

Chest x-ray

- Can be first clue to presence of PAH[1]
- Signs include:
  - enlarged main and hilar pulmonary arterial shadows (>17mm)
  - attenuation of peripheral pulmonary vascular markings (pruning)[2]
- Can also reveal presence of comorbid or causal conditions (pulmonary venous congestion, COPD, interstitial lung disease)[2]



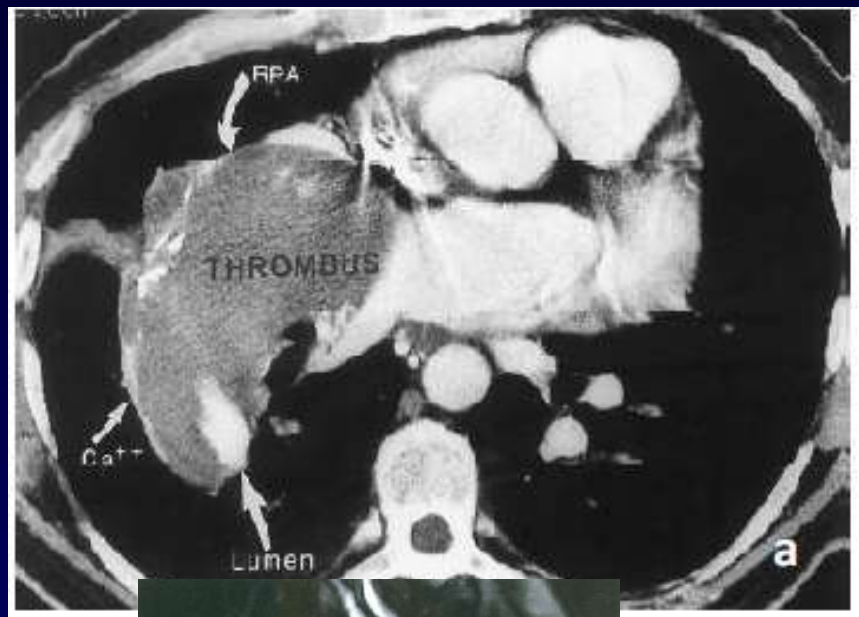
Chest radiograph of a patient with pulmonary arterial hypertension. The pulmonary arteries are enlarged and there is "pruning" of the vessels peripherally[3]

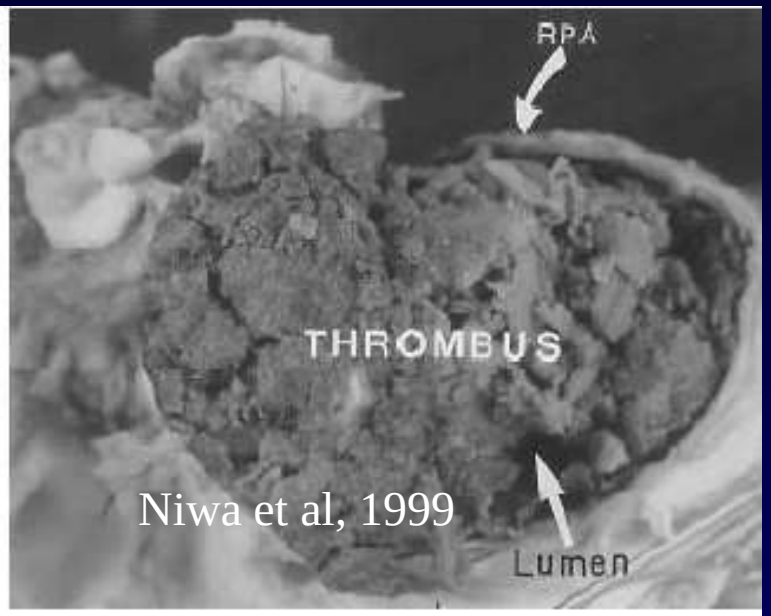


Eisenmenger PDA

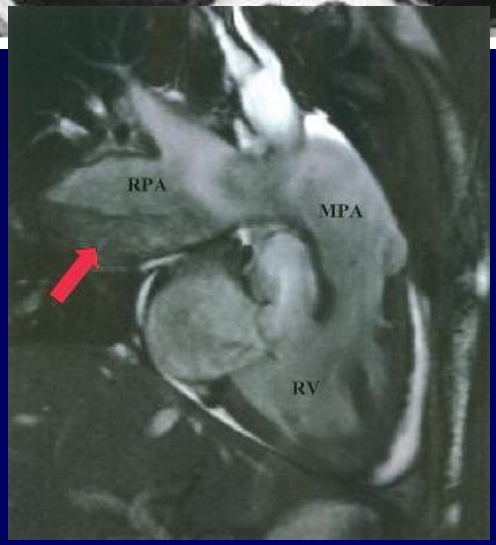
1. McLaughlin V and McGoon, M. *Circulation* 2006; 114:1417-31.
2. Rubin et al. *Ann Intern Med* 2005; 143:282-92.
3. Levine DJ. *Respir Care* 2006; 51:368–81.

Thrombosis





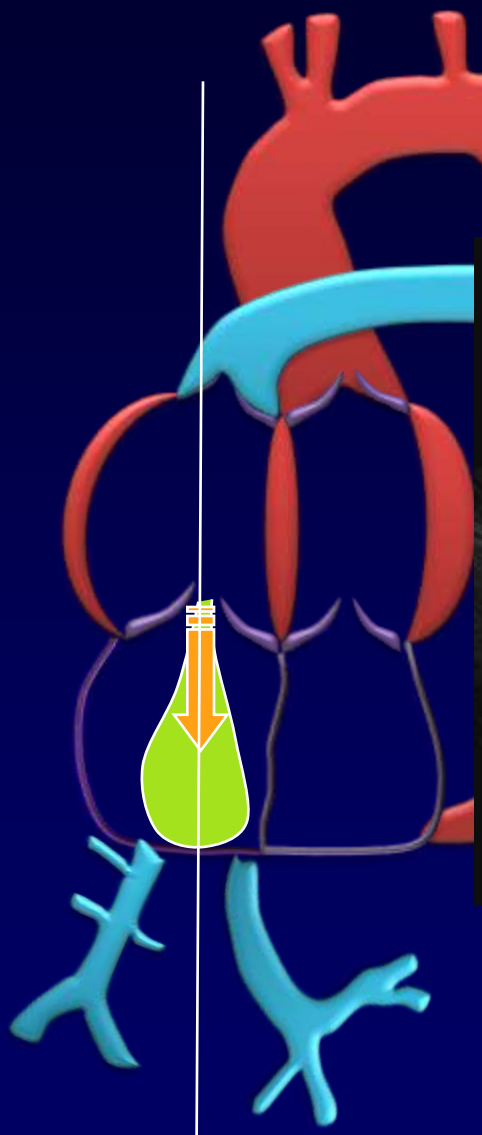
Niwa et al, 1999

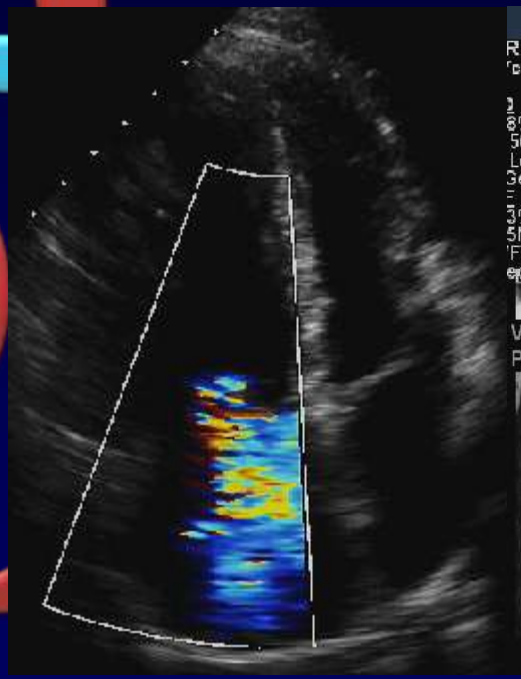


Broberg CS et al, JACC 2007

PAPsyst=TRgradient+JVP

PAPsyst=$4V^2$+JVP





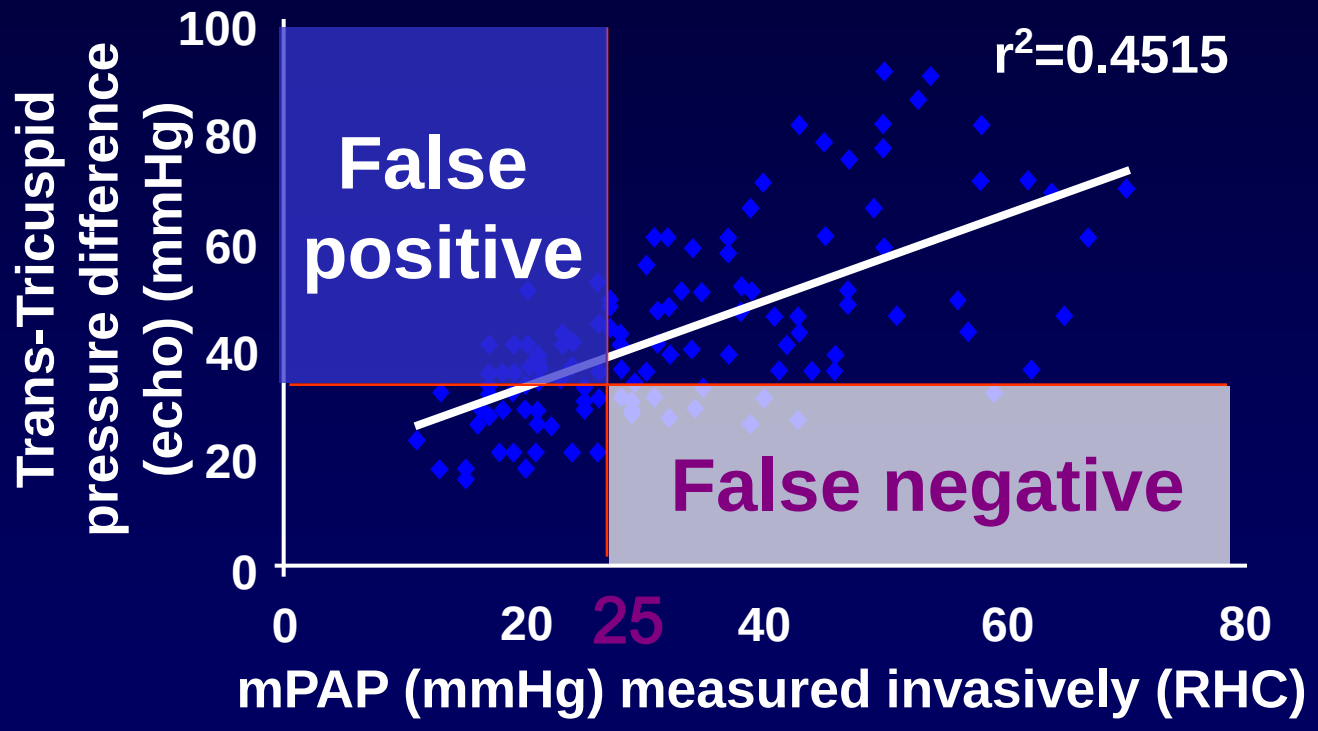
TR Velocity	PAPsystolic
3	36+JVP
4	64+JVP
5	100+JVP

Additional echocardiographic variables

- Increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA
- **Increased dimensions of right heart chambers**, abnormal shape and function of the interventricular septum
- Increased RV wall thickness, and **dilated main PA** are also suggestive of PH, but tend to occur later in the course of the disease
- Their sensitivity is questionable

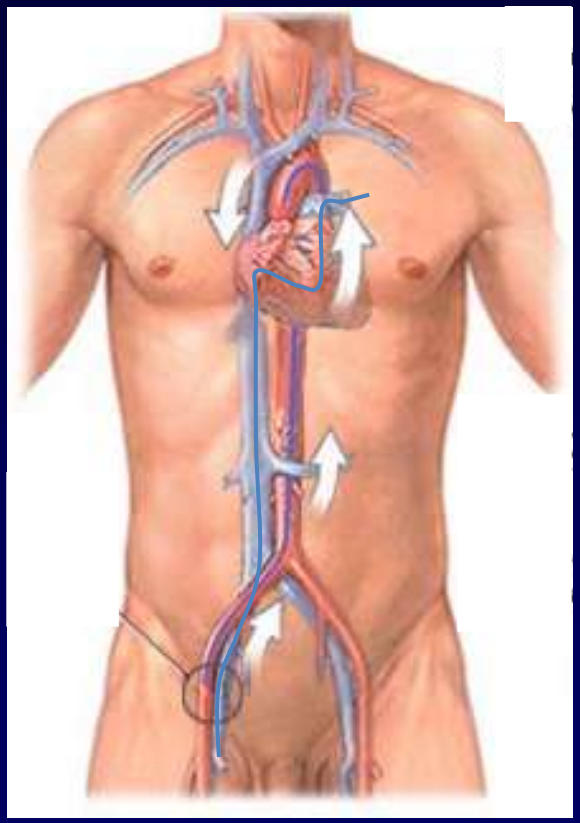
Galiè N, *et al. Eur Heart J* 2009; 30:2493-2357.

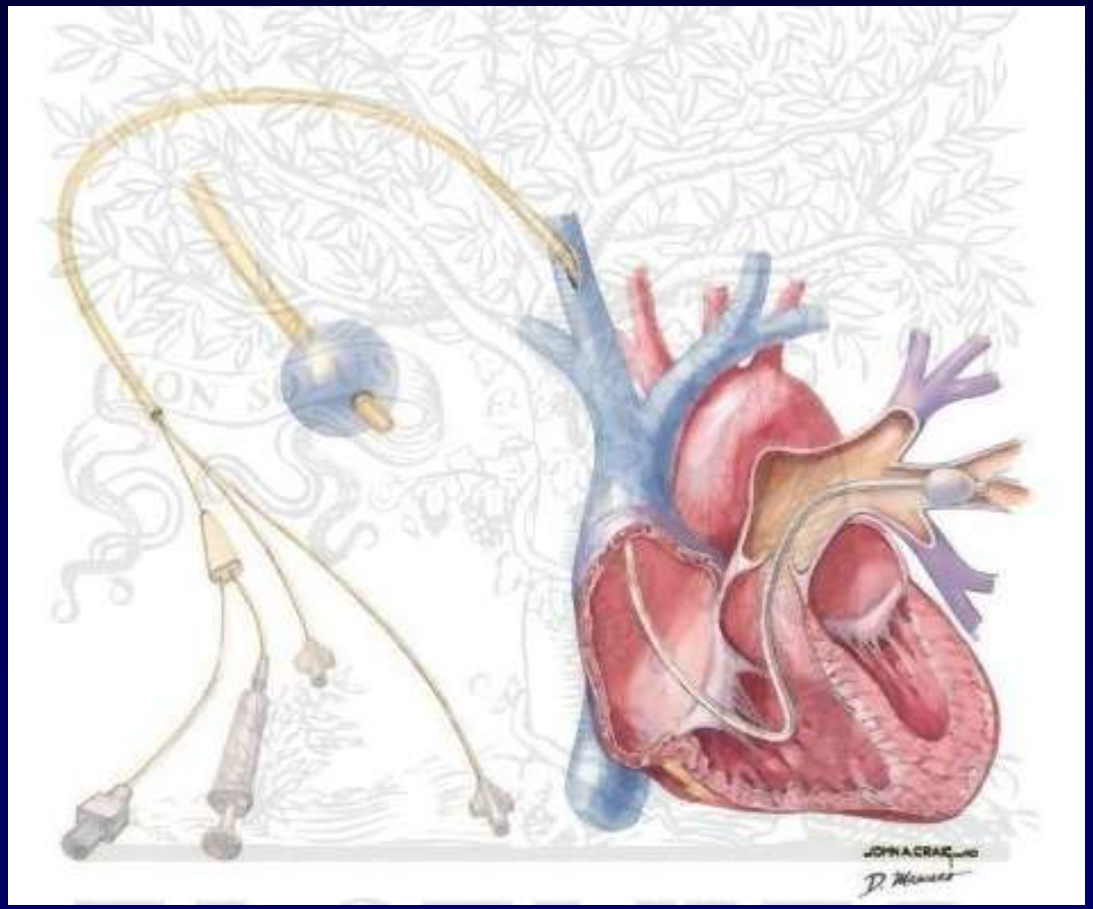
RHC is the only way to make a definitive diagnosis of PAH



1. Gibbs JSR. *Eur Respir Rev* 2007; 16:8-12.
2. Mukerjee D, *et al. Rheumatology* 2004;43:461-6.

Right heart cath





Parameters with established importance for assessing disease severity, stability and prognosis in PAK

Better prognosis	Determinants of Prognosis	Worse Prognosis
No	Clinical evidence of RV failure	Yes
Slow	Rate of progression of symptoms	Rapid
No	Syncope	Yes
I, II	WHO-FC	IV
Longer (> 500 m)*	6 MWT	Shorter (< 300 m)
Peak O_2 Consumption > 15 ml/min/kg	Cardio-pulmonary exercise testing	Peak O_2 consumption < 12 ml/min/kg
Better Prognosis	BNP/NT-proBNP plasma levels	Very elevated and rising
No pericardial effusion TAPSE > 2.0 cm	Echocardiographic findings†	Pericardial effusion TAPSE < 1.5 cm
Right atrial pressure < 8 mmHg and CI $\geq$ 2.5 L/min/m^2	Haemodynamics	RAP > 15 mmHg or CI $\leq$ 2.0 L/min/m^2

European Heart Journal 2009;30:2493-2537

Evidence based treatment algorithm for PA patients
(Group 1 only)

Avoid pregnancy (I-C)
Influenza and pneumococcal immunization (I-C)
Supervised rehabilitation (IIa-B)
Psycho-social support (IIa-C)
Avoid excessive physical activity (III-C)

General measures and supportive therapy

Expert Referra (I-C)

Acute vasoreactivity test
(I-C for IPAH) (Iib-C for APAH)

Diuretics (I-C)
Oxygen* (I-C)
Oral anticoagulants:
- IPAH, heritable PAH and PAHdue to anorexigens (IIa-C)
- APAH (IIb-C)

Digoxin (IIb-C)

VASOREACTIVE

NON VASOREACTIVE

WHO-FC I-III
CCB (I-C)

Sustained response
(WHO-FC I-III)

YES

NO

Continue CCB

INITIAL THERAPY

Recommendation-Evidence	WHO-FC II	WHO-FC III	WHO-FC IV
I-A	Ambrisentan, Bosentan, Sildenafil	Ambrisentan, Bosentan, Sildenafil Epoprostenol i.v., Iloprost inhaled	Epoprostenol i.v.
I-B	Tadalafil †	Tadalafil † Treprostinil s.c., inhaled †	
IIa-C		Iloprost i.v., Teprostinil i.v.	Ambrisentan, Bosentan, , Sildenafil, Tadalafil †, Iloprost inhaled, and i.v. Treprostinil s.c., i.v., inhaled † Initial Combination Therapy
IIb-B		Beraprost	

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European Heart Journal 2009;30:2493-2537

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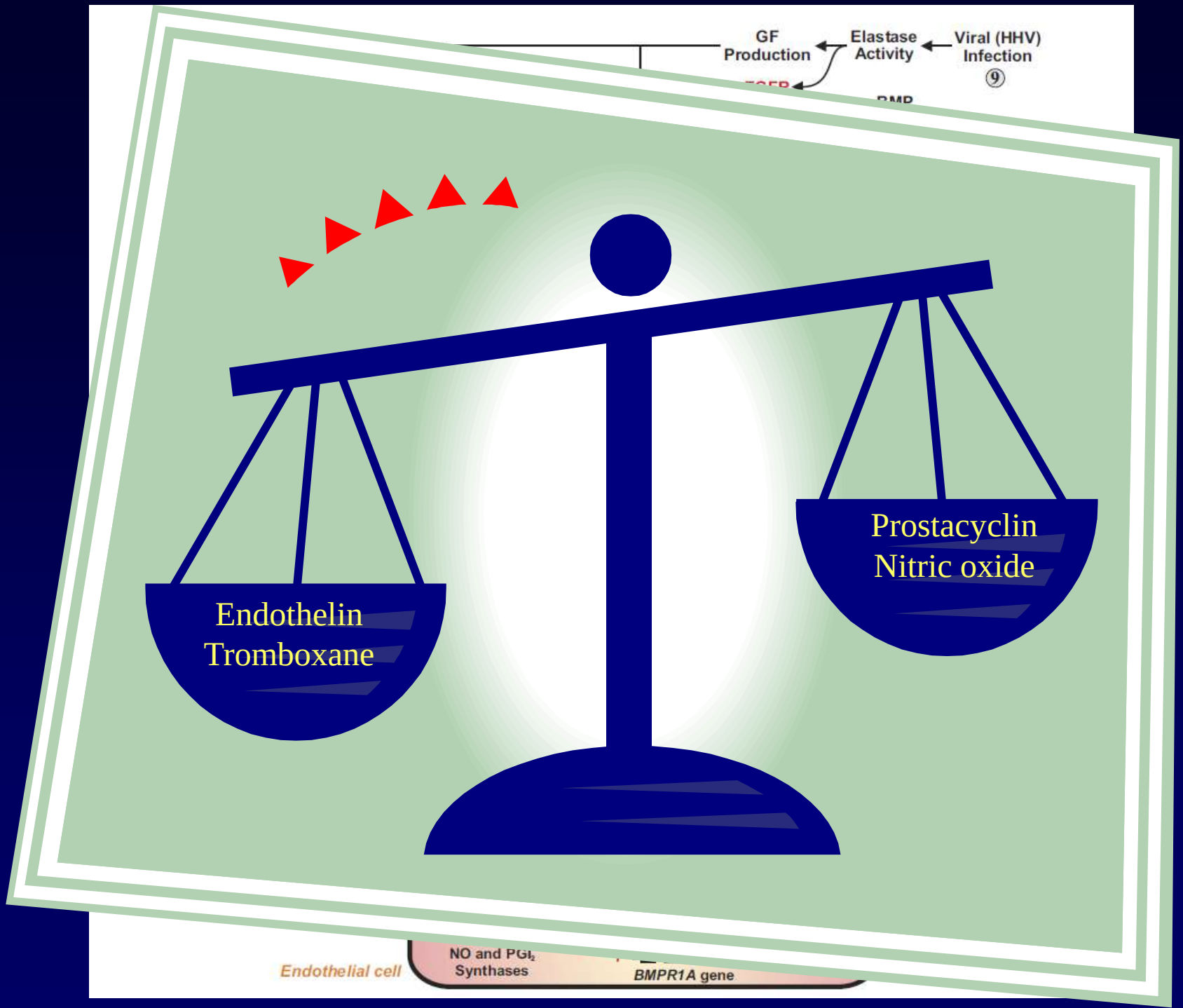
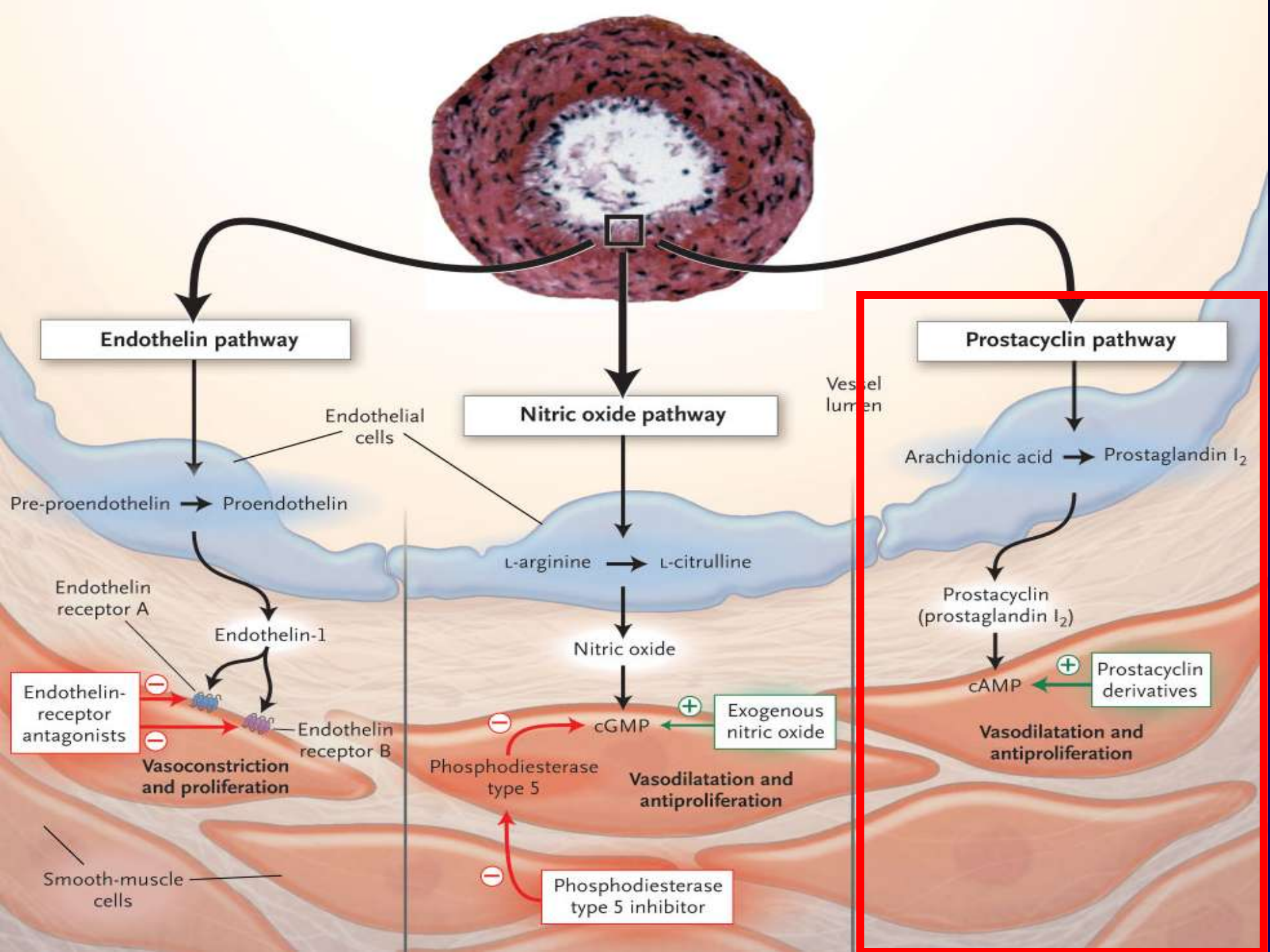
Management of PH:
Depends on type

- "Advanced" targeted therapies available for Class I patients only:

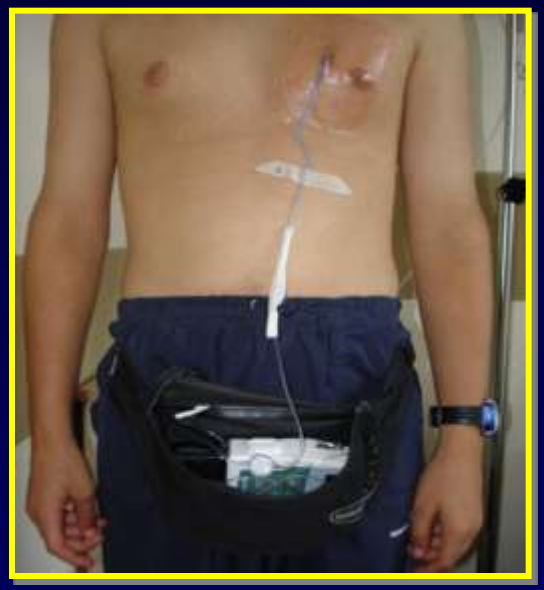
  Pulmonary ARTERIAL Hypertension


GF Production
Elastase Activity
Viral (HHV) Infection
⑨
Endothelin
Tromboxane
Prostacyclin
Nitric oxide
Endothelial cell
NO and PGI2 Synthases
BMPR1A gene


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Endothelial cells
Vessel lumen
Pre-proendothelin
Proendothelin
L-arginine
L-citrulline
Arachidonic acid
Prostaglandin I2
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I2)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Prostacyclin in PAH

Epoprostenol

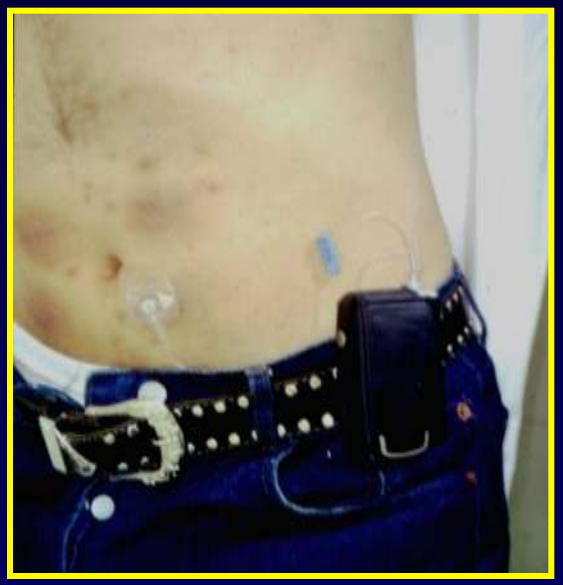


Only I.V.

Need permanent cath

Cath infections

Treprostinil



S.C. or I.V.

Local pain

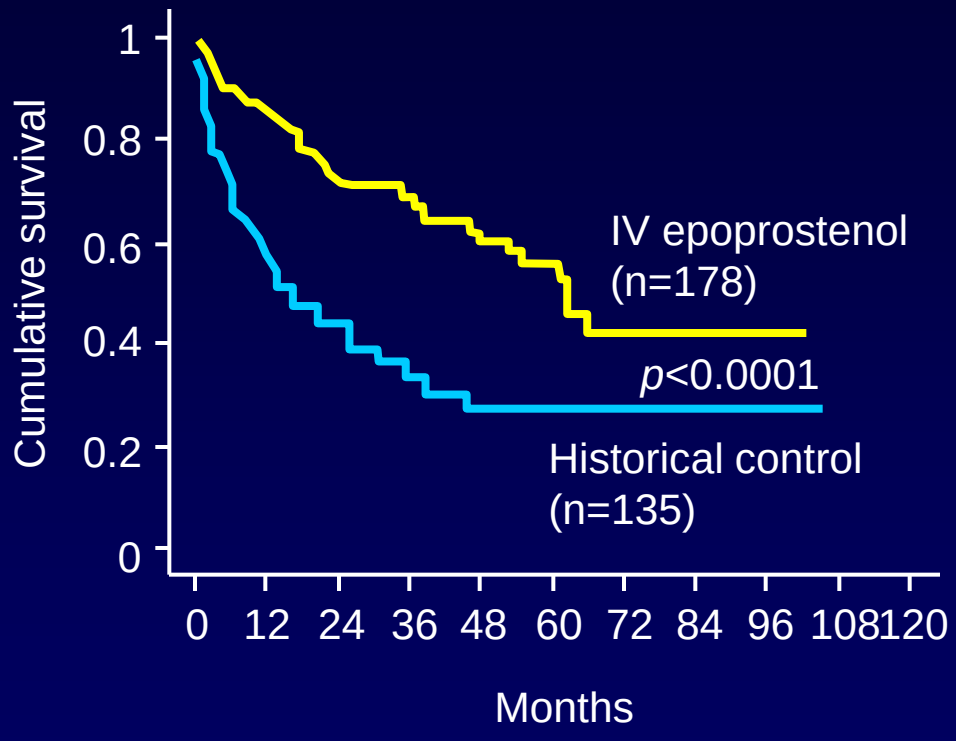
Iloprost

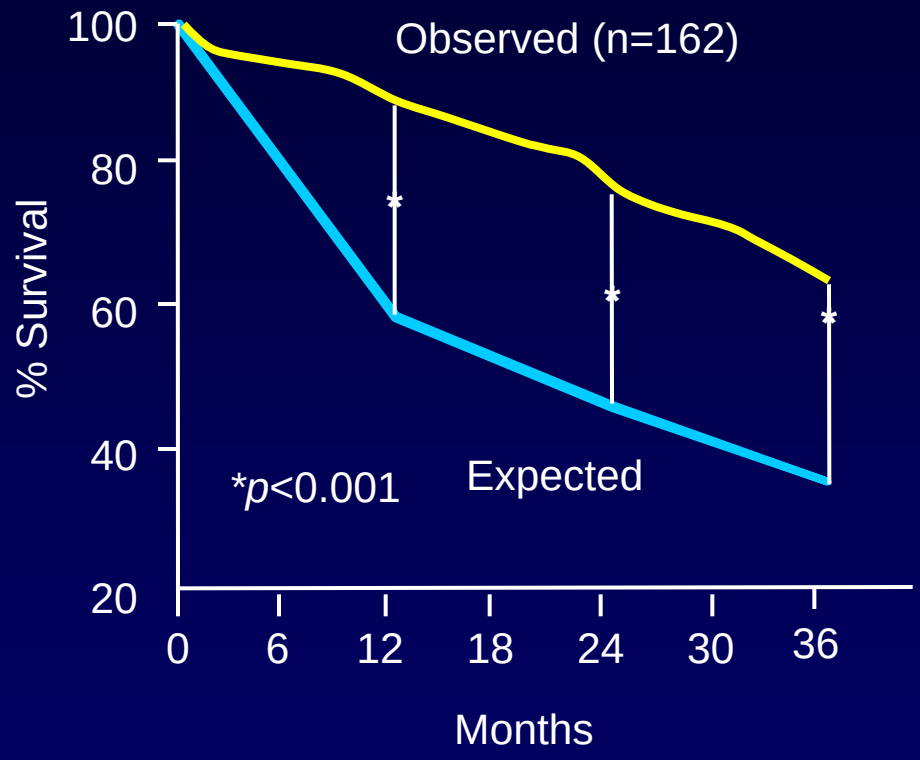
Inhale

6 to 12 times a day

Long term efficacy?

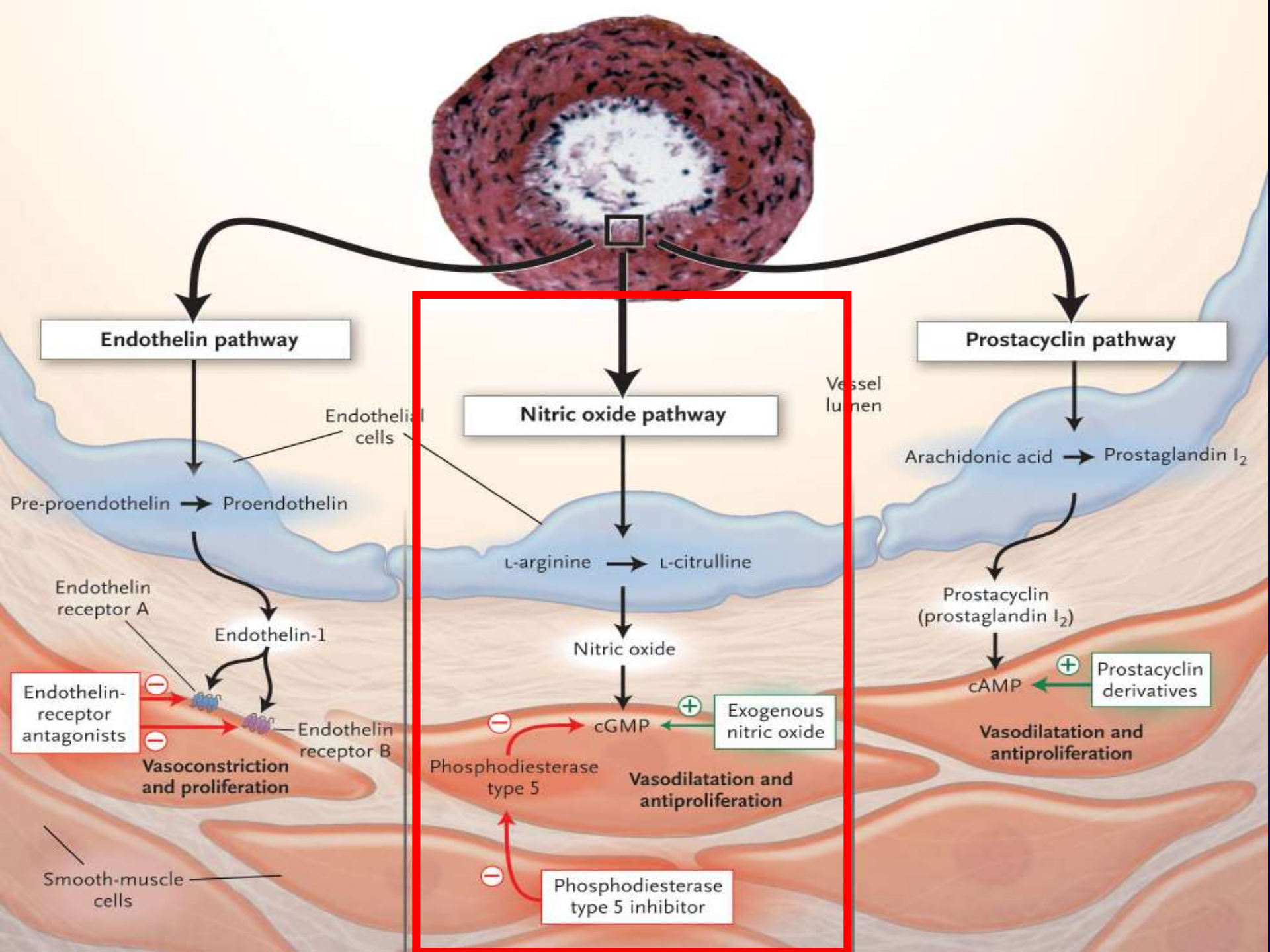
Prostacyclin in PAH





Sitbon O, et al. J Am Coll Cardiol. 2002; 40: 780-788

McLaughlin VV, et al. Circulation. 2002; 106: 1477-1482.


Endothelin pathway
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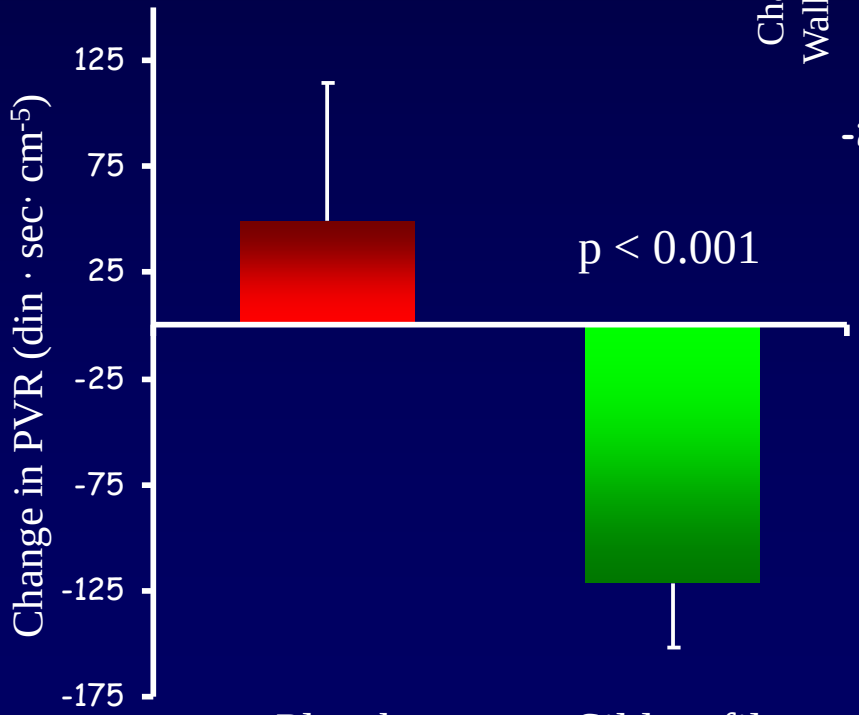
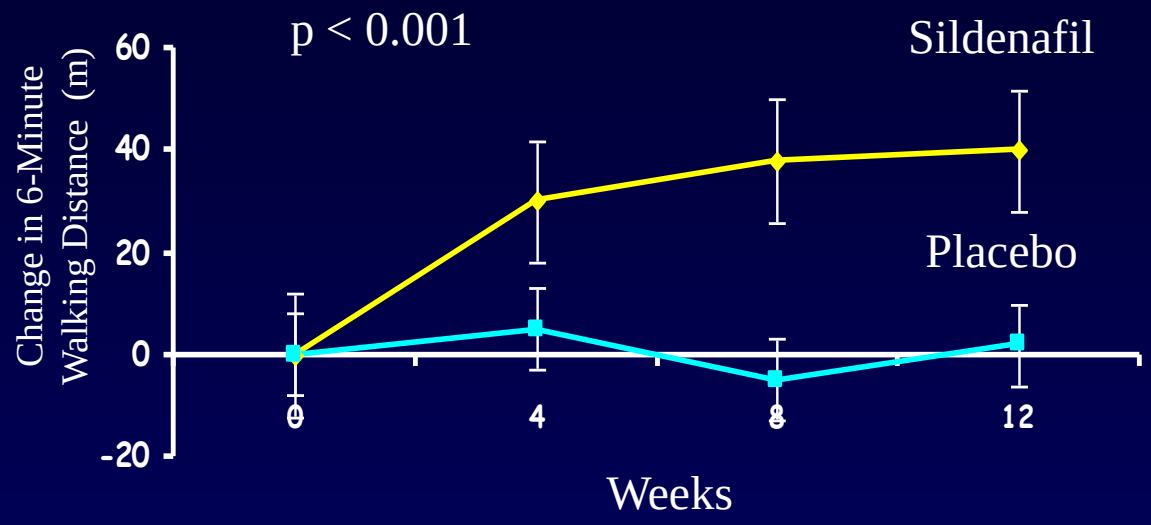
cAMP
Prostacyclin derivatives
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Vasodilatation and antiproliferation
Phosphodiesterase type 5 inhibitor
Smooth-muscle cells

PDE-5 inhibitors in PAH

Sildenafil

N=278 p



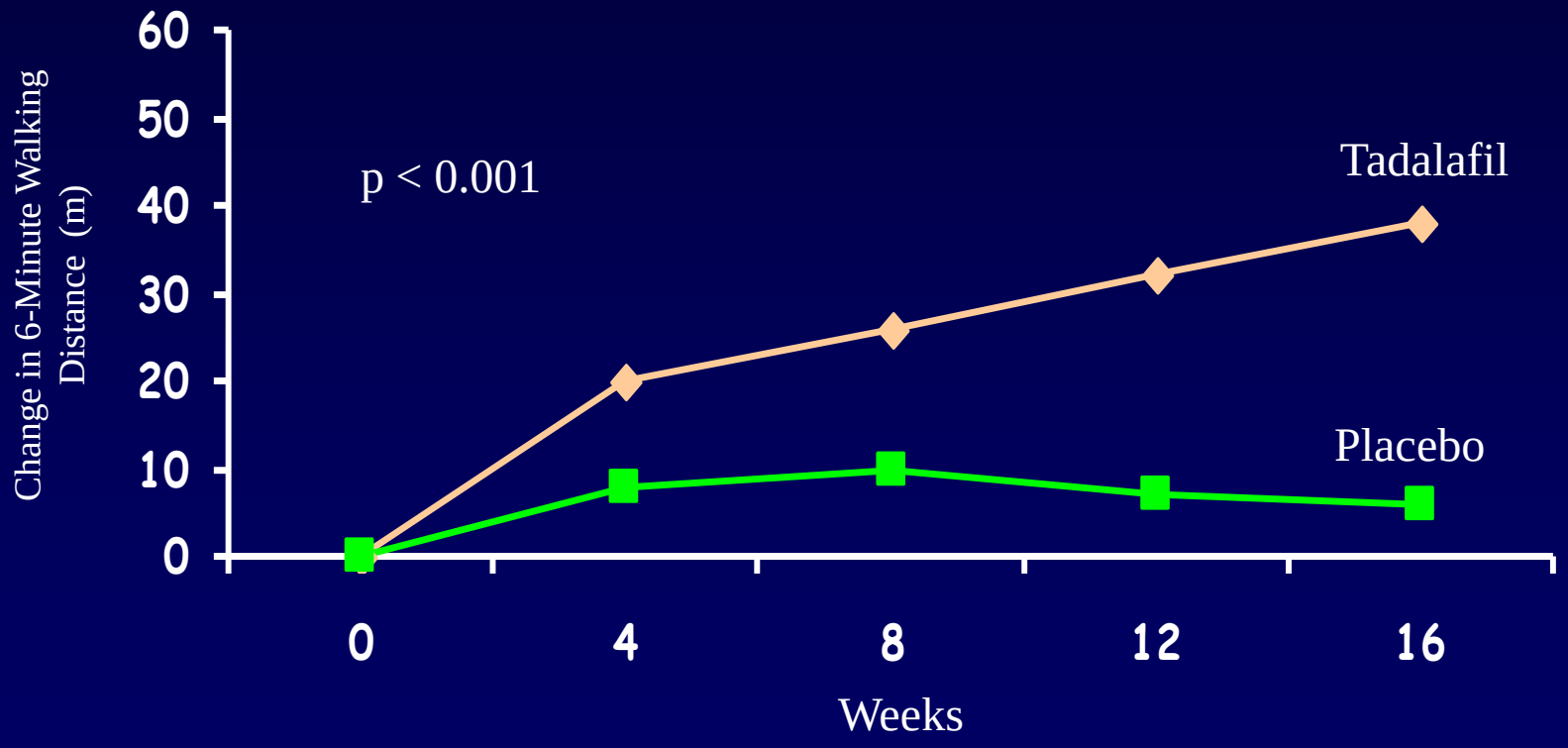


Galie N, et al. N Eng J Med 2005; 353: 2148-2157

PDE-5 inhibitors in PAH

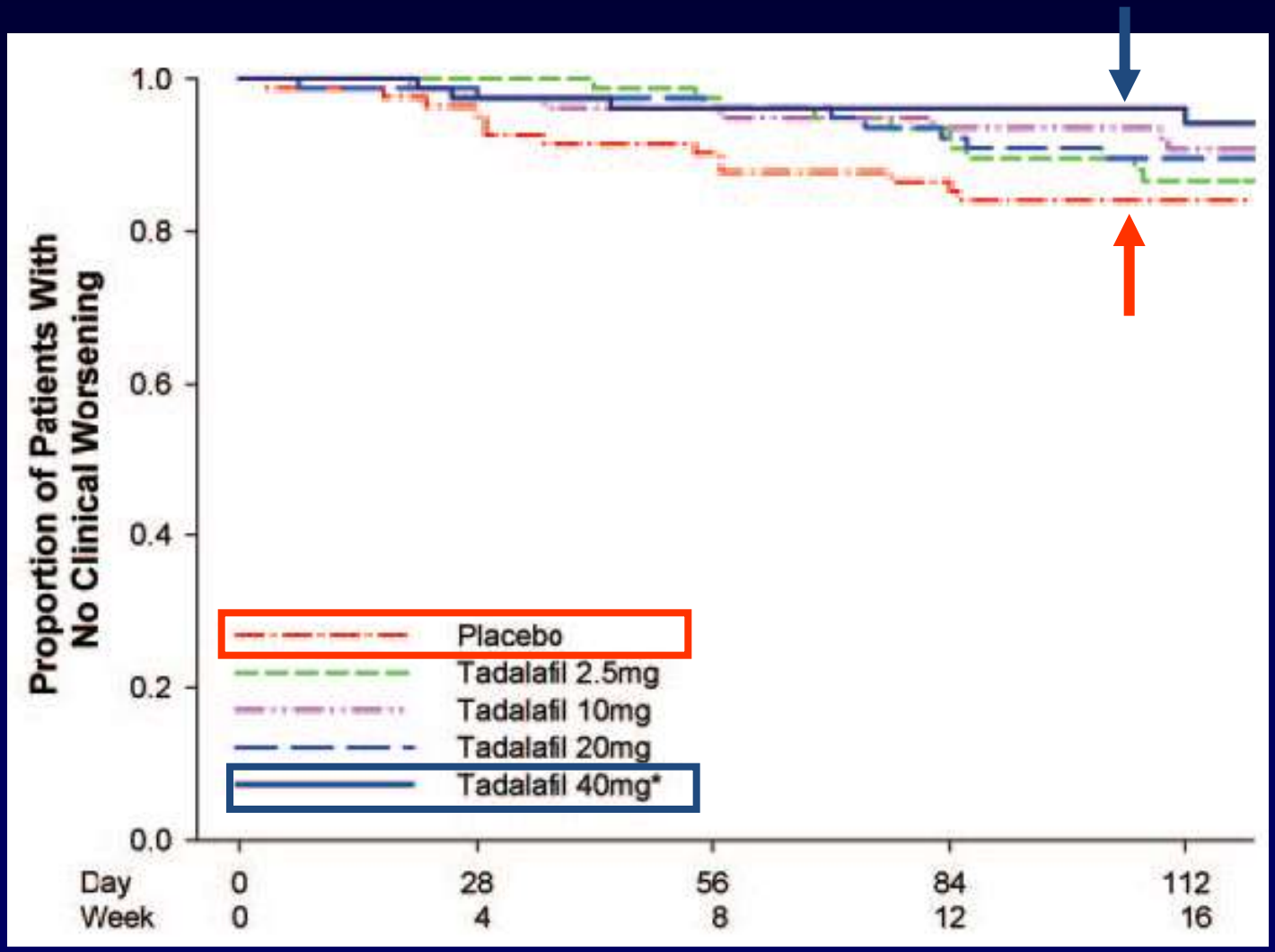
Tadalafil

N=405 p

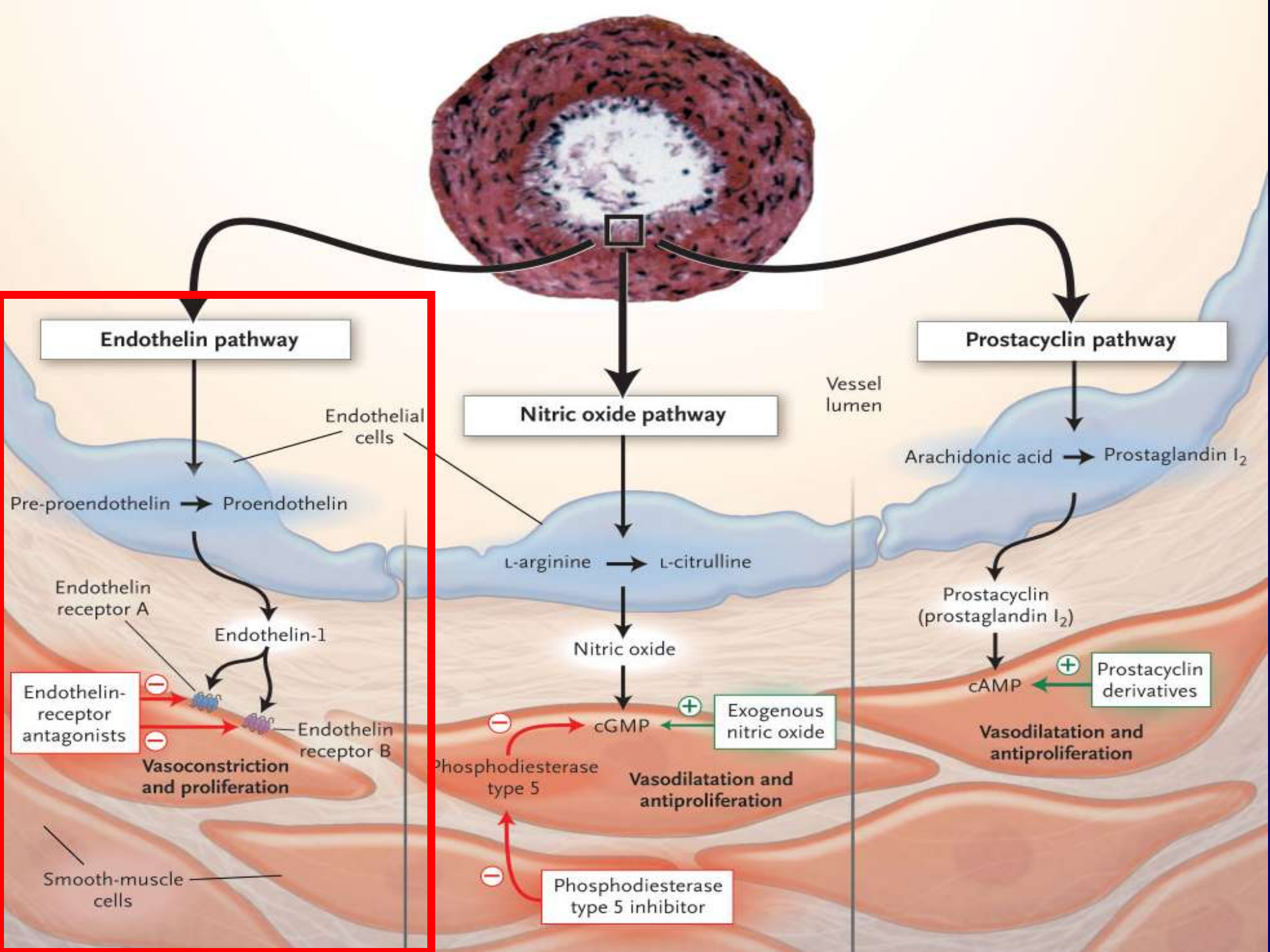


Galie N, et al. Circulation 2009; 119: 2894-2903

PDE-5 inhibitors in PAH



Galie N, et al. Circulation 2009; 119: 2894-2903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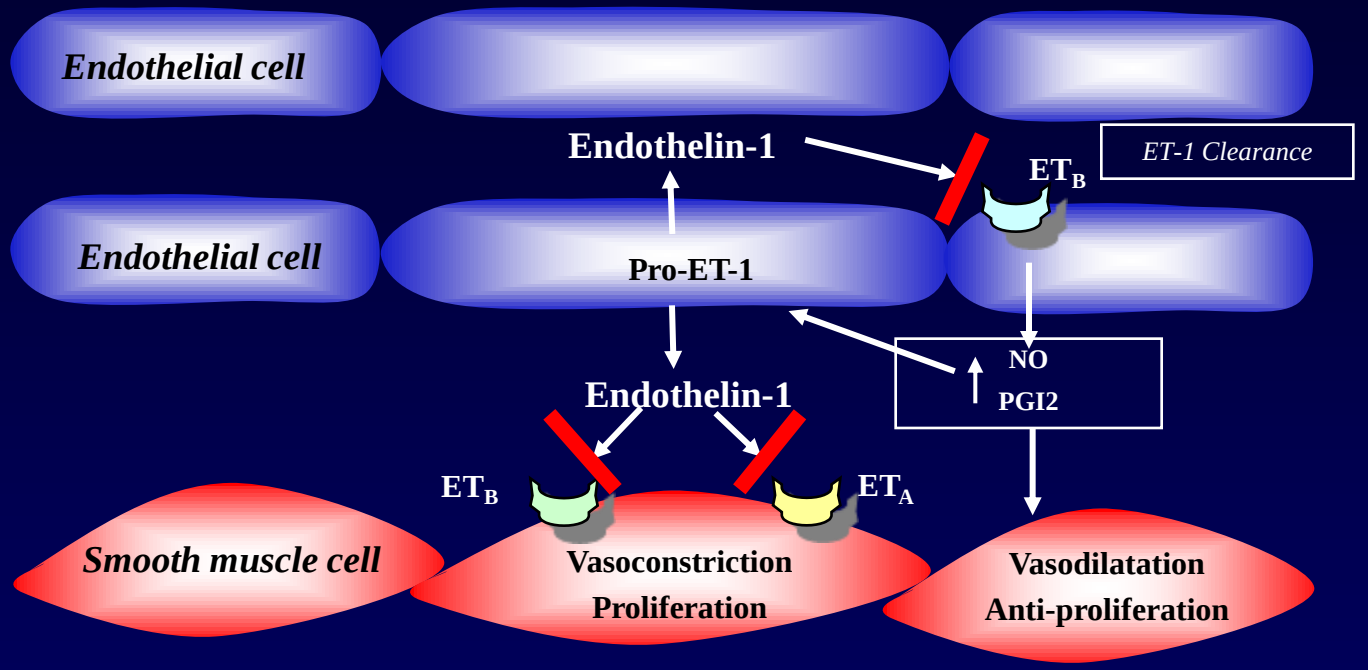
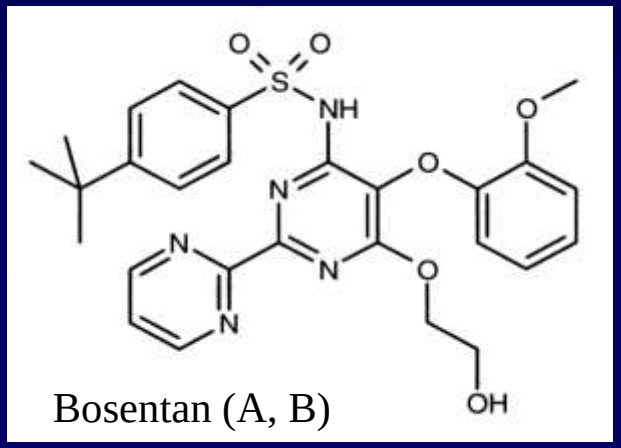
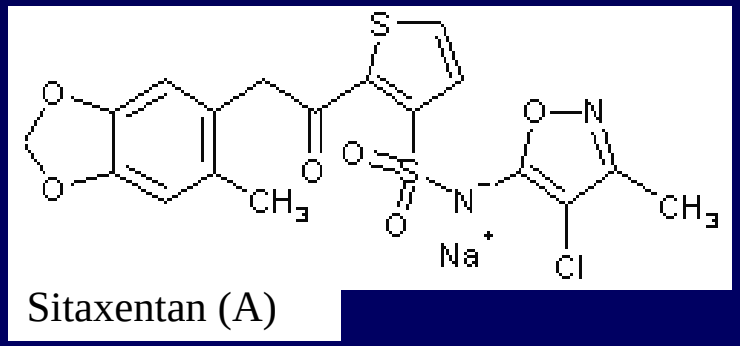
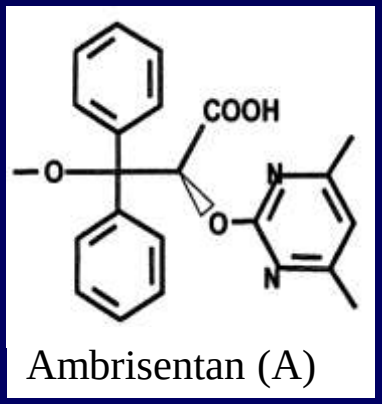
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

ERAs in PAH: Bosentan & Ambrisentan



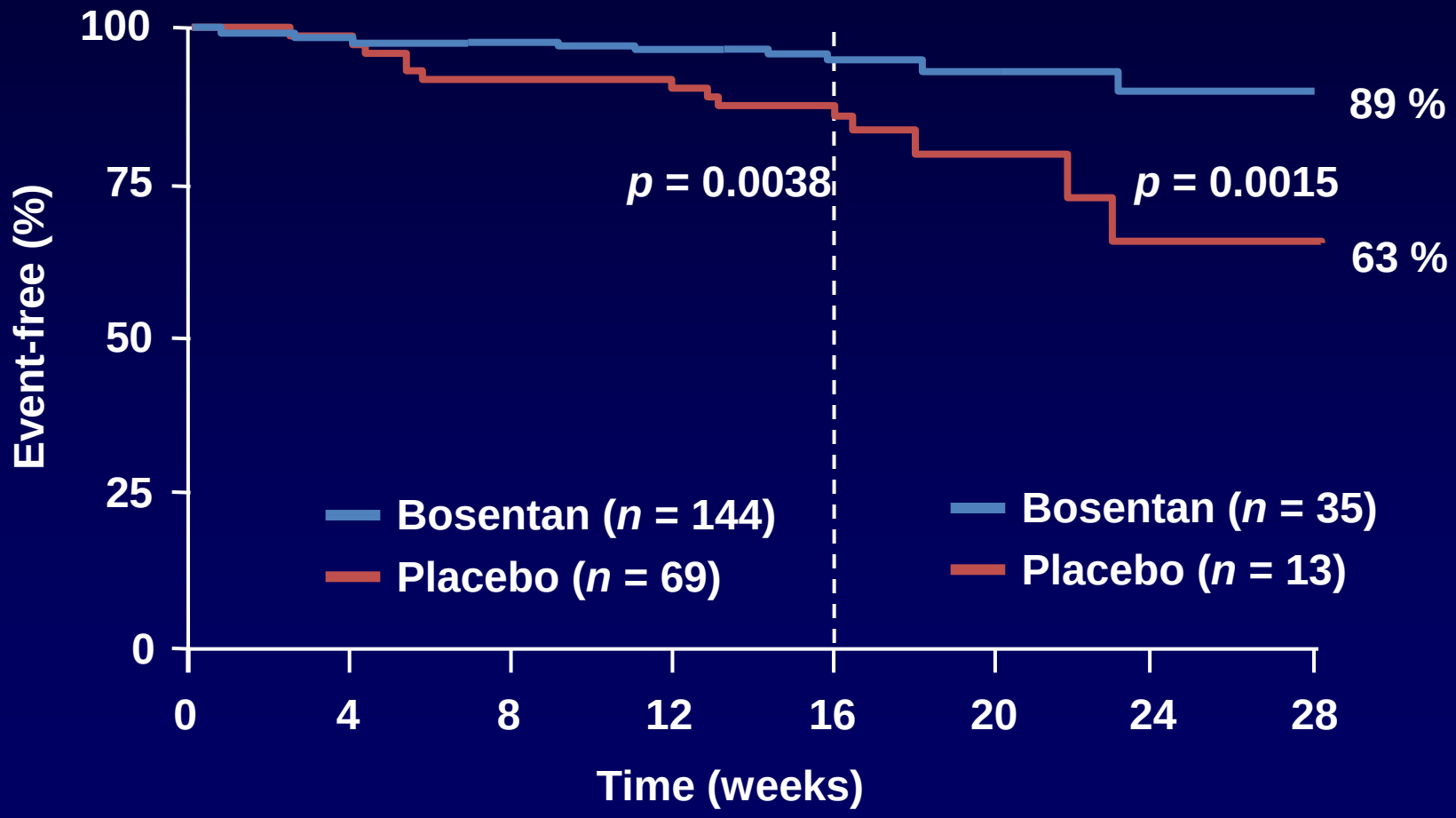






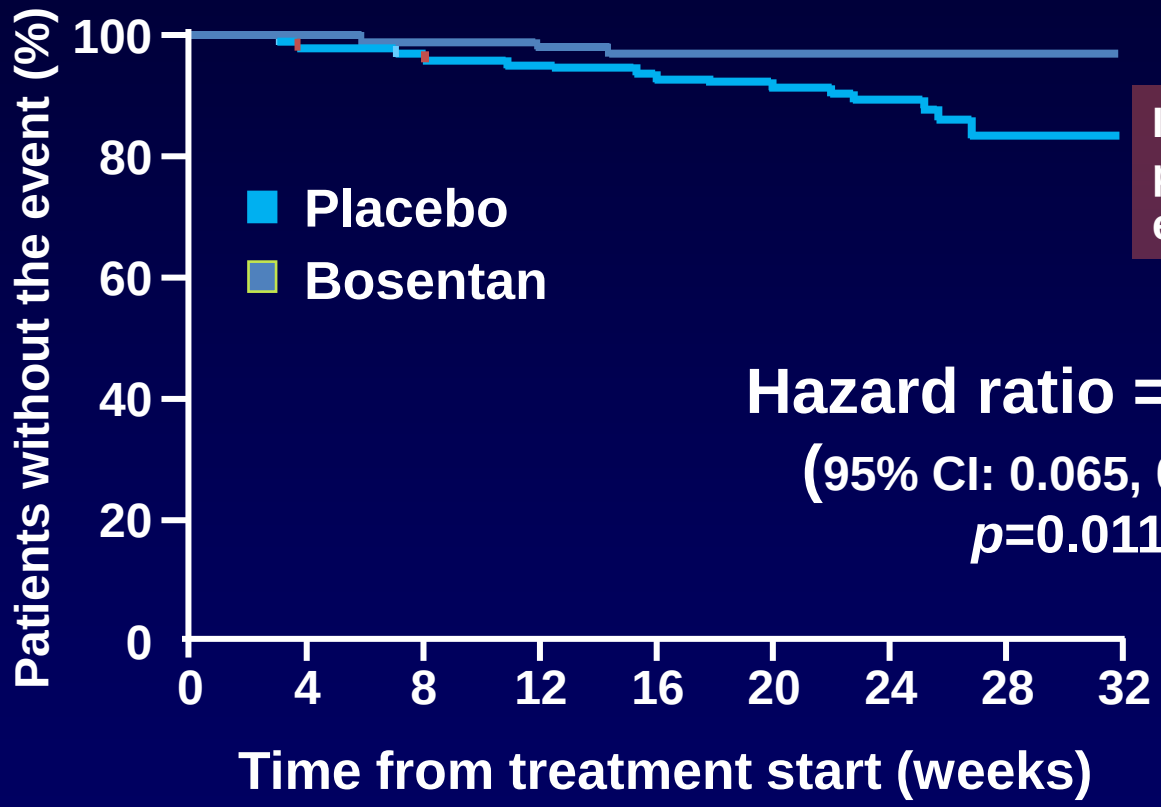
Courtesy of Dr. M. Humbert

BREATHE-1: Bosentan significantly improved TTCW up to 28 weeks



Adapted from Rubin L, *et al. NEJM* 2002; 346:896-903.

EARLY: Effect of bosentan on time to clinical worsening



In 6 months, 14% of FCII patients without treatment experienced clinical worsening

Hazard ratio = 0.227

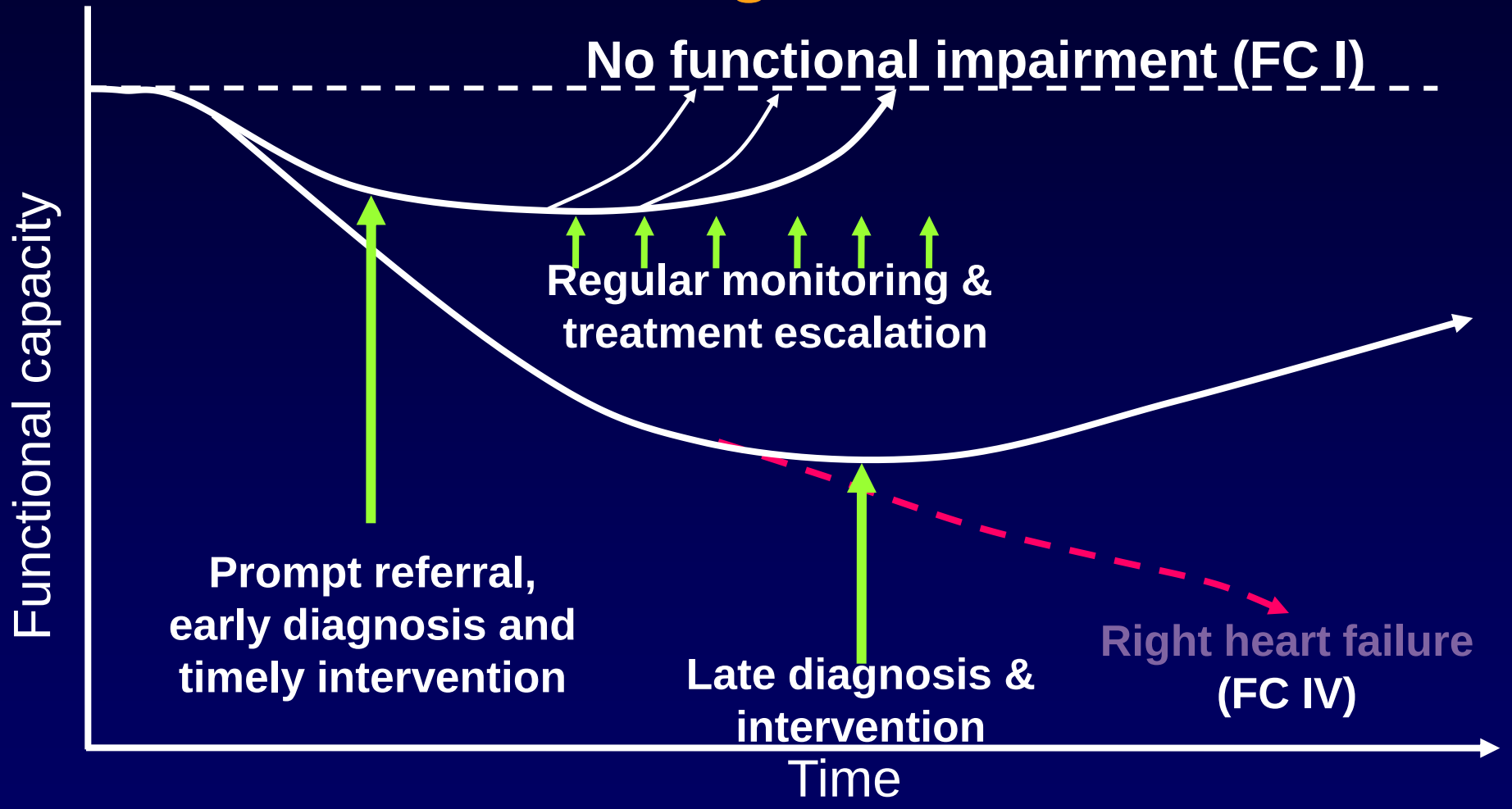
(95% CI: 0.065, 0.798)

p=0.0114

Patients at risk	92	90	89	86	84	83	77	18	9
	93	92	87	85	84	83	80	27	15

Galiè N, *et al. Lancet* 2008; 371:2093-100.

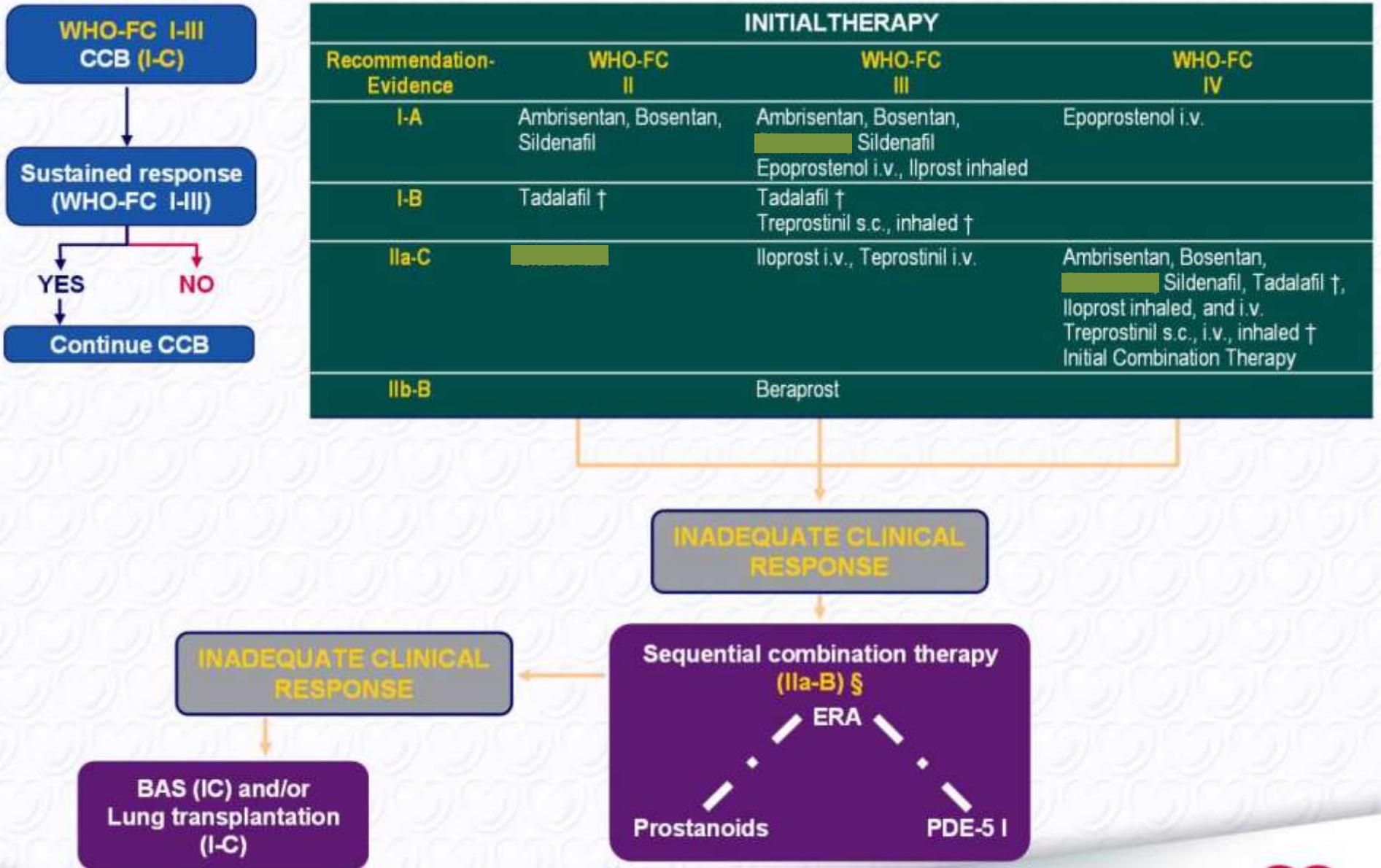
Progressive nature of PAH = Early treatment, continual monitoring & treatment escalation



Adapted from assimilated information within:
Galie N, *et al. Lancet* 2008; 371:2093-100. Provencher S, *et al*. *Eur Heart J* 2006; 27:589-95.
Hoeper MM, *et al. Eur Respir J* 2005; 26:858-63.

General measures

- General management principles
  - Avoid dehydration, extreme isometric exercise
  - Avoid high altitude (cyanosis)
  - Air travel is safe in cyanotic pts: mobilise *Broberg et al Heart 2006*
  - **Special anaesthetic management**
    - Special care around angiography and non-cardiac surgery (GA or sedation)
  - **Avoid pregnancy (30-50% maternal mortality)**
    - Contraception issues



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European Heart Journal 2009;30:2493-2537

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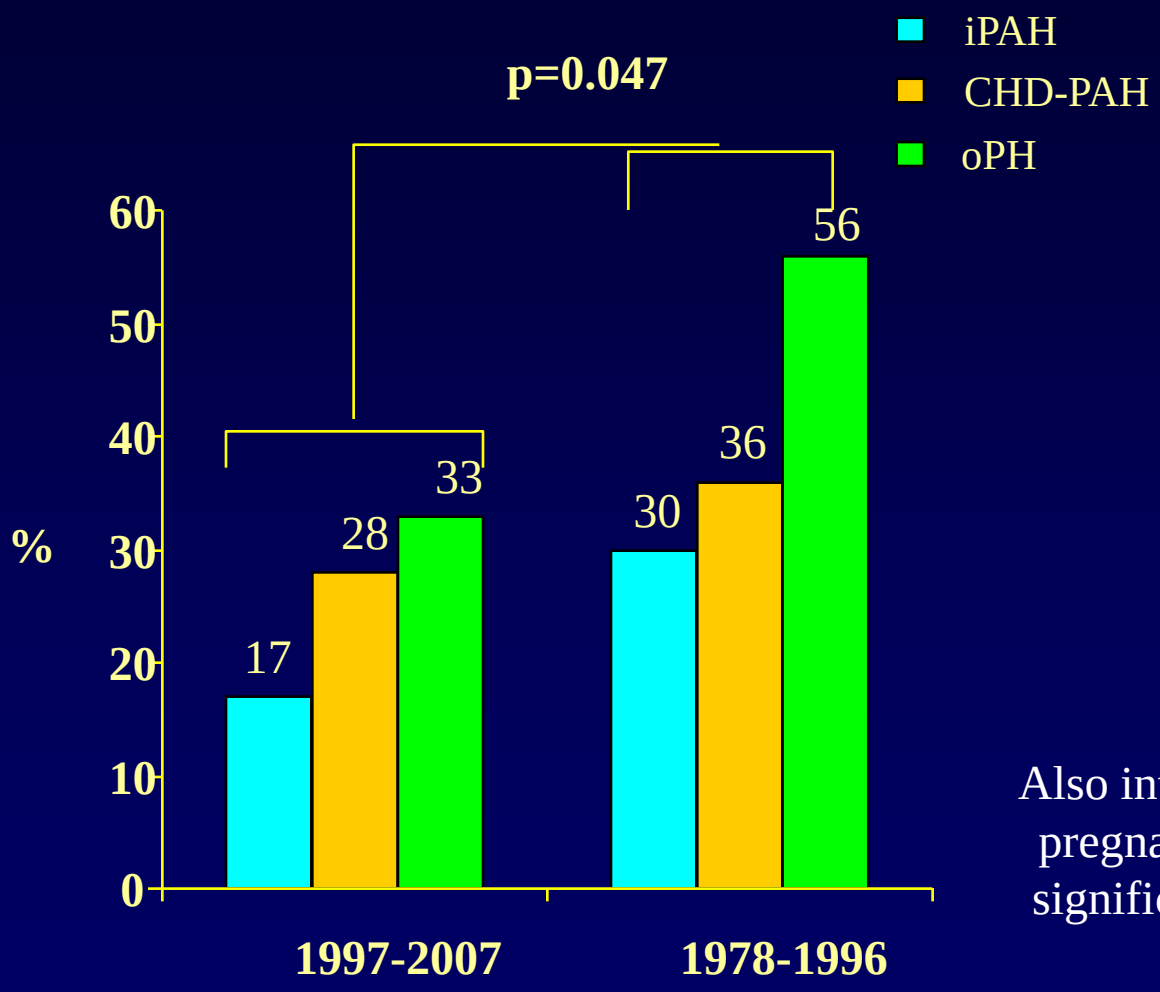
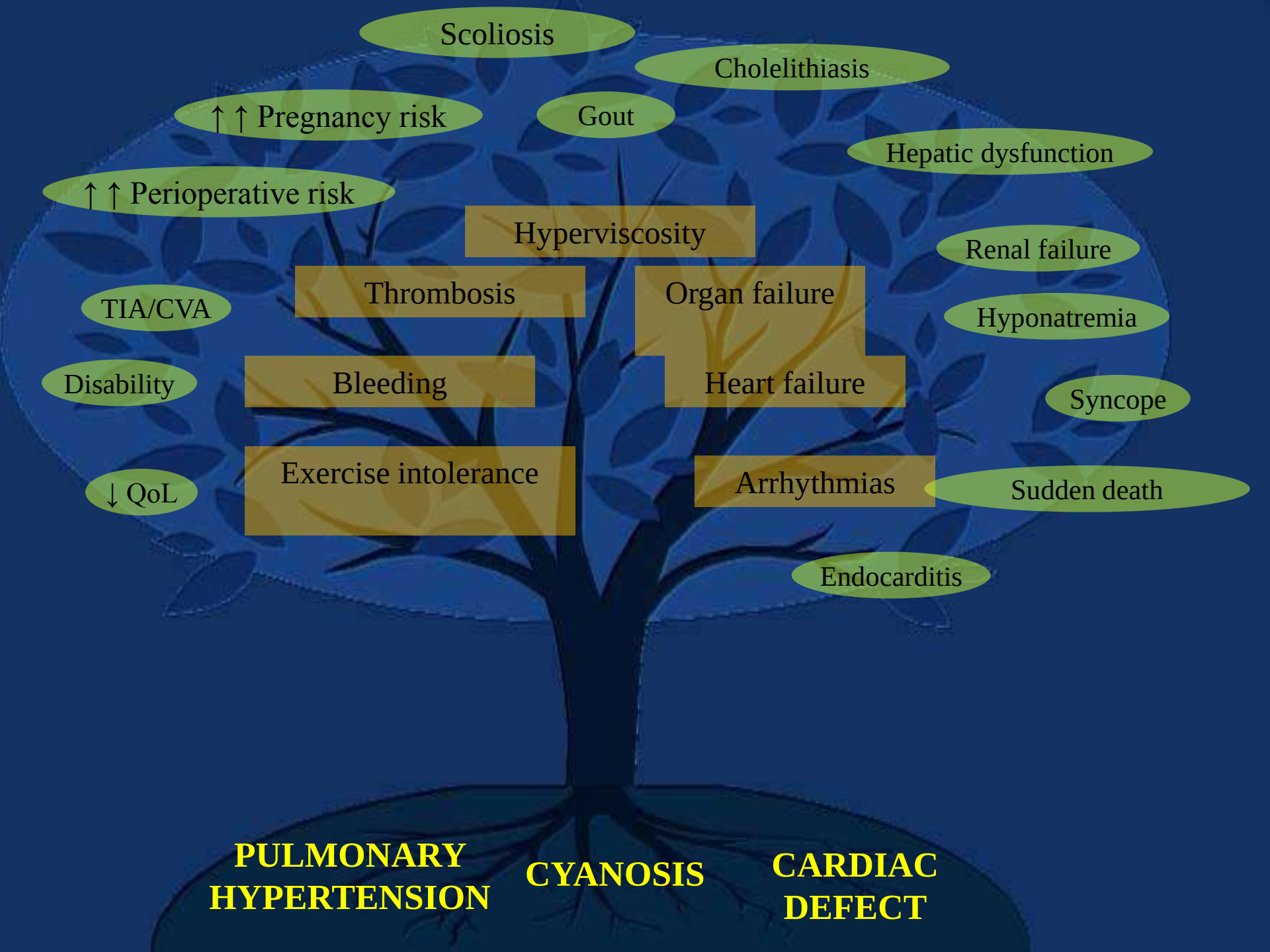
Mortality risk of pregnancy in PAH related to CHD



Also interruption of pregnancy carries significant risks!!!

Bedard, Dimopoulos, Gatzoulis, EHJ 2009


Scoliosis
Cholelithiasis
↑↑ Pregnancy risk
Gout
Hepatic dysfunction
↑↑ Perioperative risk
Hyperviscosity
Renal failure
Thrombosis
Organ failure
TIA/CVA
Hyponatremia
Disability
Bleeding
Heart failure
Syncope
Exercise intolerance
↓ QoL
Arrhythmias
Sudden death
Endocarditis
PULMONARY HYPERTENSION
CYANOSIS
CARDIAC DEFECT

SCREENING

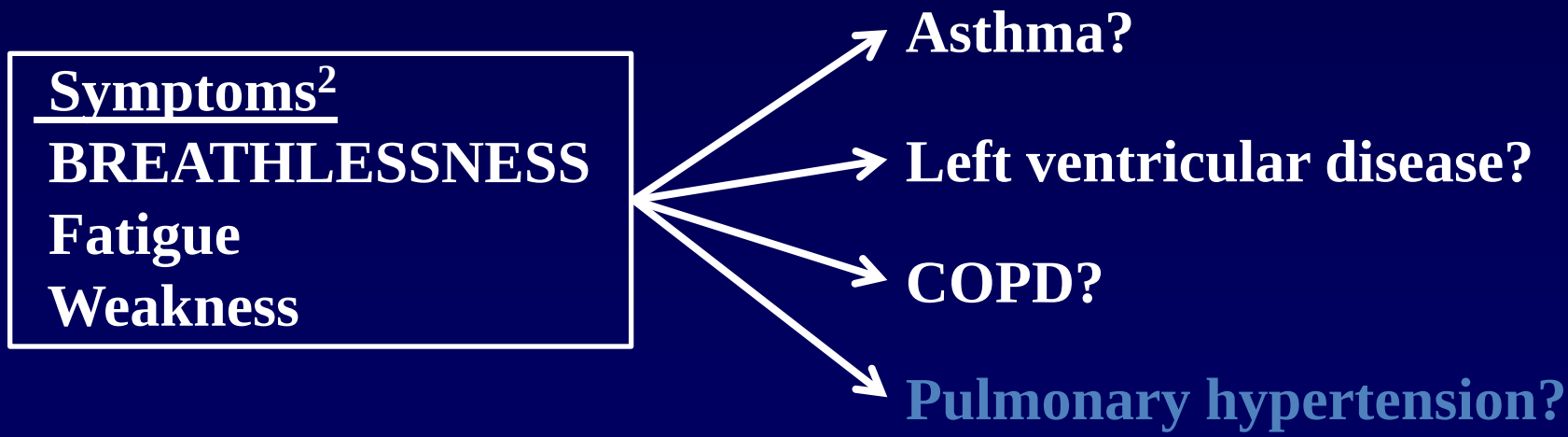
Incidence and prevalence of PAH

- IPAH:
  - ~1–8 individuals per million per year[1,2]
- PAH-CTD (SSc):
  - affects ~ 8-12% of CTD patients[3,4]
- Prevalence of PAH associated with CHD:
  - 10% of adults with CHD[5]
- Prevalence of all types of PAH is 30-50/m/y[2]

1. Taichman DB, *et al. Clin Chest* Med 2007; 28:1-22.
2. Peacock AJ, *et al. Eur Resp J* 2007; 30:104-9.
3. Hachulla E, *et al. Arthritis Rheum* 2005; 52:3792-800.
4. Mukerjee D, *et al. Ann Rheum Dis* 2003; 62:1088-93.
5. Duffels MGJ, *et al. Int J Cardiol* 2006; doi:10.1016/j.ijcard.2006.09.017:1-7.

Finding a needle in a haystack

- PAH is frequently asymptomatic until it has reached an advanced stage and prognosis is poor
- Symptoms of PAH can be subtle and overlap with other disorders



Gibbs JSR. *Eur Respir Rev* 2007; 16:8-12.
Rich S, *et al. Ann Intern Med* 1987; 107:216-23.

PAH Diagnosis – a high index of suspicion needed

- Symptoms initially insidious and nonspecific
- Diagnosis should be considered in any patient with:
  - unexplained dyspnea on exertion
  - fatigue, or exercise limitation
  - clinical signs consistent with right-heart dysfunction
  - patients with family history of pulmonary hypertension
  - conditions generally associated with high prevalence of PAH

Levine DJ. *Respiratory Care* 2006;51(4):368–381

Diagnosis of PAH is typically delayed

- Low prevalence[1,2]
- Low suspicion[3]
- Asymptomatic in early stages[4]
- Non-specific symptoms[3]

DIAGNOSIS IS TYPICALLY DELAYED BY ≥ 2 YRS[3]

1. Taichman DB, *et al. Clin Chest Med* 2007; 28:1-22.
2. Peacock AJ, *et al. Eur Resp J* 2007; 30: 104-9.
3. Gibbs JSR. *Eur Respir Rev* 2007; 16:8-12.
4. Barst R, *et al. JACC* 2004; 43: 40S–47S.

Who should be screened for PAH?

Known genetic mutation associated with PAH

- Screening frequency uncertain
- Screen first degree relatives of index IPAH patients?

Scleroderma and mixed connective tissue disease

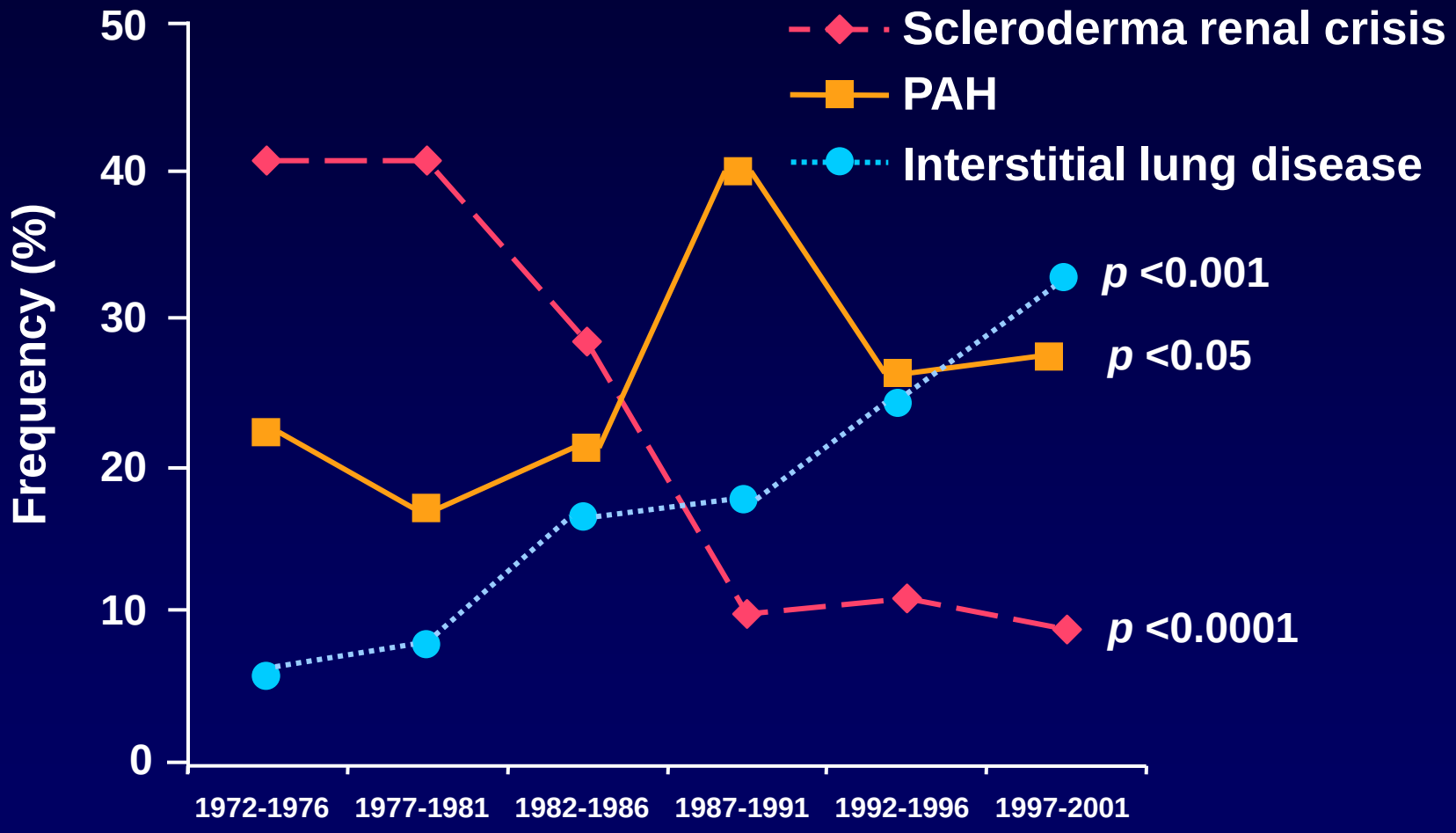
- Annual screening

Portal hypertension

- If liver transplantation considered

McGoon M, *et al*. *Chest* 2004; 126:14S-34S.

Pulmonary complications are now the leading cause of death in SSc



Steen VD and Medsger TA. *Ann Rheum Dis* 2007; 66:940-4.

Introducing the UK and EIRE specialist centres

- Glasgow: Western Infirmary
- Dublin: Mater Misericordiae
- Cambridge: Papworth
- Newcastle: Freeman
- Sheffield: Royal Hallamshire
- London Centre:
  - Royal Free
  - Royal Brompton
  - Great Ormond Street
  - Hammersmith

Gibbs S, *et al. Heart* 2008; 94 (Suppl 1):i1-41.

What do specialist centres have to offer?

High level of performance due to referral of a sufficient number of patients – *critical mass*

Specialist examinations, confirmatory and prognostic diagnostic procedures, right heart catheterisation

Specialist designated PAH centre

Multidisciplinary approach to patient care

Fully staffed and resourced for optimal investigation

Galiè N, *et al. Eur Heart J* 2009; 30:2493-2357.

Take home messages (1)

- Pulmonary Hypertension (PH), a haemodynamic and pathophysiological condition, should not be confused with Pulmonary Arterial Hypertension (PAH) a clinical group of rare diseases.
- The current clinical classification of PH includes 37 clinical conditions which are classified into six groups according to similar pathological, pathophysiological and therapeutic characteristics.
- Doppler-echocardiography does not measure pulmonary arterial pressure but gives only an estimate of it: Right heart catheterization is mandatory for the confirmation of the diagnosis of PAH.
- The correct clinical diagnosis in a patient with demonstrated PH requires the application of an appropriate diagnostic algorithm.

Take home messages (2)

- The prognostic assessment and the definition of clinical status of PAH patients is multidimensional: assessing symptoms (e.g. WHO functional class), exercise capacity (e.g. 6-minute walk test) and right ventricular function (e.g. right heart catheterization).
- The evidence-based treatment algorithm is appropriate only in patients with PAH (Clinical group 1).
- Acute vasoreactivity test preferably with inhaled nitric oxide is strongly recommended in particular in idiopathic PAH.

Take home messages (3)

- Despite recent progress, the current treatment strategy for PAH remains inadequate because the mortality rate continues to be high and the functional and haemodynamic impairment is still severe in many patients.
- Lung transplantation is often required in particular in young patients.
- The optimal treatment of the underlying **left heart disease** is recommended in patients with PH due to left heart disease. The specific PAH drugs are not recommended.
- The optimal treatment of the underlying **lung disease** including long-term O2 therapy in patients with chronic hypoxaemia is recommended in patients with PH due to lung diseases. The specific PAH drugs are not recommended.
- Surgical **pulmonary endarterectomy** is the recommended treatment for patients with chronic thromboembolic pulmonary hypertension.

Thank you

Translation: “His lips are cyanotic”

Hieroglyph for the Smith Papyrus (3000 B.C)

Special thanks to
-Dr Rafa Alonso-Gonzales
-Actelion UK

Rashkind WJ, Circulation 1983

Potentially significant drug interactions with PAH-targeted therapies (1)

PAH Drug	Mechanism of interaction	Interaction drug	Interaction
Ambrisentan	?	Cyclosporine Ketoconazole	Caution is required in the co-administration of Ambrisentan with Ketoconazole and Cyclosporine.
Bosentan	CYP3A4 inducer	Sildenafil	Sildenafil levels fall 50%; Bosentan levels increase 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	Cyclosporine	Cyclopsorine levels fall 50%; Bosentan level increase 4-fold. Combination contra-indicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazaole	Bosentan levels increase 2-fold.
	CYP3A4 substrate + bile salt pump inhibitor	Glibenclamide	Increase incidence of elevated aminotransferases. Potential decrease of hypoglycaemic effect of Glibenclamide. Combination contra-indicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole Amiodarone	Bosentan levels considerably increase. Combination potentially contra-indicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin Phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.

European Heart Journal 2009;30:2493-2537

Potentially significant drug interactions with PAH-targeted therapies (2)

PAH Drug	Mechanism of interaction	Interaction drug	Interaction
Bosentan	CYP2C9 inducer	HMG-CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with Atorvastatin, Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increase Warfarin metabolism, may need to adjust Warfarin dose. Intensified monitoring of Warfarin recommended following initiation but dose adjustment usually unnecessary.
	CYP2C9 and CYP3A4 inducers	Hormonal contraceptives	Hormone levels decrease. Contraception unreliable.
Sitaxentan	CYP2C9 inhibitor	Warfarin	Inhibits Warfarin metabolism. Warfarin dose needs to be reduced by 80% when initiating Sitaxentan and INR monitoring intensified.
	7 inhibition of OATP transporter	Cyclosporine	Increases Sitaxentan level; combination contra-indicated.
Sildenafil	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; Bosentan levels indrease 50%. May not require dose adjustments of either drug.
	CYP3A4 substrate	HMG-CoA reductase inhibitors	May increase Simvastatin/Atorvastatin levels through competition for metabolism. Sildenafil levels may increase. Possible increased risk of rhabdomyolysis.

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Potentially significant drug interactions with PAH-targeted therapies (3)

PAH Drug	Mechanism of interaction	Interaction drug	Interaction
Sildenafil	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and Saquinovir increase Sildenafil levels markedly. Sildenafil dose-adjustments are usually required.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fell.
	CYP3A4 substrate	Erythromycin	Sildenafil levels increase may not require dose adjustment for a short course.
	CYP3A4 substrate	Ketoconazole	Sildenafil levels increase. May not require dose adjustment.
	CYP3A4 substrate	Cimetidine	Sildenafil levels increase. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contra-indicated.
Tadalafil	CYP3A4 substrate	Bosentan	Tadalafil plasma levels decreases by 42%, no significant changes in Bosentan levels. May not require dose adjustment.
	cGMP	Nitrates Nicorandil	Profound systemic hypotension, combination contra-indicated.

European Heart Journal 2009;30:2493-2537