

# Treatment of PAH



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# Risk assessment

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope <sup>b</sup>	Repeated syncope <sup>c</sup>
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO <sub>2</sub> >15 ml/min/kg (>65% pred.) VE/VCO <sub>2</sub> slope <36	Peak VO <sub>2</sub> 11–15 ml/min/kg (35–65% pred.) VE/VCO <sub>2</sub> slope 36–44.9	Peak VO <sub>2</sub> <11 ml/min/kg (<35% pred.) VE/VCO <sub>2</sub> slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm <sup>2</sup> No pericardial effusion	RA area 18–26 cm <sup>2</sup> No or minimal, pericardial effusion	RA area >26 cm <sup>2</sup> Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m <sup>2</sup> SvO <sub>2</sub> >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m <sup>2</sup> SvO <sub>2</sub> 60–65%	RAP >14 mmHg CI <2.0 l/min/m <sup>2</sup> SvO <sub>2</sub> <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO<sub>2</sub> = mixed venous oxygen saturation; VE/VCO<sub>2</sub> = ventilatory equivalents for carbon dioxide; VO<sub>2</sub> = oxygen consumption; WHO = World Health Organization.

<sup>a</sup>Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may

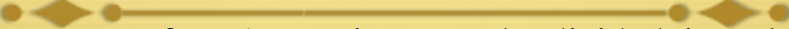
	At baseline	Every 3–6 months <sup>a</sup>	Every 6–12 months <sup>a</sup>	3–6 months after changes in therapy <sup>a</sup>	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+ <sup>e</sup>
Echo	+		+	+	+
Basic lab <sup>b</sup>	+	+	+	+	+
Extended lab <sup>c</sup>	+		+		+
Blood gas analysis <sup>d</sup>	+		+	+	+
Right heart catheterization	+		+ <sup>f</sup>	+ <sup>e</sup>	+ <sup>e</sup>

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BGA = blood gas analysis; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise testing; Echo = echocardiography; ECG = electrocardiogram; ERAs = endothelin receptor antagonists; FC = functional class; INR = international normalized ratio; lab = laboratory assessment; NT-proBNP = N-terminal pro-brain natriuretic peptide; RHC = right heart catheterization; TSH = thyroid stimulating hormone; 6MWT = 6-minute walking test.

<sup>a</sup>Intervals to be adjusted according to patient needs.

<sup>b</sup>Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP.

<sup>c</sup>Extended lab includes TSH, troponin, uric acid, iron status (free ferritin, soluble transferrin receptor) and other variables according to individual patient needs.



✦ The current treatment strategy for PAH patients can be divided into three main steps:

✦ (1) The first step : general measures

supportive therapy

referral to expert centers

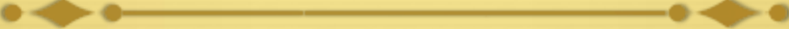
acute vasoreactivity testing for the indication of chronic CCB

. (2) The second step : initial therapy with high-dose CCB in vasoreactive patients or

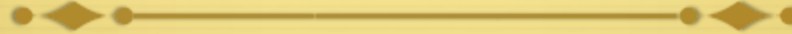
drugs approved for PAH in non-vasoreactive patients

✦ (3) The third step : response to the initial treatment strategy;

in the case of an inadequate response, the role of combinations of approved drugs and lung transplantation are proposed

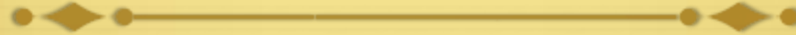
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- ✦ The overall treatment goal in patients with PAH
  - ✦ achieving a low risk status
  - ✦ good exercise capacity
  - ✦ good quality of life
  - ✦ good RV function
  - ✦ a low mortality risk
  - ✦ Specifically, this means bringing and/or keeping the patient in WHO-FC II whenever possible
  - ✦ In most patients, this will be accompanied by a near-normal or normal 6MWD

# Physical activity and supervised rehabilitation



- ✦ PAH patients should be encouraged to be active within symptom limits.
- ✦ should avoid excessive physical activity that leads to distressing symptoms,
- ✦ but when physically deconditioned, patients may undertake supervised exercise rehabilitation.
- ✦ This recommendation is limited by gaps in the knowledge the optimal method of exercise rehabilitation , intensity and duration of the training
- ✦ Exercise training programmes should be implemented by centres experienced in both PAH patient care and rehabilitation of compromised patients.
- ✦ should be treated with the best standard of pharmacological treatment and in stable clinical condition before embarking on a supervised rehabilitation programme.

# Pregnancy, birth control and post-menopausal hormonal therapy

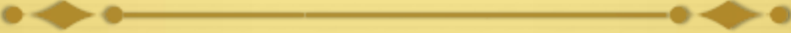


- ✦ Pregnancy -- substantial mortality rate in PAH. – 30% to 50%
- ✦ However, a recent report indicates that the outcome of pregnancies in PAH has improved, at least when PAH is well controlled .
- ✦ These data must be confirmed by larger series
- ✦ An absolute contraindication

There is less consensus relating to the most appropriate methods of birth control

- ✦ . Barrier contraceptive methods are safe for the patient, but with an unpredictable effect.
- ✦ Progesterone-only preparations such as medroxyprogesterone acetate and etonogestrel are effective approaches to contraception and avoid the potential issues of oestrogens such as those associated with the old-generation mini-pill.
- ✦ The ERA bosentan may reduce the efficacy of oral contraceptive agents.
- ✦ The levonorgestrel-releasing intrauterine coil is also effective but may rarely lead to a vasovagal reaction when inserted, which may be poorly tolerated in severe PAH
- ✦ A combination of two methods may also be utilized.



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- ✦ The patient becomes pregnant – inform the high risk and discuss termination
  - ✦ If choose to continue pregnancy -- disease-targeted therapies, planned elective delivery and effective close collaboration between obstetricians and the PAH team.
  - ✦ the use of hormonal therapy in postmenopausal women with PAH ---- no consensus. It may be considered in cases of intolerable symptoms
  - ✦ epidural is probably better tolerated than general anesthesia

# Material and methods



- ✦ Retrospective analysis
- ✦ Electronic database
- ✦ January 2000 to 2014
- ✦ Fernandez Hospital, Hyderabad
- ✦ Tertiary referral perinatal unit
- ✦ 8000 deliveries annually

# Patient Population

<b>MEDIAN AGE</b>	<b>23 YR (22-28)</b>
<b>GRAVIDA</b>	<b>2 (1-4)</b>
<b>PARA</b>	<b>1 (0-2)</b>
<b>REFERRALS</b>	<b>2(25%)</b>
<b>LATE BOOKING</b>	<b>3(50%)</b>
<b>PRE-PREG COUNSELLING</b>	<b>1(16%)</b>
<b>Δ BEFORE PREG</b>	<b>2 (33%)</b>
<b>Δ DURING PREG</b>	<b>4(67%)</b>
<b>SEVERE PAH</b>	<b>4(67%)</b>

# Baseline Characteristics

<b>NYHA CLASS III-IV</b>	<b>3(50%)</b>
<b>SpO2 DURING PREG(%)</b>	<b>96(93-100)</b>
<b>Hb DURING PREG</b>	<b>9.4(8-11.8)</b>
<b>RVSP (mm Hg)</b>	<b>85(43-100)</b>
<b>PAP systolic (mmHg)</b>	<b>94-103</b>

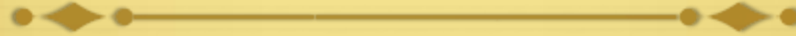
# Management

<b>GESTATIONAL AGE AT HOSPITALIZATION</b>	<b>32(29-37)</b>
<b>DELIVERY(WEEK)</b>	<b>33(30-37)</b>
<b>MODE: CS</b>	<b>6(100%)</b>
<b>MODE: VD</b>	<b>0(0%)</b>
<b>ANTENATAL STEROIDS</b>	<b>4(66%)</b>
<b>TUBECTOMY</b>	<b>1(17%)</b>

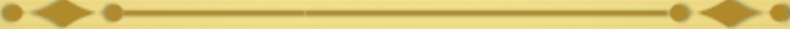


## **Infection prevention**

- ✦ Patients with PAH are susceptible to developing pneumonia, which is the cause of death in 7% of cases.
- ✦ While there are no controlled trials, it is recommended to vaccinate against influenza and pneumococcal pneumonia

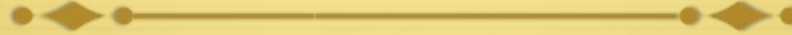


- ✦ Adherence to medical treatments needs to be checked periodically
- ✦ Genetic counseling
- ✦ Psychosocial support

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- ✦ There are no studies using flight simulation to determine the need for supplemental O<sub>2</sub> during prolonged flights in patients with PAH
  - ✦ The known physiological effects of hypoxia suggest that in-flight O<sub>2</sub> administration should be considered for patients in WHO-FC III and IV and those with arterial blood O<sub>2</sub> pressure consistently  $< 8$  kPa (60 mmHg)
  - ✦ A flow rate of 2 l/min will raise inspired O<sub>2</sub> pressure to values seen at sea level.
  - ✦ such patients should avoid going to altitudes of 1500–2000 m without supplemental O<sub>2</sub>.

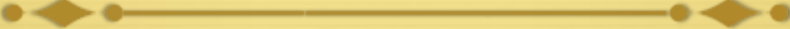


# Oral anticoagulants



## The rationale for oral anticoagulation in PAH

- ✦ There is a high prevalence of vascular thrombotic lesions at postmortem examination in patients with IPAH.
- ✦ Abnormalities in coagulation and fibrinolytic pathways have also been reported.
- ✦ This, together with the non-specific increased risk factors for venous thromboembolism, including heart failure and immobility

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- ✦ Evidence in favour of oral anticoagulation is confined to patients with IPAH, HPAH and PAH due to anorexigens
  - ✦ Is retrospective and based on single-centre experience
  - ✦ Registry and RCT data appear to be heterogeneous and inconclusive.
  - ✦ The potential benefits of oral anticoagulation in APAH is even less clear.
  - ✦ Generally patients with PAH receiving therapy with long-term i.v. prostaglandins are anticoagulated in the absence of contraindications due in part to the additional risk of catheter-associated thrombosis.
  - ✦ The role of the new oral anticoagulants in PAH is unknown

# Diuretics



- ✦ No RCTs on the use of diuretics in PAH
- ✦ clinical experience shows clear symptomatic benefit in fluid overloaded patients treated with this therapy.
- ✦ The choice and dose of diuretic therapy may be left to the PAH physician.
- ✦ The addition of aldosterone antagonists should also be considered

# O2



- ✦ Guidance may be based on evidence in patients with COPD
- ✦ when arterial blood O<sub>2</sub> pressure is consistently less than 8 kPa (60 mmHg; alternatively, ,91% of arterial O<sub>2</sub> saturation) patients are advised to take O<sub>2</sub> to achieve an arterial blood O<sub>2</sub> pressure.8 kPa.
- ✦ Ambulatory O<sub>2</sub> may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

# DIGOXIN



- ✦ Digoxin and other cardiovascular drugs
- ✦ Digoxin has been shown to improve CO acutely in IPAHA,
- ✦ its efficacy is unknown when administered chronically.
- ✦ It may be given to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias.
- ✦ No convincing data are available on the usefulness and safety of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers or ivabradine in patients with PAH.

# Anemia and iron status

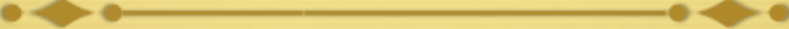


- ✦ Iron deficiency is common
  - 43% of patients with IPAH, 46% of patients with SSc-PAH
- ✦ 56% of patients with Eisenmenger syndrome.
- ✦ Data suggest - iron deficiency may be associated with reduced exercise capacity, and perhaps also with a higher mortality, independent of the presence or severity of anemia.
- ✦ regular monitoring of the iron status
- ✦ a search for potential reasons.
- ✦ Iron substitution
  - oral iron absorption is impaired in patients with PAH, so i.v. iron administration may be preferable.
- ✦ However, controlled trials are lacking.

# CALCIUM CHANNEL BLOCKERS

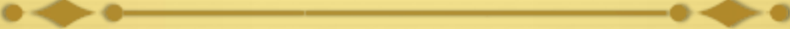


- ✦ only a small number of patients with IPAH who demonstrate a favorable response to acute vasodilator testing at the time of RHC do well with CCBs.
- ✦ The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem and amlodipine,
- ✦ The choice of CCB is based on the patient's heart rate at baseline,
- ✦ The daily doses of these drugs that have shown efficacy in IPAH are relatively high:
  - 120–240 mg for nifedipine,
  - 240–720 mg for diltiazem
  - up to 20 mg for amlodipine.
- ✦ start with an initial lower dose, e.g. 30 mg of slow release nifedipine BD or 60 mg of diltiazem (t.i.d.) or 2.5 mg of amlodipine OD, and increase cautiously and progressively to the maximum tolerated dose.

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- ✦ Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral oedema.
  - ✦ Patients who meet the criteria for a positive vasodilator response and are treated with CCBs - follow closely – complete reassessment after 3–4 months of therapy including RHC.
  - ✦ no adequate response - additional PAH therapy should be instituted.
  - ✦ In some cases the combination of CCB with the approved PAH drugs is required because of further clinical deterioration in case of CCB withdrawal attempts.
  - ✦ not undergone a vasoreactivity study or those with a negative study should not be started on CCBs because of potential severe side effects (e.g. hypotension, syncope and RV failure).
  - ✦ Vasodilator responsiveness does not appear to predict a favorable long-term response to CCB therapy in patients with PAH in the setting of CTD, HIV, Porto-pulmonary hypertension (PoPH) and PVOD



Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref. <sup>c</sup>
High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH who are responders to acute vasoreactivity testing	I	C	84,85
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH and DPAH treated by high doses of CCBs	I	C	84,85
Continuation of high doses of CCBs is recommended in patients with IPAH, HPAH and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization)	I	C	84,85
Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses of CCBs	I	C	84,85
High doses of CCBs are not indicated in patients without a vasoreactivity study or non-responders unless standard doses are prescribed for other indications (e.g. Raynaud's phenomenon)	III	C	

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- ✦ **Endothelin receptor antagonists**
  - ✦ **Phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators**
  - ✦ **Prostacyclin analogues and prostacyclin receptor agonists**

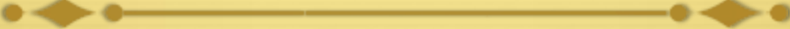
**Table 4. FDA-Approved Medications in the Treatment of PAH**

Drug (Brand)	FDA Indication	Route of Administration	Usual Starting Dose and Titration Schedule*	Half-life	Adverse Effects
<b>Prostacyclin Analogs</b>					
Epoprostenol (Flolan)	PAH with NYHA class 3-4 and PAH associated with scleroderma	Continuous infusion via central IV line; place catheter	2 ng/kg/min increased by 2 ng/kg/min every 15 min until dose-limiting side effect occurs	2.7 min	Central line infections, flushing, n/v, hypotension, headache, flulike symptoms, jaw pain
Treprostinil (Remodulin)	NYHA class 2-4	Continuous infusion via central IV line or continuous SC infusion	1.25 ng/kg/min increased by 1.25 ng/kg/min weekly for first 4 wk then 2.5 ng/kg/min thereafter	4 h	Headache, n/v, infusion site reactions and pain, flulike symptoms, jaw pain
Treprostinil (Tyvaso)	NYHA class 3	Oral inhalation	3 inhalations (total of 18 mcg) 4 times daily increased by 3 inhalations 4 times a day every 1-2 wk until target or max dose 9 inhalations (54 mcg) 4 times daily is reached; space doses by 4 h	4 h	Headache, flushing, nausea, cough, throat irritation
Iloprost (Ventavis)	NYHA class 3-4	Aerosolized inhalation	2.5 mcg 6-9 times per day (no more frequently than every 2 h); increase to 5 mcg 6-9 times per day (max)	20-30 min	Flushing, hypotension, headache, flulike symptoms, trismus, cough
<b>Endothelin Receptor Antagonists (ERAs)</b>					
Bosentan (Tracleer)	WHO class II-IV	Oral tablet	62.5 mg twice daily for 4 wk then increase to 125 mg twice daily; if <40 kg, dose remains 62.5 mg twice daily	5 h	Respiratory tract infections, peripheral edema, headache, anemia, chest pain, syncope; black box warnings for hepatotoxicity and teratogenicity
Ambrisentan (Letairis)	WHO class II-III	Oral tablet	5 mg daily then increase to 10 mg daily	9-15 h	Peripheral edema, headache, nasal congestion, flushing; black box warnings for potential hepatotoxicity and contraindication in pregnancy
<b>Phosphodiesterase-5 (PDE-5) Inhibitors</b>					
Sildenafil (Revatio)	WHO class I-IV	Oral tablet IV bolus	20 mg 3 times daily (~4-6 h apart) 10 mg (12.5 mL) 3 times daily	4 h	Epistaxis, headache, dyspnea, flushing, NAION, hearing loss
Tadalafil (Adcirca)	WHO class I-IV	Oral tablet	40 mg once daily	35 h	Headache, myalgias, nasopharyngitis, flushing, respiratory tract infections, hypotension, hearing or vision loss

IV: intravenous; max: maximum; min: minute; NAION: nonarteritic ischemic optic neuropathy; n/v: nausea/vomiting; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; SC: subcutaneous; WHO: World Health Organization.

\* Refer to package inserts for renal and hepatic impairment dosing as well as specific medication considerations.

Source: References 16-23.



✦ Vardenafil – oral PDE5I

✦ 5mg bd

✦ Similar side effect profile

✦ Beraprost : first chemically stable and orally active prostacyclin analogue

✦ RCT,s have shown improvement in exercise capacity that persists upto 3-6 months, no hemodynamic or longterm outcome benefits

✦ Adverse events : headache, flushing, diarrhea, jawpain



## ✦ **Macitentan**

✦ The dual ERA

✦ RCT ( SERAPHIN )742

✦ 3 mg or 10 mg macitentan

✦ as compared with placebo for an average of 100 weeks.

✦ The primary endpoint : time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with i.v. or subcutaneous prostanoids or worsening of PAH.

✦ significantly reduced this composite endpoint of morbidity and mortality (45%) and also increased exercise capacity.

✦ Benefits shown both in monotherapy and add On therapy

✦ no liver toxicity,

✦ reduction in blood hemoglobin  $\leq 8$  g/dl was observed in 4.3% of patients receiving 10 mg of macitentan.

**Web Table VIA** Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the endothelin pathway (Endothelin receptors antagonists)

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main Results
Ambrisentan	ARIES-1 <sup>10</sup>	202	12	No	6MWD	6MWD improved TTCW not improved
	ARIES-2 <sup>10</sup>	192	12	No	6MWD	6MWD improved TTCW improved
Bosentan	Study-351 <sup>11</sup>	32	12	No	6MWD	6MWD improved TTCW improved
	BREATHE-1 <sup>12</sup>	213	16	No	6MWD	6MWD improved TTCW improved
	EARLY <sup>13</sup>	185	24	No, or Sildenafil (16%)	PVR, 6MWD	PVR improved TTCW improved 6MWD not improved
	BREATHE-5 <sup>14</sup>	54	12	No	SaO <sub>2</sub> , PVR	PVR improved 6MWD improved
	COMPASS-2 <sup>15</sup>	334	99	Sildenafil	TTCW	TTCW not improved 6MWD improved NT-proBNP improved
Macitentan	SERAPHIN <sup>16</sup>	742	115	No, or Sildenafil, or Inh iloprost	TTCW	TTCW improved in monotherapy and combination

6MWD = 6-minute walking distance; PVR = pulmonary vascular resistance; SaO<sub>2</sub> = finger oxygen saturation; TTCW = time to clinical worsening.

## ✦ **Riociguat**



- ✦ sGC stimulators enhance cGMP production.
- ✦ Moreover, pre-clinical studies with sGC stimulators have antiproliferative and antiremodelling properties in various animal models.
- ✦ An RCT ( PATENT 1 ) in 443 PAH patients (44% and 6% on background therapy with ERAs or prostanoids, respectively) treated with riociguat up to 2.5 mg t.i.d. has shown favourable results on exercise capacity, haemodynamics, WHO-FC and time to clinical worsening.
- ✦ The increase in exercise capacity was also demonstrated in patients on background therapy.
- ✦ The most common serious adverse event in the placebo group and in the 2.5-mg group was syncope (4% and 1% respectively).
- ✦ The combination of riociguat and PDE-5i is contraindicated due to hypotension and other relevant side effects detected



✦ **PATENT 2:**

- ✦ Long term extension study
- ✦ Results after one year of treatment
- ✦ 6MWD continued to increase (48 +\_72m compared to baseline)
- ✦ FC – 68% were in class 1 or 2 after 1 year of treatment

✦ **CHEST 1 : CTEPH patients**

- ✦ 16 wks
- ✦ significant increase in 6MWD , decreased PVR, NT pro BNP , improvement in FC
- ✦ USFDA approved for inoperable CTEPH or operable CTEPH with recurrent PH
- ✦ No evidence till then , PAH specific therapies were useful in CTEPH

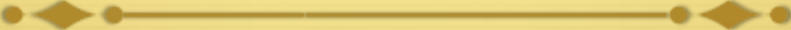


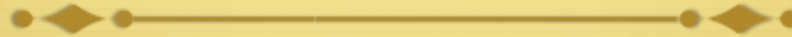
**Web Table VIB** Characteristics of randomised controlled trials with pulmonary arterial hypertension drugs interfering with the nitric oxide pathway (Soluble guanylate cyclase stimulators, Phosphodiesterase type-5 inhibitors)

Drug(s) tested	Study	Number of patients	Duration (weeks)	Background therapy	Primary endpoint	Main results
Riociguat	PATENT <sup>17</sup>	443	12	No, or bosentan, or prostanoids	6MWD	6MWD improved Haemodynamics improved
	PATENT plus <sup>18</sup>	30	18	Sildenafil	Supine SBP	Terminated for excess of SAE in the treated group
Sildenafil	SUPER-1 <sup>19</sup>	277	12	No	6MWD	6MWD improved TTCW not improved
	Sastry <sup>20</sup>	22	12	No	TT	TT improved
	Singh <sup>21</sup>	20	6	No	6MWD	6MWD improved
	PACES <sup>22</sup>	264	16	Epoprostenol	6MWD	6MWD improved TTCW and haemodynamics improved
	Iversen <sup>23</sup>	20	12	Bosentan	6MWD	6MWD not improved
	Pfizer study A1481243	103	12	Bosentan	6MWD	6MWD not improved
Tadalafil	PHIRST <sup>24</sup>	405	16	No, or bosentan (54%)	6MWD	6MWD improved (In bosentan treated patients +23 m, 95% CI -2 to 48 m) TTCW improved
Vardenafil <sup>a</sup>	EVALUATION <sup>25</sup>	66	12	No	6MWD	6MWD improved TTCW improved

6MWD = 6-minute walking distance; SAE = serious adverse events; TTCW = time to clinical worsening; TT = treadmill test.

<sup>a</sup>This drug is not approved by the EMA at the time of publication of these guidelines.

- 
- ✦ FREEDOM C trial : addition of **ORAL TREPROSTINIL** therapy to background ERA or PDE5I
  
  - ✦ No significant increase in 6MWD and borg dyspnea score



## ✦ **Selexipag**

- ✦ an orally available, selective prostacyclin IP receptor agonist.
- ✦ Although selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin (IP receptor agonism), they are chemically distinct from prostacyclin with a different pharmacology.
- ✦ In a pilot RCT in PAH patients (receiving stable ERA and/or PDE-5i therapy), selexipag reduced PVR after 17 weeks.  
non significant increase in 6MWD.



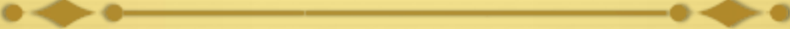
✦ **GRIPHON STUDY:**

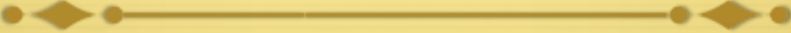
- ✦ Multicentre, double blind, placebo controlled
- ✦ 1156 adults with group 1 PAH
- ✦ 1: 1 randomized
- ✦ Treated for 4.3 years
- ✦ 100micrograms BD uptitrated to 800 micro g BD
- ✦ Patients on ERA'S or PDE5Is, or a combination for 3 months
- ✦ Primary end point : time to mortality or first morbidity (hospitalization, disease progression, initiation of I.V, SC prostanoids, need for BAS or LT) --- improved by 39%
- ✦ adverse events – similar to other prostaglandins
- ✦ 14% of selexipag patients discontinued as opposed to 7% placebo

Beraprost*	ALPHABET <sup>26</sup>	130	12	No	6MWD	6MWD improved Haemodynamics not improved
	Barst <sup>27</sup>	116	52	No	CW	CW not improved
Epoprostenol	Rubin <sup>28</sup>	23	12	No	6MWD	6MWD improved Haemodynamics improved
	Barst <sup>29</sup>	81	12	No	6MWD	6MWD improved Haemodynamics improved Survival improved
	Badesch <sup>20</sup>	111	12	No	6MWD	6MWD improved
Inhaled Iloprost	AIR <sup>31</sup>	203	12	No	6MWD & FC	6MWD & WHO-FC improved Haemodynamics improved at peak
	STEP <sup>32</sup>	67	12	Bosentan	6MWD	6MWD improved (P = 0.051) TTCW improved
	COMBI <sup>33</sup>	40	12	Bosentan	6MWD	Terminated for futility 6MWD not improved No clinical improvement
Treprostinil	SC – Pivotal study <sup>34</sup>	470	12	No	6MWD	6MWD improved Haemodynamics improved Pain at infusion site
	Inhal <sup>3</sup> TRIUMPH <sup>35</sup>	235	12	Bosentan or sildenafil	6MWD	6MWD improvement (+20 m at peak, +12 m at trough) TTCW not improved
	PO <sup>3</sup> - Freedom M <sup>36</sup>	185	16	No	6MWD	6MWD improvement (+26 m at peak, +17 m at trough) TTCW not improved
	PO <sup>3</sup> - Freedom C1 <sup>37</sup>	354	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
	PO <sup>3</sup> - Freedom C2 <sup>38</sup>	310	16	ERA and/or PDE-5i	6MWD	6MWD not improved TTCW not improved
Selexipag <sup>8</sup>	Phase - 2 <sup>39</sup>	43	17	ERA and/or PDE-5i	PVR	PVR improved 6MWD not improved

# Recommendations for monotherapy

Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C	194
	Bosentan		I	A	I	A	IIb	C	196–200
	Macitentan <sup>e</sup>		I	B	I	B	IIb	C	201
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C	205–208
	Tadalafil		I	B	I	B	IIb	C	211
	Vardenafil <sup>g</sup>		IIb	B	IIb	B	IIb	C	212
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C	214
Prostacyclin analogues	Epoprostenol	Intravenous <sup>e</sup>	-	-	I	A	I	A	220–222
		Iloprost	Inhaled	-	-	I	B	IIb	C
	Intravenous <sup>g</sup>		-	-	IIa	C	IIb	C	232
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C	233
		Inhaled <sup>g</sup>	-	-	I	B	IIb	C	237
		Intravenous <sup>f</sup>	-	-	IIa	C	IIb	C	234
		Oral <sup>g</sup>	-	-	IIb	B	-	-	238–240

- 
- ✦ Combination therapy
  - ✦ As in cardiac failure and hypertension
  - ✦ The 3 main mechanistic pathways of PAH - endothelin, NO, prostacyclin pathways
  - ✦ Historically based on clinical experience and expert opinion
  - ✦ Recent years , data from RCT'S - shift towards evidence based use of combination therapy
  - ✦ US REVEAL study - 34.9% of patients receive only monotherapy at the time of death

- 
- ✦ 5<sup>th</sup> world symposium – 2013 upgraded the recommendations
  - ✦ Sequential combination therapy to class 1(A)
  - ✦ Initial combination therapy in WHO FC 3 or 4 as 2b (c)



✦ evidence for **sequential combination therapy**

✦ Initial trials did not show a benefit (FREEDOM C1 and FREEDOMC2 - oral trepostinil on a background of bosentan and or sildenafil)

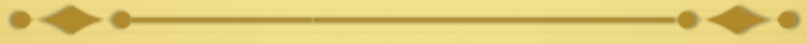
✦ Later trials have shown benefits of combination therapy

✦ **PATENT -1 :**

ERA's or prostanoids compared with ERA,s or prostanoids + riociguat

12wks

Significant increase in 6MWD



✦ **Compass – 2** : long term study

✦ bosentan added to background sildenafil

✦ did not meet the primary end point of reducing time to first morbidity or mortality event

✦ improvement in 6MWD at week 16

✦ risk reduction of 17%

✦ Subgroup analysis of **SERAPHIN** study : 317 pts

✦ median treatment duration 2.2 years

✦ Addition of macitentan to patients on background therapy with PDE5Is ( predominantly sildenafil ) reduced the risk of a composite morbidity and mortality by 38%

Measure/ treatment	Class <sup>a</sup> -Level <sup>b</sup>						Ref. <sup>c</sup>
	WHO-FC II		WHO-FC III		WHO-FC IV		
Macitentan added to sildenafil <sup>d</sup>	I	B	I	B	IIa	C	201
Riociguat added to bosentan	I	B	I	B	IIa	C	214
Selexipag <sup>e</sup> added to ERA and/or PDE-5i <sup>d</sup>	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



✦ **upfront combination therapy**

✦ BREATHE 2 trial

✦ Double blind

✦ Placebo controlled

✦ Combined bosentan + epoprostenol versus epoprostenol alone

✦ Severe PAH pts

✦ Improvement in FC, exercise capacity and hemodynamic improvements at week 16 were more in combination therapy, but did not achieve statistical significance.

✦ TRIUMPH, PACES subgroup of EARLY, PHIRST – non significant improvement



✦ **AMBITION TRIAL**

✦ Double blinded, RCT

✦ Efficacy of first line combination therapy with AMBRISENTAN + TADALAFIL to monotherapy with AMBRISENTAN or TADALAFIL

✦ 500 PAH patients in NYHA class 2 or 3

✦ Randomised 2:1:1

✦ Ambrisentan -- 5mg OD uptitrated to 10mg OD

✦ Tadalafil -- 20mg OD uptitrated to 40mg OD

✦ Follow up for            days

✦ primary end points : time to first clinical failure event

✦ death

✦ hospitalization for worsening of PAH

✦ disease progression

✦ unsatisfactory long term clinical response

✦ Secondary end points :

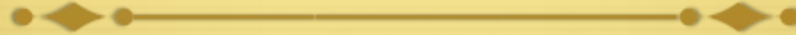
✦ NT pro BNP

✦ 6MWD

✦ borg dyspnea index

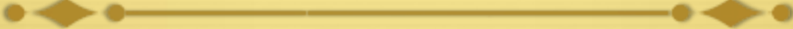
✦ WHO functional class

✦ % of patients with satisfactory clinical response



## ✦ Results

- ✦ Decrease in the risk of clinical failure events by 50%
- ✦ Driven mainly by a reduced risk of hospitalizations by 63%
- ✦ Class 2 responded better than class 3
- ✦ improvements in all the secondary end points

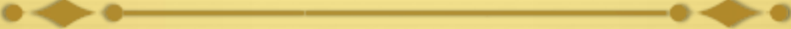
- 
- ✦ No significant increase in adverse events
  - ✦ Peripheral edema C – 45, A – 33, T- 28%
  - ✦ Headache C - 42, A – 33%, T – 35%
  - ✦ Nasal congestion C- 21 , A – 15%, T – 12%
  - ✦ Anemia C- 15%, A- 6%, T- 12%

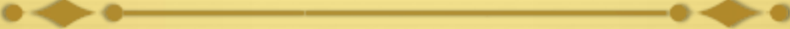


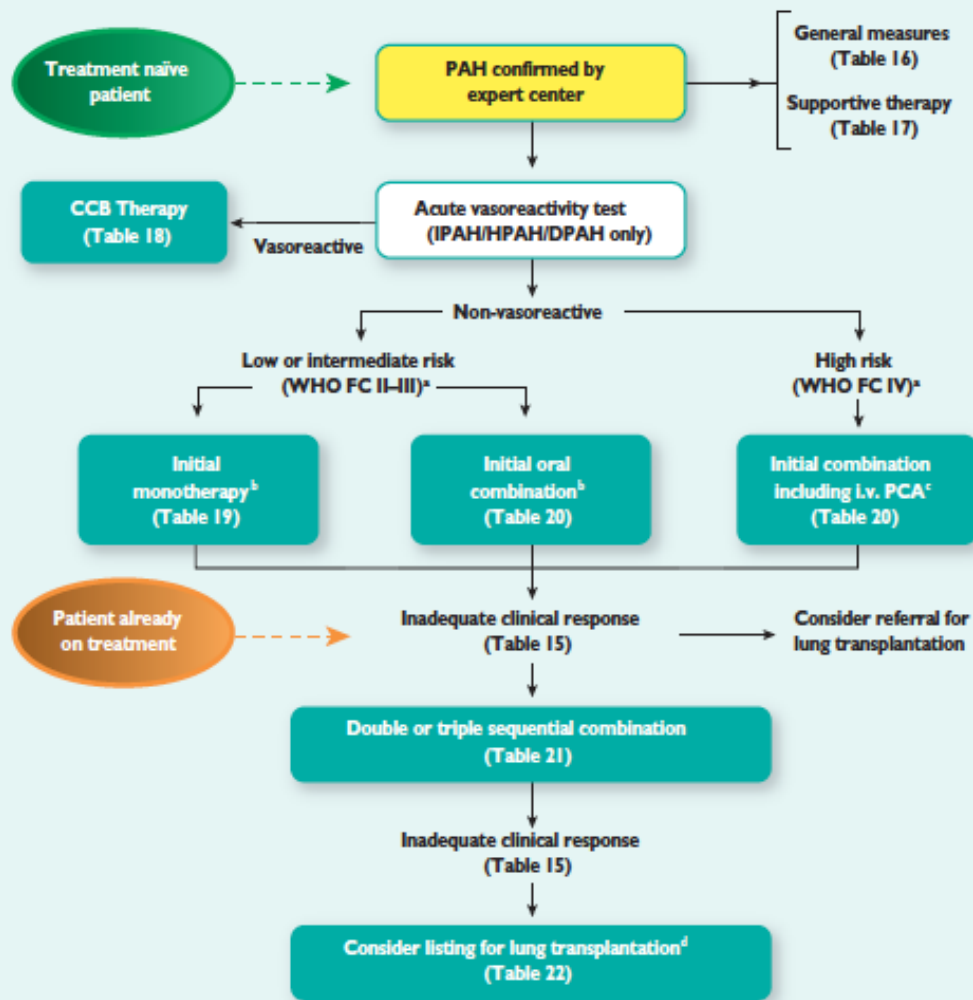


ESC has made the initial upfront therapy with ambrisentan and tadalafil a class 1 recommendation in class 2 or 3 PAH patients

Measure/ treatment	Class <sup>a</sup> -Level <sup>b</sup>						Ref. <sup>c</sup>
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil <sup>d</sup>	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	-

- 
- ✦ Whether the favorable results of ambrisentan – tadalafil combination stem from a class or drug effect
  - ✦ Can the favourable results of this combination extend to different ERA,s and PDE5 I's combinations
  - ✦ No head to head trials
  - ✦ Hypothesis - 1. selective ETA receptor antagonist ( ambrisentan) but not nonselective ETA and ETB receptor antagonists would act synergistically with PDE5I's

- 
- ✦ 2 : no significant drug to drug interactions in ambrisentan and tadalafil.
  - ✦ Tadalafil is metabolised by CYP3A4 isoenzyme
  - ✦ Ambrisentan has no influence on CYP3A4 ( it itself is a substrate of CYP3A4 and CYP2C9)
  - ✦ Tadalafil + Bosentan not favorable because Bosentan is an inducer of CYP3A4 ( same with sildenafil + Bosentan )
  - ✦ Sildenafil is a CYP3A4 Inhibitor, sildenafil can increase the systemic levels of bosentan
  - ✦ 3. patient compliance and convenience



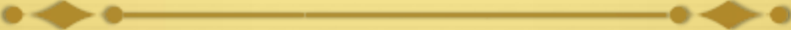
CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.

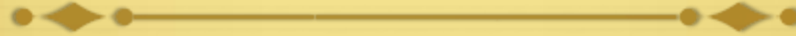
<sup>a</sup>Some WHO-FC III patients may be considered high risk (see Table 13).

<sup>b</sup>Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.

<sup>c</sup>Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.

<sup>d</sup>Consider also balloon atrial septostomy.

- 
- ✦ Arrhythmias
  - ✦ Ventricular arrhythmias rare
  - ✦ Supraventricular arrhythmias occur with an incidence of 2.8%
  - ✦ Atrial flutter and atrial fibrillation equally common
  - ✦ Invariably lead to clinical deterioration
  - ✦ Treatment of atrial flutter proved to be more successful than atrial fibrillation
  - ✦ Persistent Af – 2yr mortality is 80%
  - ✦ Restoration of stable sinus rhythm – long term survival favourable
  - ✦ Electrical cardioversion , and radiofrequency ablation in refractory cases have proven to be effective
  - ✦ Amiodarone preferred .



## ✦ **Hemoptysis**

- ✦ More frequent in HPAH, PAH associated with CHD, and CTEPH
- ✦ Prevalance 1% to 6%
- ✦ Bronchial artery embolisation – an acute emergency procedure
- ✦ may represent a contraindication to anticoagulant therapy

Selexipag			To be determined
Sildenafil <sup>(43)</sup>	CYP3A4 substrate	Bosentan	Sildenafil levels fall 50%; bosentan levels increase 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.
	CYP3A4 substrate	HIV protease inhibitors	Ritonavir and saquinovir increase sildenafil levels markedly.
	CYP3A4 inducer	Phenytoin	Sildenafil level may fall.
	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 Molsidomine	Profound systemic hypotension, combination contraindicated.
Tadalafil <sup>(44)</sup>	CYP3A4 substrate	Bosentan	Tadalafil exposure decreases by 42%, no significant changes in bosentan levels. <sup>(44)</sup> May not require dose adjustment.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.
Riociguat <sup>(18)</sup>	cGMP	Sildenafil, other PDE-5 inhibitors	Hypotension, severe side effects, combination contraindicated.
	cGMP	Nitrates, Nicorandil	Profound systemic hypotension, combination contraindicated.



**Web Table VII Potentially significant drug interactions with pulmonary arterial hypertension drugs<sup>a</sup>**

PAH drug	Mechanism of interaction	Interacting 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	Cyclosporine levels fall 50%; bosentan levels increase 4-fold. Combination contraindicated.
	CYP3A4 substrate	Erythromycin	Bosentan levels increase. May not require dose adjustment of bosentan during a short course.
	CYP3A4 substrate	Ketoconazole	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 contraindicated.
	CYP2C9 and CYP3A4 substrate	Fluconazole, amiodarone	Bosentan levels increase considerably. Combination contraindicated.
	CYP2C9 and CYP3A4 inducers	Rifampicin, phenytoin	Bosentan levels decrease by 58%. Need for dose adjustment uncertain.
	CYP2C9 inducer	HMG CoA reductase inhibitors	Simvastatin levels reduce 50%; similar effects likely with atorvastatin. Cholesterol level should be monitored.
	CYP2C9 inducer	Warfarin	Increases 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.
Macitentan			To be determined



✦ **Upfront triple combination therapy :**

✦ Sitbon et al

✦ 19 patients

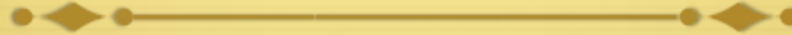
✦ severe PAH : cardiac index <2

PVR >- 1000dyn.sec. cm<sup>5</sup> ie 12.5 w.u  
mean right atrial pressure > 20mmhg m

✦ Group 1 PAH – IPAH,HPAH, DPAH

✦ Treated at the outset with incremental dosing of intravenous epoprostenol simultaneous standardly dosed bosentan

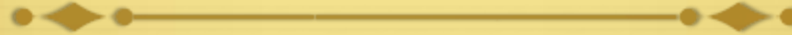
✦ with added sildenafil after 5 days



- ✦ Nonrandomised, not controlled
- ✦ 100% 3 year survival
- ✦ All achieved a functional class 1 or 2
- ✦ All the mechanisms addressed
- ✦ synergistic approach
- ✦ Shotgun approach to use the “right” medication from the start.

✦ **Pediatric pulmonary hypertension:**

✦ lack of RCT,S



✦ Specific treatment algorithm similar to that of adults

✦ **SILDENAFIL :**

✦ approved in Europe for 1-17 years of age

✦ high doses should not be used in children

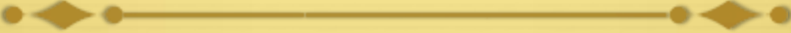
✦ Max dose : 1mg/kg in children less than 8kgs

✦ 10mg/dose in 8 to 20 kgs

✦ 20mg/dose in pts > 20kgs

✦ **BOSENTAN :** a pediatric formulation is available in europe.

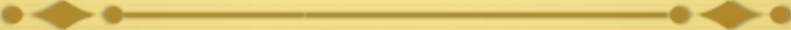
✦ **TADALAFIL :** trials underway to define to the dosage.

- 
- ✦ Ambrisentan : data is scarce .
  - ✦ Combination therapy is class 2a recommendation
  - ✦ Specific treatment goals should be applied for children. -  
FC, TAPSE, NT Pro BNP have been recognised as  
treatment goals



✦ **Portal HTN :**

- ✦ often have increased bleeding risk , hence anticoagulation is not recommended
- ✦ Betablockers often used to lower portal pressure , should be avoided as they worsen hemodynamics
- ✦ Have been excluded from almost all RCT,S ( except for the PATENT study-13 pts )
- ✦ Anecdotal reports - all three groups may be used in this population
- ✦ Hepatotoxicity of bosentan ( tends to accumulate in pts with severely impaired liver function )
- ✦ Ambrisentan and macitentan have a theoretical advantage over bosentan

- 
- ✦ mild PH with normal or near normal PVR in the presence of high CO is well tolerated and tends to be reversible after transplantation
  - ✦ PAH in contrast is a major risk factor
  - ✦ mPAP : >- 50mmhg -- 100% mortality
  - ✦ mPAP: 35- 50 mmhg -- 50% mortality
  - ✦ Class 3 recommendation in severe and uncontrolled PAH patients
  - ✦ May be considered( 2b ) in selected patients responding well to PAH therapy.



✦ **HIV infection :**

✦ HAART + PAH specific therapy

✦ Anticoagulation not recommended -- increased bleeding risk

✦ drug-drug interactions

✦ compliance issues

✦ Sildenafil , drug dose should be reduced if ritonavir or saquinavir are co-administered

✦ Bosentan – breathe trial - improved outcomes

✦ Uncontrolled studies - prostaglandins are useful





PVOD :

no established medical therapy

Refer to lung transplantation as soon as the diagnosis is established

Reports of sustained clinical improvement in individual patients treated with vasodilators , IV epoprostenol, but must be used with great caution, because of the high risk of severe drug induced pulmonary edema



## ✦ **PH- LHD**

- ✦ Optimize the management of underlying heart disease ( class 1 )
- ✦ Identify other cause of PH ie COPD or sleep apnea and treat them
- ✦ PAH specific therapies are not recommended (class 3 )
- ✦ Vasoreactivity testing recommended except in candidates for heart transplantation and /or LV assist devices implantation

✦ Eisenmengers syndrome:

✦ Operability :

**Table 24** Recommendations for correction of congenital heart disease with prevalent systemic-to-pulmonary shunts

Recommendations			Class <sup>a</sup>	Level <sup>b</sup>	Ref. <sup>c</sup>
PVRI (WU • m <sup>2</sup> )	PVR (WU)	Correctable <sup>d</sup>			
<4	<23	Yes	Ila	C	317
>8	>46	No	Ila	C	317
4–8	23–46	Individual patient evaluation in tertiary centres	Ila	C	317

PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index; WU = Wood units.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Reference(s) supporting recommendations.

<sup>d</sup>With surgery or intravascular percutaneous procedure.



✦ **Anticoagulant therapy** : controversial

- ✦ High incidence of PA thrombosis and stroke, but there is also an increased risk of hemorrhage and homoptysis
- ✦ No data exist and no specific recommendation
- ✦ CCB'S are dangerous
- ✦ Evidence for bosentan – BREATHE
- ✦ Evidence available for other ERA'S , sildenafil, tadalafil, and IV epoprostenol
- ✦ “Treat to close “ concept not supported by available data
- ✦ Heart – lung or lung transplantation with heart surgery is the option for cases not responding to medical treatment

✦ **Imatinib:**

✦ Antiproliferative agent

✦ Inhibitory effect on platelet derived growth factor and C – KIT signaling

✦ Initial case study – class 4 patients as an add on to oral bosentan, inhaled iloprost , and sildenafil

✦ Improvements in the 6MWD, hemodynamics, functional class, effect sustained after 6 months of treatment

✦ Phase 2 study : improvements were seen in PVR and cardiac output

✦ Phase 3 IMPRES study : improved exercise capacity, hemodynamics, .

✦ Did not provide a benefit in terms of functional class, time to clinical worsening or mortality

✦ Adverse events im IMPRES were similar to that of imatinib used in other conditions

✦ High incidence of subdural hematoma when given in addition to oral anticoagulants

Investigating drugs : newer drugs in the early phase of development.

VIP

Endothelial NO synthase couplers

RHO kinases

Serotonin

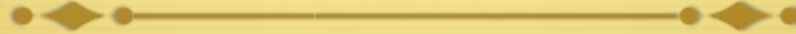
Apelin

- ✦ Immunosuppressants
- ✦ Growth factors receptor blockers
- ✦ Mitochondrial dysfunction – dichloro acetate
- ✦ PPAR gamma agonists
- ✦ Stem cells

- ✦ BAS
- ✦ Decompresses Rt heart chambers
- ✦ Increases LV preload , CO
- ✦ Despite arterial desaturation , increased systemic oxygen transport
- ✦ Decreased sympathetic hyperactivity
  
- ✦ Graded balloon dilatation technique is preferred
- ✦ Not included in treatment algorithms
- ✦ Bridging or palliative procedures to transplantation
- ✦ Shows improvements in CI and decreases in RAP , improves in 6MWD.
- ✦ Should be avoided in end stage pts with a baseline mean RAP >20mmhg and o2 saturation at rest ,85% on room air

## ✦ ICU

✦ icu treatment for right ventricular failure or a comorbid condition



✦ Mortality is 41% underscoring the poor prognosis

✦ Treatment of triggering factors like anaemia, arrhythmias, infections or other comorbidities

✦ Optimisation of fluid balance usually with IV diuretics

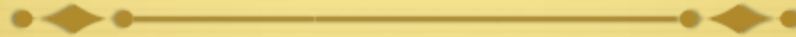
✦ Reduction of RV afterload, usually with parenteral prostaglandin analogues

✦ Improvement of CO with inotropes with dobutamine being the preferred inotrope,

✦ Intubation should be avoided

✦ CPR has a poor outcome





- ✦ ECMO
- ✦ Bridge to transplantation
- ✦ Bridge to recovery
  
- ✦ Venoarterial ECMO is preferred
- ✦ Venovenous approach may improve oxygenation but does not unload the RV , which makes it unsuitable for this patient population



## ✦ Transplantation

- ✦ An important option for those who fail on optimal medical therapy and remain in FC 3 or 4
- ✦ 5 yr survival following transplantation was 45-50%
- ✦ More recent data - survival has increased to 50-75% at 5 years, 45-66% at 10 years
- ✦ PVOD and PCH have poorest prognosis , these patients should be listed for transplantation at the diagnosis
- ✦ heart lung or double transplantation
- ✦ Eisenmengers - isolated lung transplantation with repair of the cardiac defect or heart – lung transplantation



Thank you