PULMONARY HYPERTENSION

ACHD training day 2017

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Introduction

- Definition and classification
- Demographics
- Prognosis
- Diagnosis
- Treatment

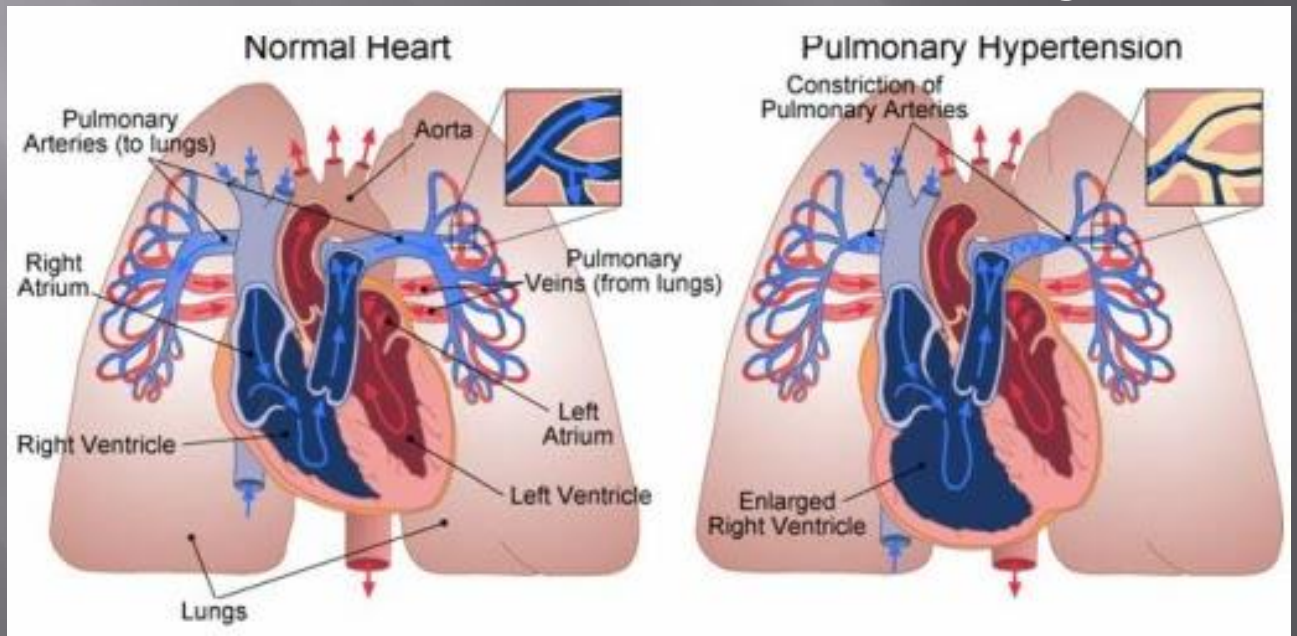
Definition Pulmonary hypertension

- Mean pulmonary artery pressure > 25mmHg at rest as assessed by right heart catheterization (RHC)

- Normal mPAP 14 ± 3 mmHg, upper limit of normal 20mmHg
- No definition of PH on exercise

Definition Pulmonary hypertension

- Pulmonary *arterial* hypertension (PAH):
  - Pre-capillary PH
  - Pulmonary artery wedge pressure ≤15 mmHg
  - Pulmonary vascular Resistance > 3 Wood Units
  - Absence of other causes (CTEPH, lung diseases)



Haemodynamic definitions of pulmonary hypertension

Definition	Characteristics*	Clinical group(s)[b]
PH	PAPm ≥25 mmHg	All
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg	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	PAPm ≥25 mmHg PAWP >15 mmHg	2. PH due to left heart disease 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG <7 mmHg and/or PVR ≤3 WU[c]	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥7 mmHg and/or PVR >3 WU[c]	

CO = cardiac output; DPG = diastolic pressure gradient (diastolic PAP - mean PAWP); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.

[a]All values measured at rest; see also section 7.
[b]According to Table 4.
[c]Wood Units are preferred to dynes.s.cm^{-5}.

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European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Comprehensive clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension

1.1 Idiopathic

1.2 Heritable
- 1.2.1 BMPR2 mutation
- 1.2.2 Other mutations

1.3 Drugs and toxins induced

1.4 Associated with:
- 1.4.1 Connective tissue disease
- 1.4.2 human immunodeficiency virus (HIV) infection
- 1.4.3 Portal hypertension
- 1.4.4 Congenital heart disease (Table 5)
- 1.4.5 Schistosomiasis

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

1′.1 Idiopathic

1′.2 Heritable
- 1′.2.1 EIF2AK4 mutation
- 1′.2.2 Other mutations

1′.3 Drugs, toxins and radiation induced

1′.4 Associated with:
- 1′.4.1 Connective tissue disease
- 1′.4.2 HIV infection

1″. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

2.1 Left ventricular systolic dysfunction

2.2 Left ventricular diastolic dysfunction

2.3 Valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

2.5 Congenital/acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern

3.4 Sleep-disordered breathing

3.5 Alveolar hypoventilation disorders

3.6 Chronic exposure to high altitude

3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

4.1 Chronic thromboembolic pulmonary hypertension

4.2 Other pulmonary artery obstructions
- 4.2.1 Angiosarcoma
- 4.2.2 Other intravascular tumors
- 4.2.3 Arteritis
- 4.2.4 Congenital pulmonary arteries stenoses
- 4.2.5 Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms

5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy

5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

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Anatomical-pathophysiological

Classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension

1. Type

1.1 Simple pre-tricuspid shunts

- 1.1.1 Atrial septal defect (ASD)
  - 1.1.1.1 Ostium secundum
  - 1.1.1.2 Sinus venous
  - 1.1.1.3 Ostium primum
- 1.1.2 Total or partial unobstructed anormalous pulmonary venous

1.2 Simple post-tricuspid shunts

- 1.2.1 Ventricular septal defect (VSD)
- 1.2.2 Patent ductus arteriosus

1.3 Combined shunts

Describe combination and define predominant defect

1.4 Complex congenital heart disease

- 1.4.1 Complete atrioventricular septal defect
- 1.4.2 Truncus arteriosus
- 1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
- 1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
- 1.4.5 Other

2. Dimension (specify for each defect if more than one congenital heart defect exists)

2.1 Haemodynamic (specify Qp/Qs)[a]

- 2.1.1 Restrictive (pressure gradient accross the defect)
- 2.1.2 Non-restrictive

2.2 Anatomic[b]

- 2.2.1 Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
- 2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt

3.1 Predominantly systemic-to-pulmonary

3.2 Predominantly pulmonary-to-systemic

3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status

5.1 Unoperated

5.2 Palliated (specify type of operation/s, age at surgery)

5.3 Repaired (specify type of operation/s, age at surgery)

[a] Ratio of pulmonary (Qp) to systemic (Qs) blood flow.
[b] The size applies to adult patients.

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Eisenmenger's syndrome

- Congenital systemic-to-pulmonary shunt (L→R)
- Increased right sided blood volume and pressure leads to fibrosis of pulmonary capillaries → pulmonary hypertension
- Right ventricular hypertrophy
- Pulmonary > systemic pressures
- Reversal of shunt (R→L) → cyanosis

Clinical classification of pulmonary arterial hypertension associated with congenital heart disease

1. Eisenmenger's syndrome

Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.

2. PAH associated with prevalent systemic-to-pulmonary shunts

- Correctable[a]
- Non-correctable

Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.

3. PAH with small/coincidental[b] defects

Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contra-indicated.

4. PAH after defect correction

Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions.

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.
[a]With surgery or intravascular percutaneous procedure.
[b]The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect, and also the pressure gradient, the shunt size and direction, & the pulmonary to systemic flows ratio should be considered
(Web Table II on the web at; www.escardio.org/guidelines).

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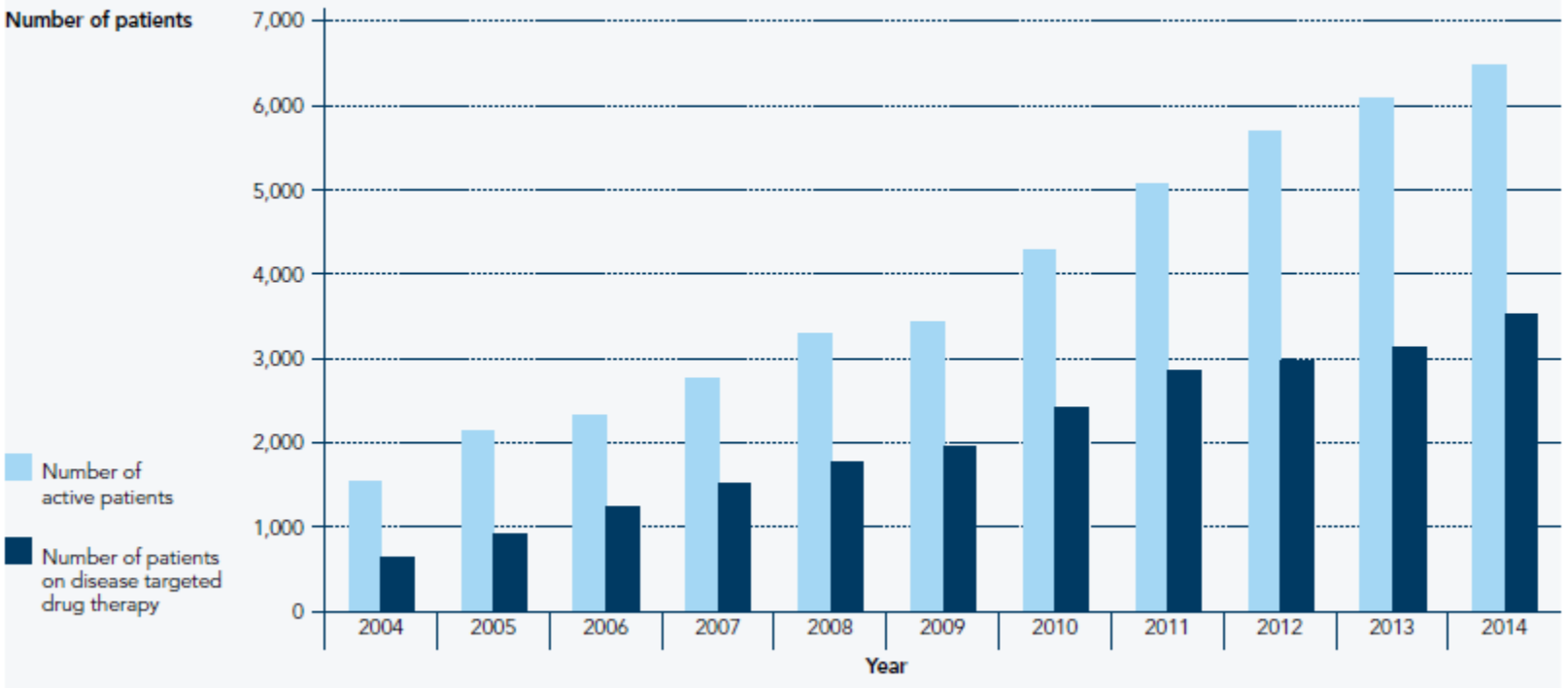
Demographics

- UK: 97 cases per one million (65 million → 6305)
- 8 tertiary referral hospitals for PH in UK (one paediatric)
- In 2014 6484 patients seen in these hospitals
  - 45 % pulmonary arterial hypertension
    - One third related to congenital heart disease, ≈ 1000 patients
  - 20% Chronic thromboembolic pulmonary hypertension
  - 3% related to left heart disease
- Female > male, ratio UK 1.8:1

Demographics

Figure 1
Number of patients active under the service and number of patients on disease targeted therapies for pulmonary hypertension on 31 March



Source: National Audit of Pulmonary Hypertension 2014

Demographics

Table 2
Number of patients active and alive on 31 March by specialised centre

Specialised pulmonary hypertension centre	Total 2010	Total 2011	Total 2012	Total 2013	Total 2014
Golden Jubilee National Hospital	291	329	375	428	494
Great Ormond Street Hospital for Children NHS Foundation Trust	300	319	244	361	350
Imperial College Healthcare NHS Trust	664	764	914	942	936
Papworth Hospital NHS Foundation Trust	591	625	716	777	809
Royal Brompton and Harefield NHS Foundation Trust	492	640	776	968	902
Royal Free London NHS Foundation Trust	581	774	997	980	1,049
Sheffield Teaching Hospitals NHS Foundation Trust	1,074	1,291	1,393	1,212	1,489
The Newcastle upon Tyne Hospitals NHS Foundation Trust	294	320	318	422	455
Total patients seen at specialised centres	**4,287**	**5,062**	**5,733**	**6,090**	**6,484**

Source: National Audit of Pulmonary Hypertension 2014

Demographics

Table 3a
Percentage of patients active on 31 March 2014 by Dana Point diagnosis classification and by specialised centre

Description	Total	Golden Jubilee National Hospital	Great Ormond Street Hospital for Children NHS Foundation Trust	Imperial College Healthcare NHS Trust	Papworth Hospital NHS Foundation Trust	Royal Brompton and Harefield NHS Foundation Trust	Royal Free NHS Foundation Trust	Sheffield Teaching Hospitals NHS Foundation Trust	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Total number of patients	**6,484**	**494**	**350**	**936**	**809**	**902**	**1,049**	**1,489**	**455**
Pulmonary arterial hypertension	45%	51%	39%	46%	36%	47%	32%	55%	55%
Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	0%	0%	0%	1%	0%	0%	0%	0%	0%
Pulmonary hypertension due to left heart disease	3%	3%	1%	4%	2%	3%	6%	2%	2%
Pulmonary hypertension due to lung disease and/or hypoxia	4%	2%	22%	1%	1%	8%	2%	3%	1%
Chronic thromboembolic pulmonary hypertension	20%	20%	0%	27%	49%	6%	10%	21%	20%
Pulmonary hypertension with unclear/multifactorial mechanisms	3%	4%	5%	2%	2%	6%	1%	1%	3%
Not pulmonary hypertension	11%	11%	12%	12%	1%	17%	18%	6%	7%
No final diagnosis possible	0%	0%	0%	0%	0%	1%	0%	0%	0%
No diagnosis	14%	9%	21%	7%	9%	11%	30%	11%	11%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Source: National Audit of Pulmonary Hypertension 2014

Demographics

Table 3b
Percentage of patients active on 31 March 2014 with a latest diagnosis of pulmonary arterial hypertension by subcategory and by specialised centre

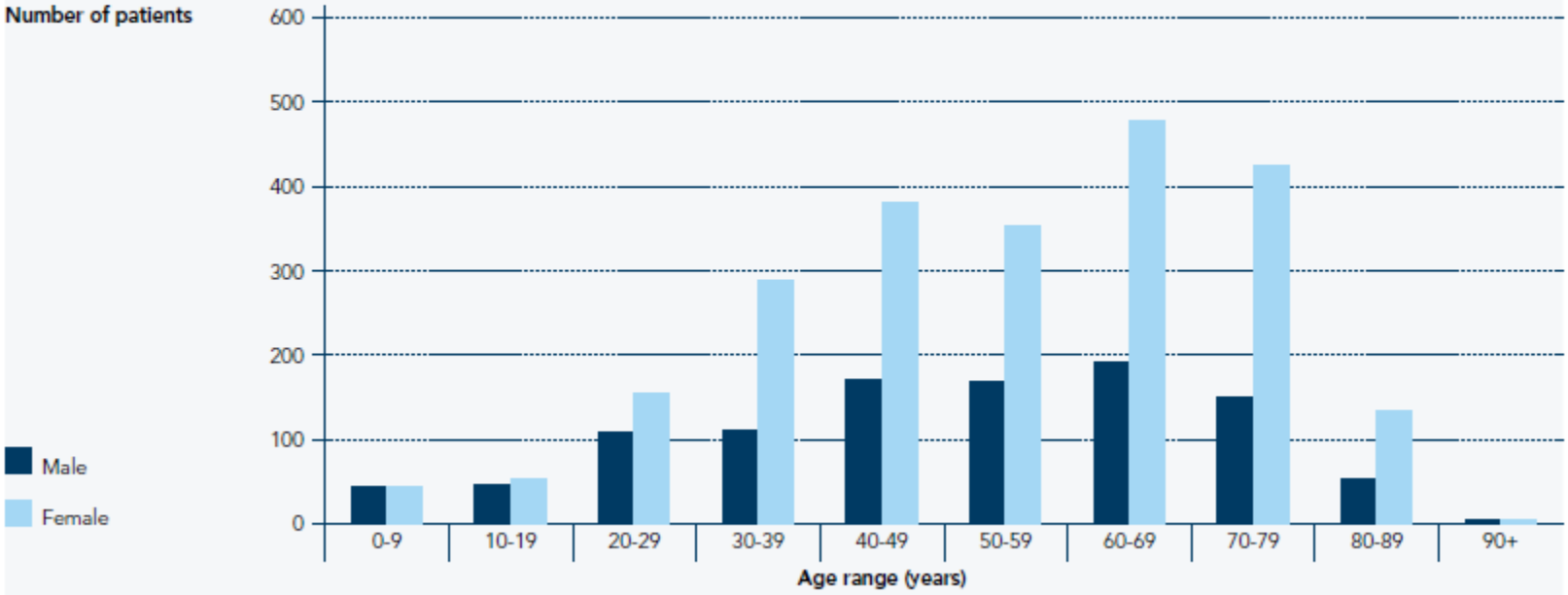
Description	Total	Golden Jubilee National Hospital	Great Ormond Street Hospital for Children NHS Foundation Trust	Imperial College Healthcare NHS Trust	Papworth Hospital NHS Foundation Trust	Royal Brompton and Harefield NHS Foundation Trust	Royal Free NHS Foundation Trust	Sheffield Teaching Hospitals NHS Foundation Trust	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Number of pulmonary arterial hypertension patients	**2,940**	**250**	**135**	**430**	**291**	**428**	**331**	**823**	**252**
Idiopathic/heritable/drug induced pulmonary arterial hypertension	33%	46%	24%	48%	35%	16%	17%	37%	31%
Pulmonary arterial hypertension associated with connective tissue disease	23%	21%	4%	12%	21%	13%	56%	26%	19%
Pulmonary arterial hypertension associated with portal hypertension	4%	8%	1%	4%	3%	1%	4%	3%	5%
Pulmonary arterial hypertension associated with congenital heart disease	34%	23%	70%	28%	24%	68%	7%	33%	33%
Other	2%	1%	1%	6%	1%	1%	1%	1%	1%
No sub diagnosis	5%	0%	0%	2%	15%	1%	15%	1%	12%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Source: National Audit of Pulmonary Hypertension 2014

Demographics

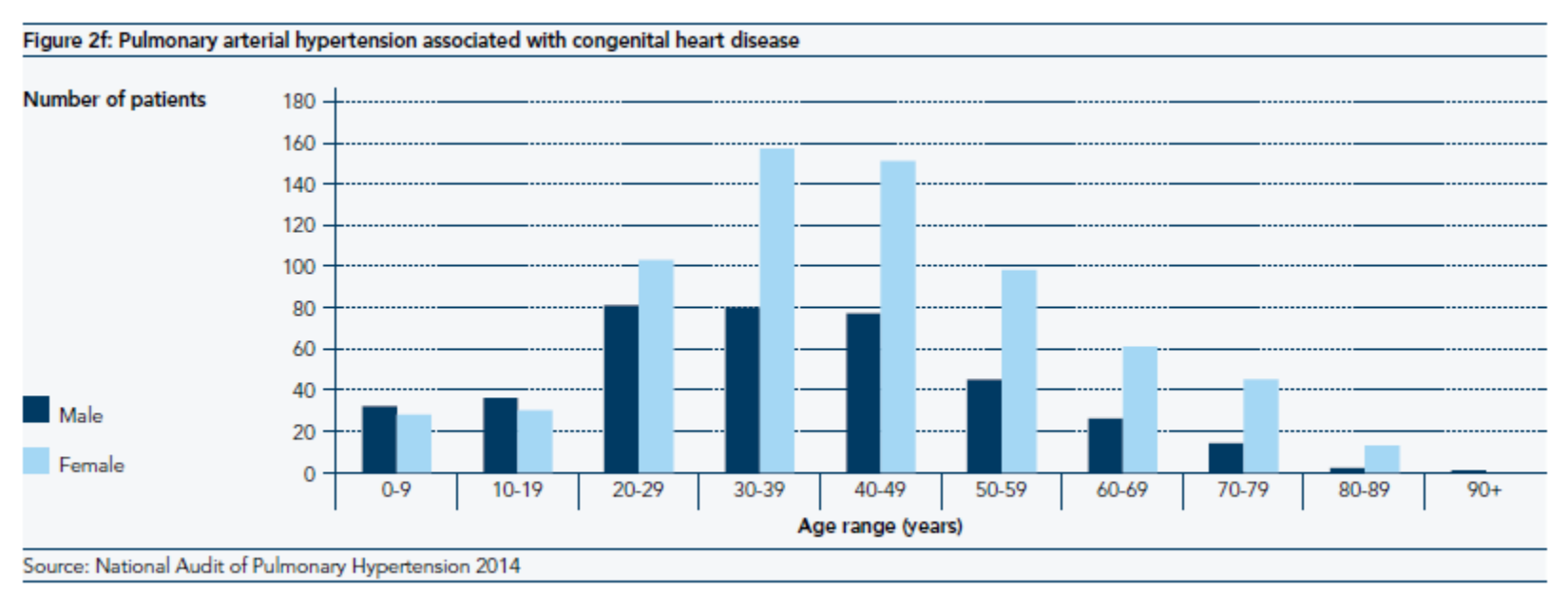
Figure 2
Age and gender distribution of patients active at any point during 2013/14 according to diagnosis

Figure 2a: Pulmonary arterial hypertension



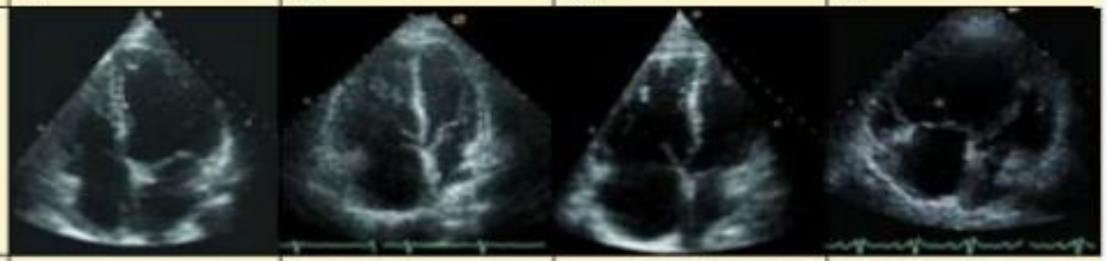
Source: National Audit of Pulmonary Hypertension 2014

Demographics



Prognosis

PULMONARY ARTERIAL HYPERTENSION: CLINICAL COURSE AND PROGRESSION

PHASE	ASYMPTOMATIC COMPENSATED	SYMPTOMATIC DECOMPENSATING		ADVANCED DECOMPENSATED
		SUBTLE	OVERT	
Symptoms and signs	None	Shortness of breath, fatigue	Shortness of breath, fatigue, pedal edema, dizziness, abdominal swelling, right ventricular dysfunction	Right ventricular failure, syncope, death
Functional class	I	II	III	IV
Echocardiographic appearance				
Hemodynamic trends (not drawn to scale)				

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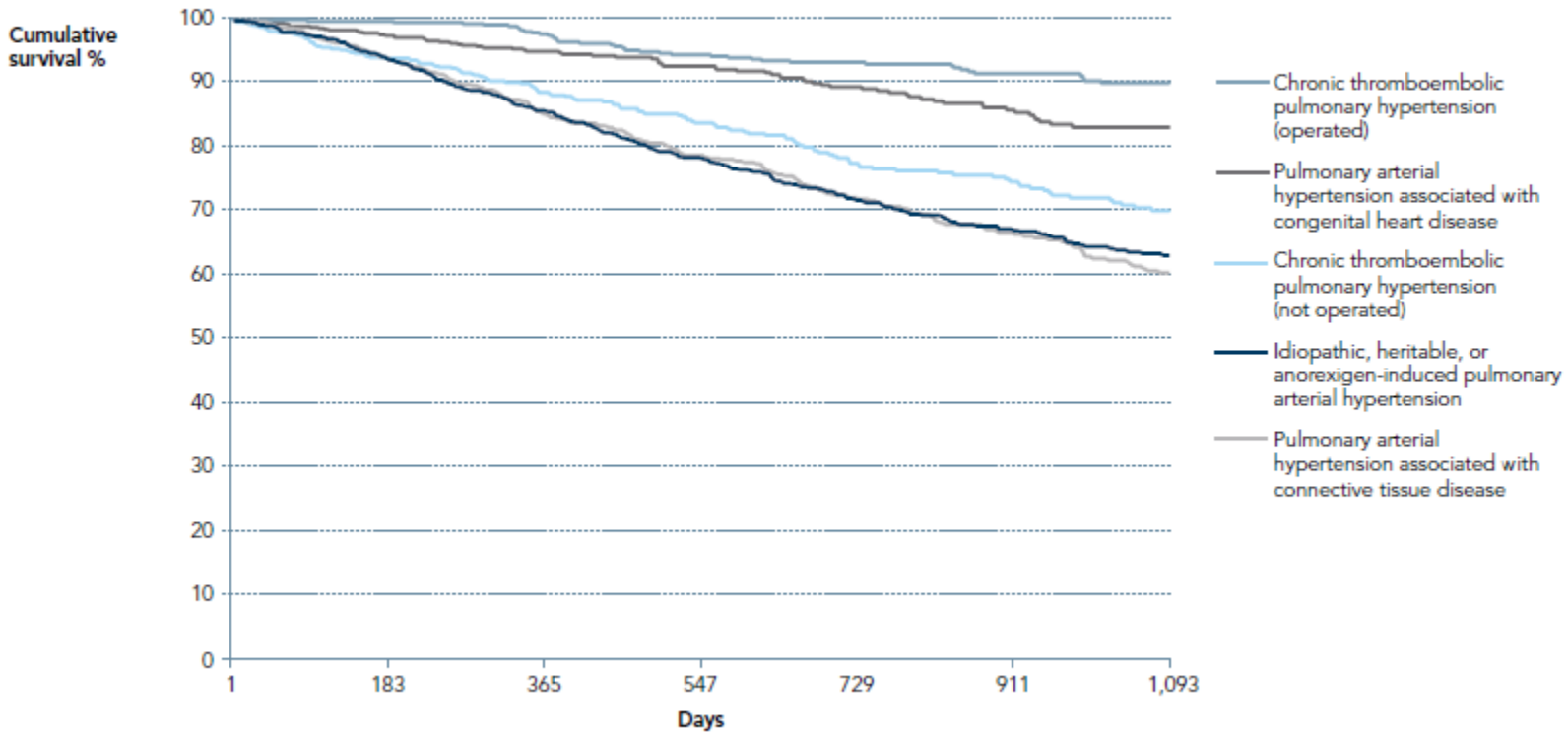
Prognosis

Figure 11
Kaplan Meier curve showing the time from referral to death by latest diagnosis group
Only for patients within cohort for longitudinal analysis



Source: National Audit of Pulmonary Hypertension 2014

Prognosis

Table 14
One and three year survival rates by latest diagnosis group taken from Figure 11
Only for patients within cohort for longitudinal analysis

Diagnosis group	1 year survival rate	3 year survival rate
Idiopathic, heritable, or anorexigen-induced pulmonary arterial hypertension	86%	63%
Pulmonary arterial hypertension associated with connective tissue disease	85%	60%
Pulmonary arterial hypertension associated with congenital heart disease	95%	83%
Chronic thromboembolic pulmonary hypertension (operated)	98%	90%
Chronic thromboembolic pulmonary hypertension (not operated)	88%	70%

Source: National Audit of Pulmonary Hypertension 2014

Diagnostics

- Symptoms:
  - Shortness of breath (on exertion)
  - Palpitations
  - Chest discomfort
  - Fatigue
  - Fluid retention

Diagnostics

- Possible signs on physical examination:
  - Observations normal
  - Systolic murmur related to TR
  - Raised JVP
  - Pleural effusion
  - Ascites
  - Hepatomegaly
  - Peripheral oedema

Diagnostic investigations utilised in patients with PH

- Electrocardiogram
- Chest radiograph
- Echocardiography
- Pulmonary function tests and arterial blood gases
- Ventilation/perfusion lung scan
- High-resolution computed tomography, contrast enhanced computed tomography
- Cardiac magnetic resonance imaging
- Blood tests and immunology
- Abdominal ultrasound scan
- Right heart catheterization and vasoreactivity
- Pulmonary Angiography

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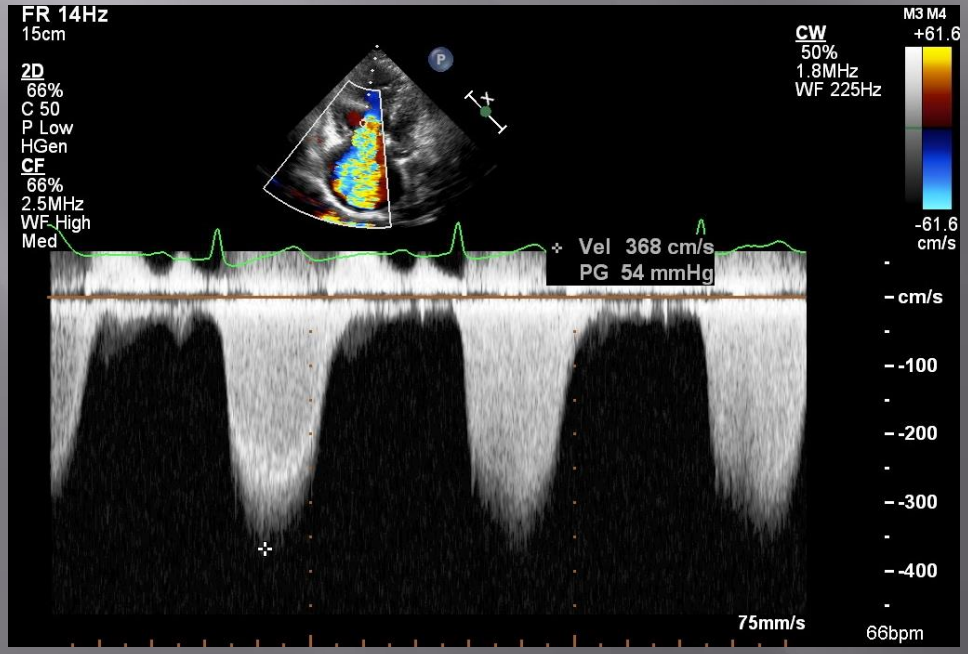
Diagnostics

- Echo:
  - Indirect measurement of ***systolic*** PAP by summation of peak pressure gradient over tricuspid valve and estimation of right atrial pressure



Size of IVC	IVC size On Inspiration	Right atrial pressure(mmhg)
Small < 1.5cm	Near total collapse	0 - 5
Normal (1.5-2.5cm)	Decrease > 50%	5 - 10
Normal	Decrease < 50%	10 - 15
Dilated > 2.5cms	Decrease < 50%	15 - 20
Both IVC & Hepatic veins dilated	No change	> 20

Diagnostics

- Echo:
  - LV dysfunction, systolic and diastolic
  - RV dysfunction
  - PA dimension
  - Valve abnormalities
  - Congenital abnormalities

Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension according with PTRV & additional signs

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo "PH signs"	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and right atrium
Right ventricle/ left ventricle basal diameter ratio >1.0.	Right ventricular outlflow Doppler acceleration time <105 m/sec and/or midsystolic notching.	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 %with a sniff or <20 % with quiet inspiration).
Flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole).	Early diastolic pulmonary regurgitation velocity >2.2 m/sec.	Right atrial area (end-systole) >18 cm^2.
	PA diameter >25 mm..	

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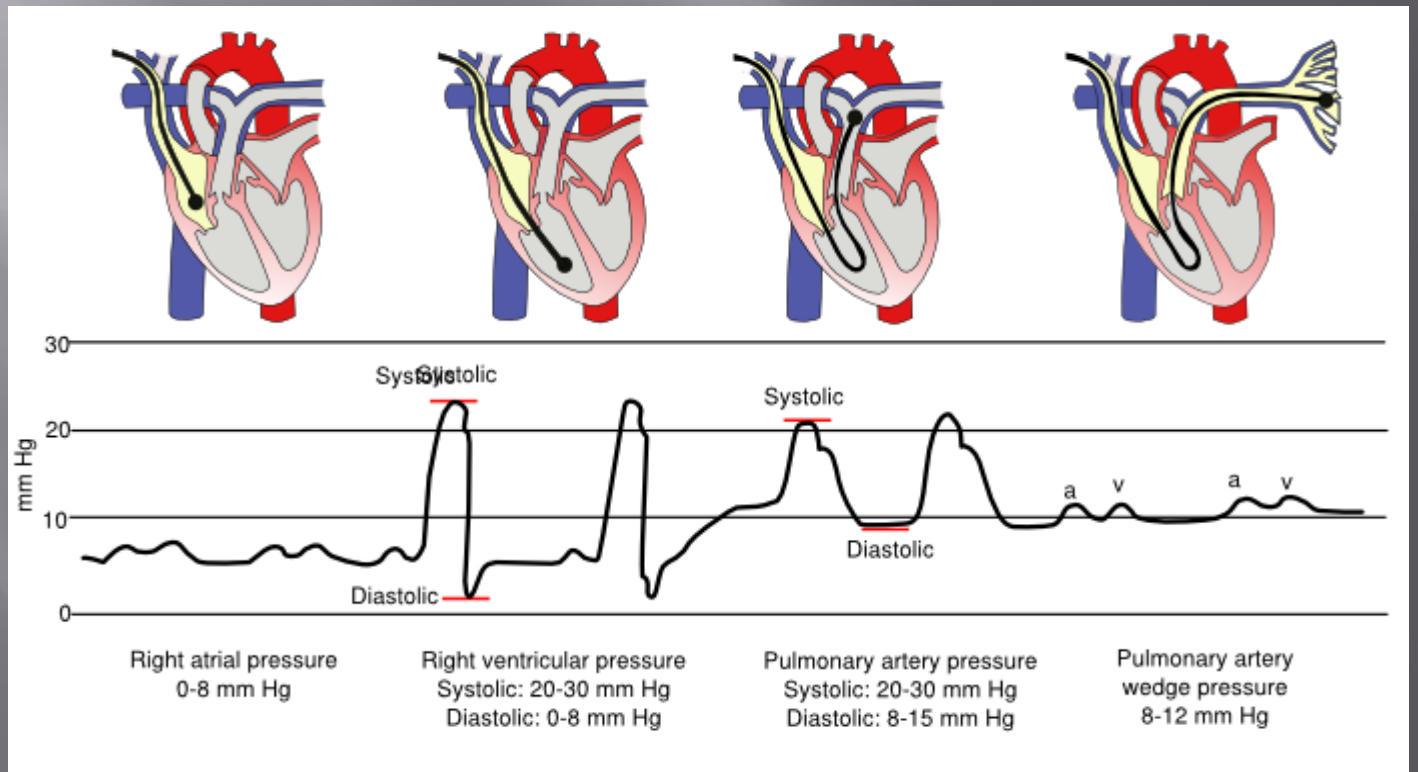
Right heart catheterization

- Required to confirm diagnosis of PAH (pre-capillary) and CTEPH
- Assess severity of haemodynamic effects
- Consider left heart catheterization and LVEDP measurements, esp. if suspicion of left sided heart disease
- In expert centres low morbidity (1.1%) and mortality (0.055%)

Right heart catheterization

- Correct zeroing of pressure transducer
- Pressure recordings of RA, RV, PA, PAWP (as surrogate for LA pressure)



Right heart catheterization

- Saturation samples of SVC, IVC, RA, PA
- Cardiac output measurement by
  - Thermodilution, but unreliable in presence of intracardiac shunt
  - indirect Fick method:
    - Cardiac output = $\frac{Oxygen\ consumption}{arteriovenous\ oxygen\ difference}$
- Pulmonary Vascular Resistance measurement:
  - $\frac{mean\ pulmonary\ artery\ pressure - mean\ PA\ wedge\ pressure}{cardiac\ output}$
- Acute volume loading (500 ml) and vasoreactivity test (Nitric oxide) if indicated

Right heart catheterization in pulmonary hypertension

Recommendations	Class	Level
RHC is recommended to confirm the diagnosis of pulmonary arterial hypertension (Group 1) and to support treatment decisions.	I	C
In patients with PH, it is recommended to perform RHC in expert centres (Table 34) as it is technically demanding and may be associated with serious complications.	I	B
RHC should be considered in pulmonary arterial hypertension (Group 1) to assess the treatment effect of drugs (Table 12).	IIa	C
RHC is recommended in patients with congenital cardiac shunts to support decisions on correction (Table 23).	I	C
RHC is recommended in patients with PH due to left heart disease (Group 2) or lung disease (Group 3) if organ transplantation is considered .	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and support treatment decisions.	IIb	C
RHC is indicated in patients with Chronic Thromboembolic Pulmonary Hypertension (Group 4) to confirm the diagnosis and support treatment decisions.	I	C

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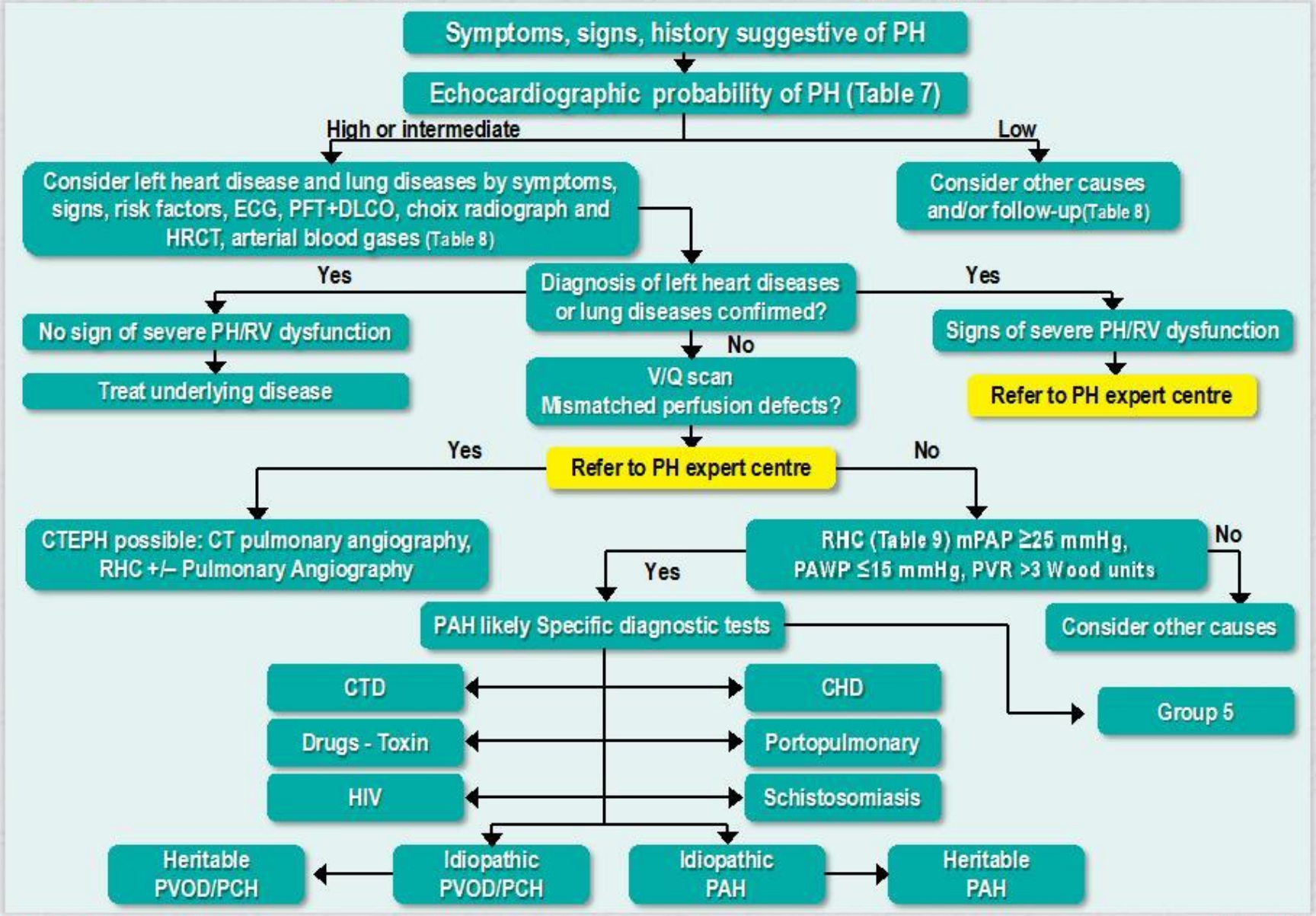
Diagnostic Algorithm for Pulmonary Hypertension



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Examples of key factors suggestive of Group 2 pulmonary hypertension

Clinical presentation	Echocardiography	Other features
Age >65 years	Structural left heart abnormality · Disease of left heart valves · LA enlargement (>4.2 cm) · Bowing of the IAS to the right · LV dysfunction · Concentric LV hypertrophy and/or increased LV mass	ECG · LVH and/or LAH · AF/Afib · LBBB · Presence of Q waves
Symptoms of left heart failure	Doppler indices of increased filling pressures · Increased E/e' · >Type 2-3 mitral flow abnormality	Other imaging · Kerley B lines · Pleural effusion · Pulmonary oedema · LA enlargement
Features of metabolic syndrome	Absence of: · RV dysfunction · Mid systolic notching of the PA flow · Pericardial effusion	
History of heart disease (past or current)		
Persistent atrial fibrillation		

AF = atrial flutter; Afib = atrial fibrillation; ECG = electrocardiogram; IAS = inter-atrial septum; LA = left atrium; LAH = left anterior hemiblock; LBBB= left bundle branch block; LV = left ventricle; LVH = left ventricular hypertrophy; PA = pulmonary artery; RV = right ventricle.

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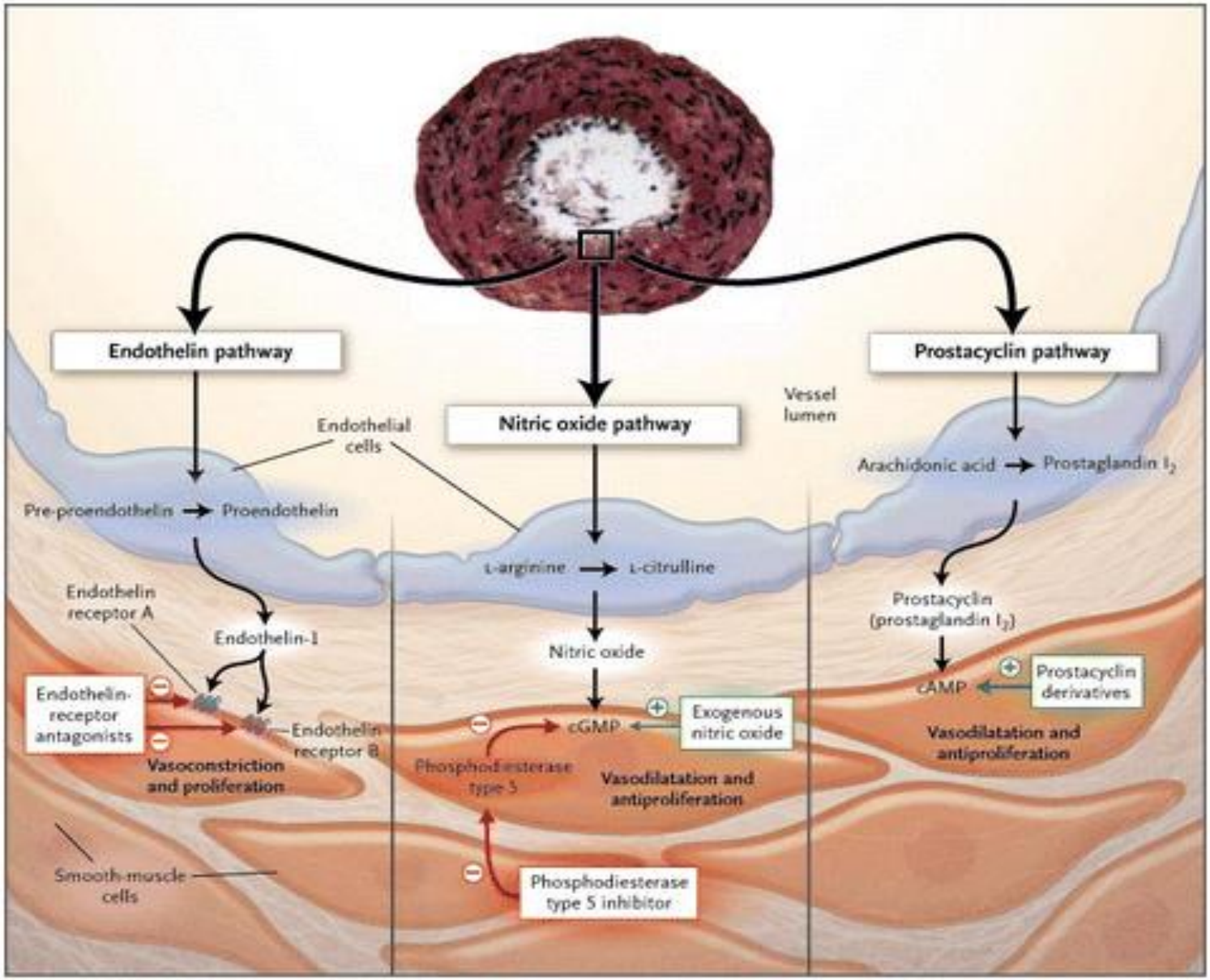
Treatment

- Shared care:
  - Tertiary centre (Hammersmith, London)
  - Secondary centre more local (professor R. Tulloh)
- Ongoing research into treatment options

- Current medical treatment:
  - Endothelin receptor antagonists (-afil)
  - Phosphodiesterase type 5 inhibitors (-entan)
  - Prostanoids (-prost-)
  - Guanylate cyclase stimulators (Riociguat)


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

Efficacy of drug monotherapy, for PAH (Group 1)

Recommendations			Class - Level					
Measure/treatment			**WHO-FC II**		**WHO-FC III**		**WHO-FC IV**	
Calcium channel blockers			I	C	I	C	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[d]		I	B	I	B	IIb	C
Phosphodiesterase type-5 inhibitors	Sildenafil		I	A	I	A	IIb	C
	Tadalafil		I	B	I	B	IIb	C
	Vardenafil*		IIb	B	IIb	B	IIb	C
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C
Prostanoids	Epoprostenol	intravenous[d]	-	-	I	A	I	A
	Iloprost	Inhaled	-	-	I	B	IIb	C
		Intravenous*	-	-	IIa	C	IIb	C
	Treprostinil	subcutaneous	-	-	I	B	IIb	C
		Inhaled*	-	-	I	B	IIb	C
		Intravenous[e]	-	-	IIa	C	IIb	C
		Oral*	-	-	IIb	B	-	-
	Beraprost*		-	-	IIb	B	-	-
IP-receptor agonists	Selexipag (oral)*		I	B	I	B	-	-

[c]Only in responders to acute vasoreactivity tests: Class I for idiopathic PAH, heritable PAH and PAH due to drugs;Class IIa for APAH conditions. - [d]Time to clinical worsening as primary end-point in RCTs or drugs with demonstratedreduction in all-cause mortality. - [e]In patients not tolerating the subcutaneous form.

*This drug is not approved by the EMA at the time of publication of these guidelines.

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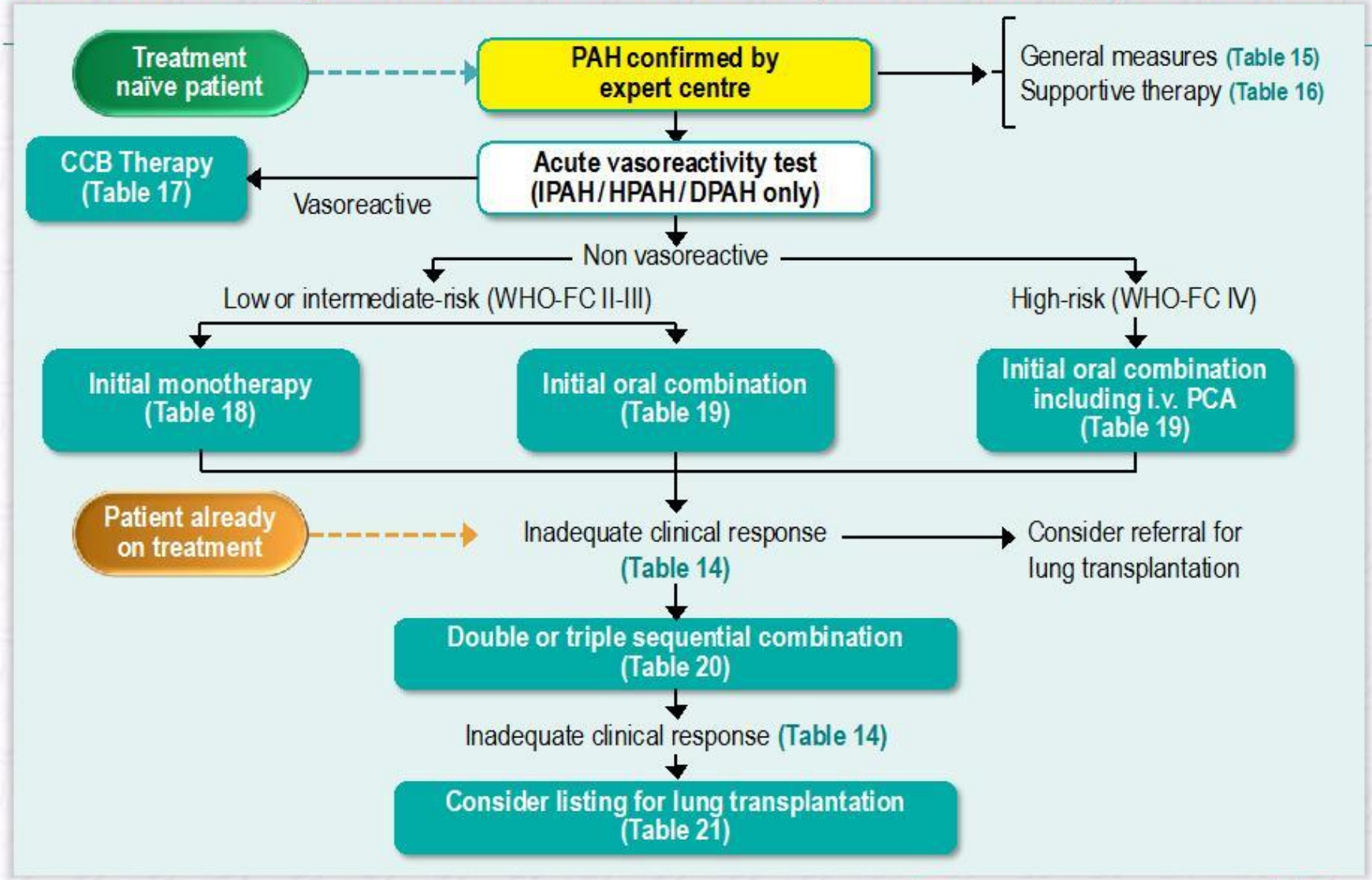
Efficacy of sequential drug combination therapy, for PAH (Group 1)

Recommendations	Class - Level					
Measure/treatment	**WHO-FC II**		**WHO-FC III**		**WHO-FC IV**	
Macitentan added to sildenafil	I	B	I	B	IIa	C
Riociguat added to bosentan	I	B	I	B	IIa	C
Selexipag added to ERA and/or PDE-5i	I	B	I	B	IIa	C
Sildenafil added to epoprostenol	-	-	I	B	IIa	B
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C
Bosentan added to epoprostenol	-	-	IIb	C	IIb	C
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C
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

European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Treatment Algorithm for Pulmonary Arterial Hypertension



European Heart Journal 2016:37;67–119 -doi:10.1093/eurheartj/ehv317
European Respiratory Journal 2015 46: 903-975;

Treatment

Table 9
Number of drug prescriptions on 31 March including monotherapy and combination therapy

Drug	Total prescriptions 2010	Total prescriptions 2011	Total prescriptions 2012	Total prescriptions 2013	Total prescriptions 2014
Sildenafil	1,414	1,869	2,166	2,376	2,689
Tadalafil	5	6	31	97	138
Bosentan	909	1,208	1,145	1,108	1,161
Ambrisentan	120	277	328	425	514
Sitaxsentan	88	0	0	0	0
Iloprost	96	120	111	119	153
Treprostinil	88	89	75	51	45
Epoprostenol	39	69	73	75	84
Calcium channel blockers	22	25	38	19	49
Unknown	91	78	64	79	117
Total	**2,872**	**3,741**	**4,031**	**4,349**	**4,950**

Unknown includes clinical trial medication. Note that sitaxsentan was withdrawn from clinical use in late 2010.

Source: National Audit of Pulmonary Hypertension 2014

Pulmonary arterial hypertension associated with congenital heart disease

Recommendations	Class	Level
Bosentan is recommended in WHO-FC III patients with Eisenmenger's syndrome.	I	B
Other ERAs, PDE-5i, and prostanoids should be considered in patients with Eisenmenger's syndrome.	IIa	C
In the absence of significant haemoptysis, oral anticoagulant treatment may be considered in patients with PA thrombosis or signs of heart failure.	IIb	C
The use of supplemental O_2 therapy should be considered in cases in which it produces a consistent increase in arterial oxygen saturation and reduces symptoms.	IIa	C
If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%.	IIa	C
The use of supplemental iron treatment may be considered in patients with low ferritin plasma levels.	IIb	C
Combination drug therapy may be considered in patients with Eisenmenger's syndrome.	IIb	C
The use of CCBs is not recommended in patients with Eisenmenger's syndrome.	III	

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Conclusion

- PH is a life-limiting and activity-limiting disease
- Correct diagnosis of PH important for treatment and prognosis
- PH associated with congenital heart disease is pulmonary arterial hypertension (group I)
- Consider referral to specialist/tertiary centre, especially if PAH or CTEPH
- Shared care between BRI and tertiary centre

Literature

- ESC guidelines on pulmonary hypertension (2015)
- UK guidelines on pulmonary hypertension (2008)
- National Audit of pulmonary hypertension (2014)

Pulmonary arterial hypertension associated with adult congenital heart disease

Recommendations			Class	Level
PVRi (Wu · m²)	PVR (Wu)	Correctable[a]		
<4	<2.3	Yes	IIa	C
>8	>4.6	No	IIa	C
4-8	2.3-4.6	Individual patient evaluation in tertiairy centres	IIa	C

PVR = pulmonary vascular resistance.
PVRi = pulmonary vascular resistance inde.
WU = Wood units.
[a]With surgery or intravascular percutaneous procedure.

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Vasoreactivity testing

Recommendations	Class	Level
Vasoreactivity testing is indicated only in expert centres.	I	C
Vasoreactivity testing is recommended in patients with IPAH, HPAH and PAH associated with drugs use to detect patients who can be treated with high doses of a calcium channel blocker.	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥10 mmHg to reach an absolute value of mean PAP ≤40 mmHg with an increased or unchanged cardiac output.	I	C
Nitric oxide is recommended for performing vasoreactivity testing.	I	C
Intravenous epoprostenol is considered for performing vasoreactivity testing as an alternative.	I	C
Adenosine should be considered for performing vasoreactivity testing as an alternative.	IIa	C
Inhaled iloprost may be considered for performing vasoreactivity testing as an alternative.	IIb	C
The use of oral or intravenous calcium channel blockers in acute vasoreactivity testing is not recommended.	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a calcium channel blocker is not recommended in patients with PAH other than IPAH, HPAH and PAH associated with drugs use, and is not recommended in pulmonary hypertension Groups 2, 3, 4 and 5.	III	C

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Table 1
Specalised pulmonary hypertension centres in the United Kingdom

Golden Jubilee National Hospital
Great Ormond Street Hospital for Children NHS Foundation Trust
Imperial College Healthcare NHS Trust
Papworth Hospital NHS Foundation Trust
Royal Brompton and Harefield NHS Foundation Trust
Royal Free London NHS Foundation Trust
Sheffield Teaching Hospitals NHS Foundation Trust
The Newcastle upon Tyne Hospitals NHS Foundation Trust