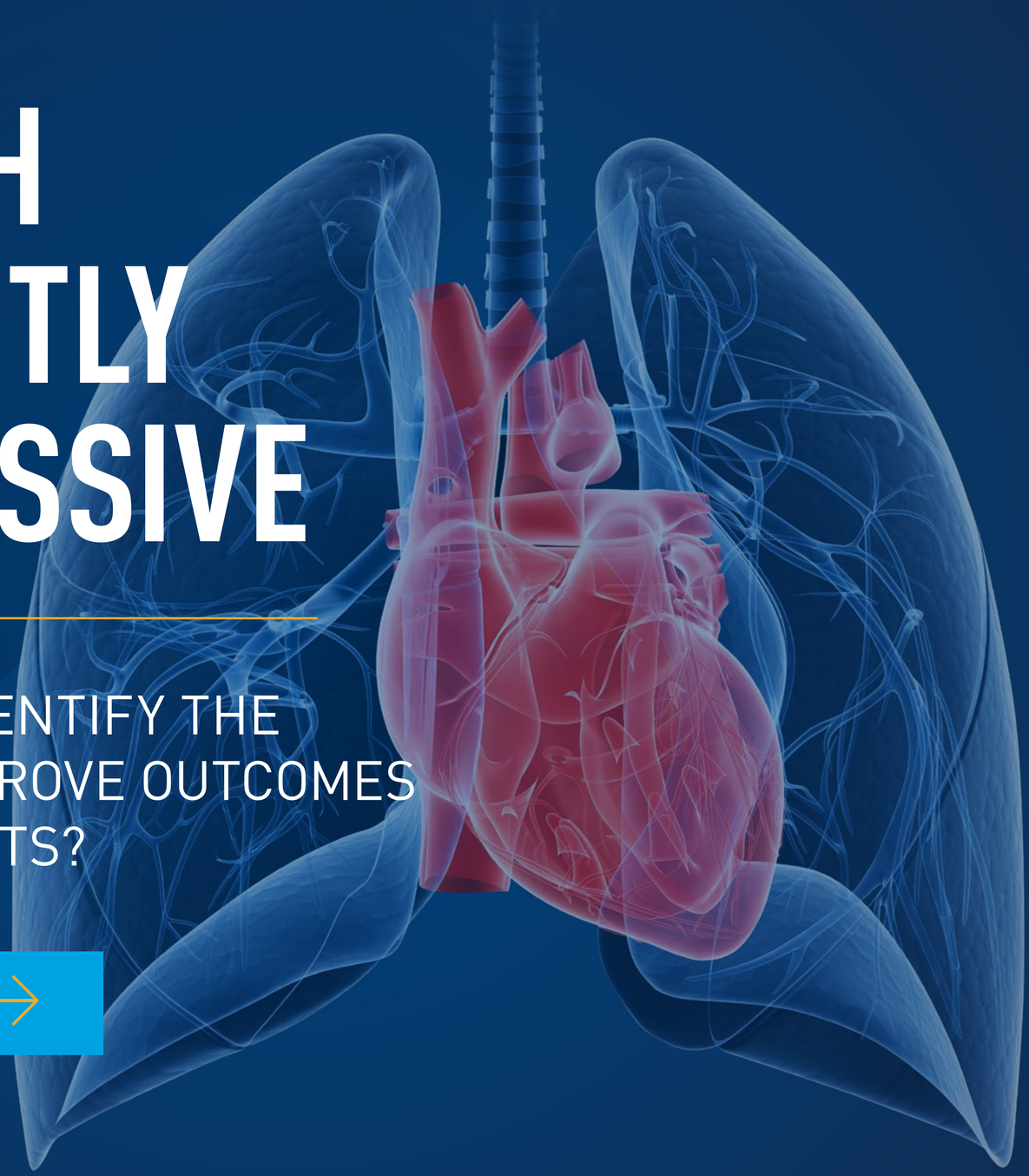
CHD-PAH IS SILENTLY PROGRESSIVE



HOW CAN YOU IDENTIFY THE DISEASE AND IMPROVE OUTCOMES FOR YOUR PATIENTS?

FIND OUT MORE

CHD, congenital heart disease; PAH, pulmonary arterial hypertension

CP-194576 | January 2021

SELECT A TOPIC TO EXPLORE HOW YOU CAN HELP YOUR PATIENTS WITH CHD-PAH

The risk of PAH in CHD

- What is PAH?
- How does PAH manifest in CHD?
- Does defect correction prevent the development of PAH?
- How common is PAH in patients with corrected CHD?
- What is the prognosis of patients with corrected CHD-PAH?

Early identification of PAH in CHD

- What are the benefits of regular screening for PAH in CHD?
- What are the barriers to identifying CHD-PAH early?

Early treatment of CHD-PAH

- What could timely PAH treatment mean for patients with corrected simple CHD-PAH?
- How can OPSUMIT (macitentan) make a difference for your patients with corrected simple CHD-PAH?
- How can UPTRAVI (selexipag) make a difference for your patients with corrected simple CHD-PAH?

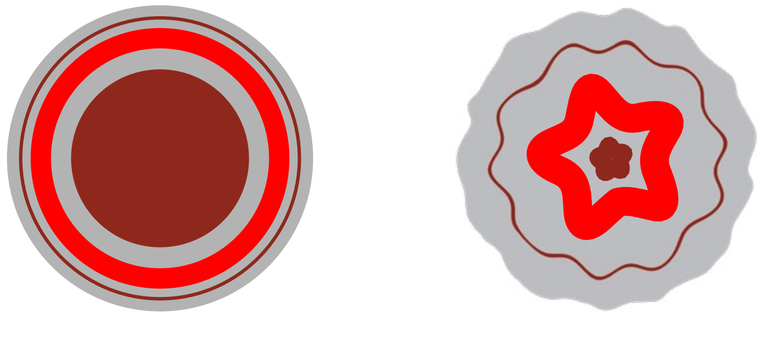
Summary

- How can you identify CHD-PAH early and improve outcomes for your patients?

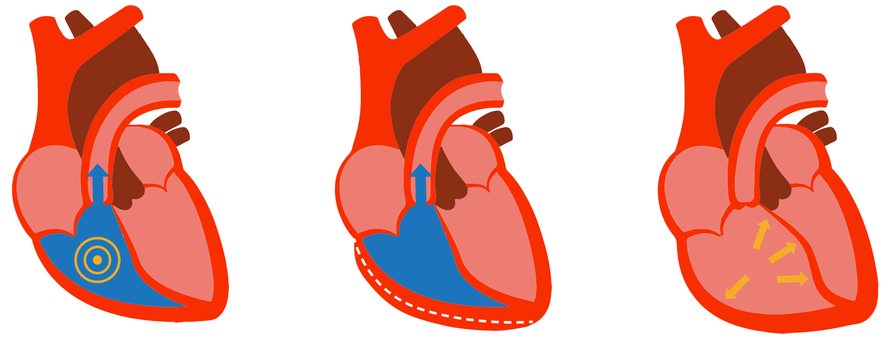
CHD, congenital heart disease; PAH, pulmonary arterial hypertension

PAH IS A SILENTLY PROGRESSIVE DISEASE[1]

PAH, a subgroup of pulmonary hypertension,[2] is a rare, severe and progressive disease characterised by chronic elevation in pulmonary vascular resistance and arterial pressure.*[3] **If left untreated, PAH eventually results in right ventricular failure and death.**[3,4]



Vascular remodelling in PAH leads to **narrowing** of the pulmonary arteries and increased pulmonary vascular resistance[3]



Increased pulmonary vascular resistance leads to high right ventricular **afterload**, **hypertrophy**, **dilatation** and, eventually, **right heart failure**[5]

Adapted from Galiè *et al.* 2010[3] and Vonk Noordegraaf *et al.* 2017[5]

EARLY IDENTIFICATION AND INTERVENTION IS KEY TO CHANGING THE COURSE OF PAH[6]

mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance
*The current haemodynamic definition of PAH is mPAP ≥25 mmHg, PAWP ≤15 mmHg and PVR >3 Wood units.[2]

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5. Vonk Noordegraaf A *et al. J Am Coll Cardiol* 2017; 69(2):236–243.

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PAH IS A COMMON COMPLICATION OF CHD[1,2]

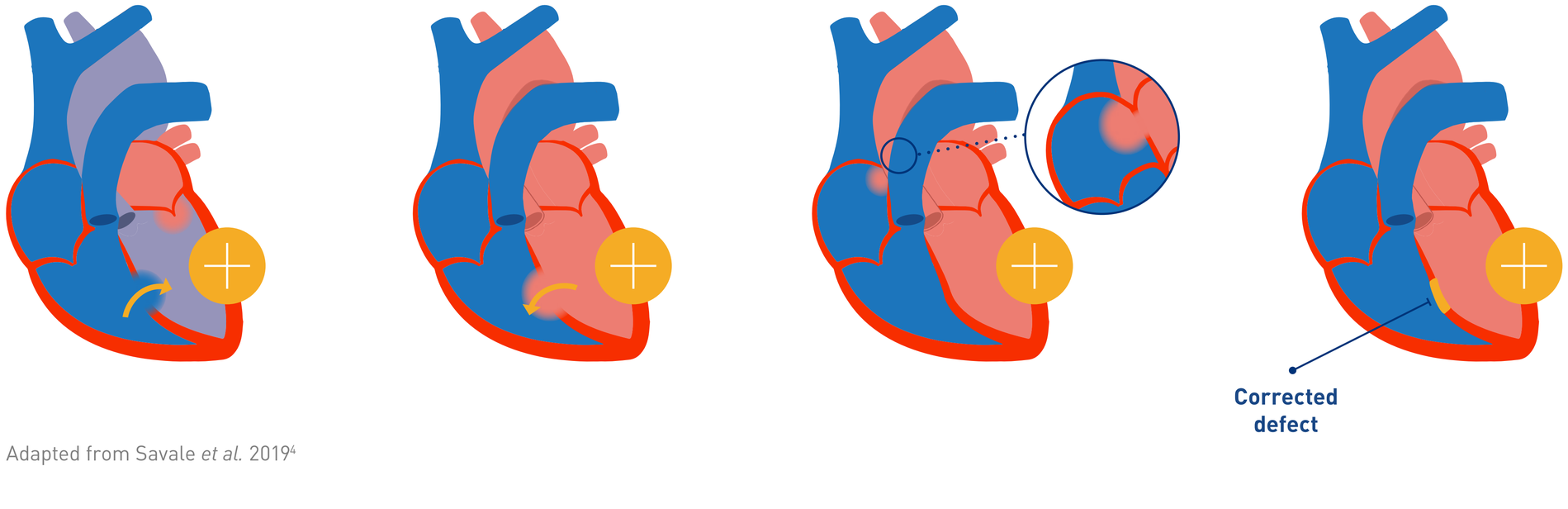
CHD-PAH is a common PAH subtype, accounting for 10–20% of cases,[3] and represents a heterogeneous patient population.[2] Patients with CHD-PAH can be classified into one of four main subgroups according to the 2015 ESC/ERS guidelines:[2]

1 **Eisenmenger's syndrome**

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

3 **PAH with small/ coincidental defects**

4 **PAH after defect correction**

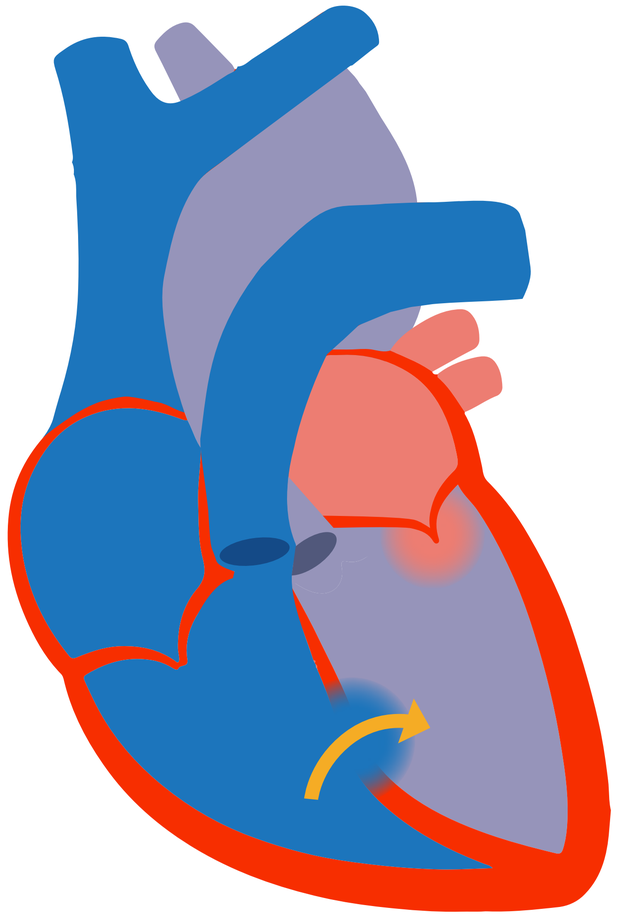


Adapted from Savale *et al.* 2019[4]

PATIENTS WITH CHD ARE AT RISK OF PAH, EVEN WHEN CONGENITAL HEART DEFECTS ARE CORRECTED[5]

CHD, congenital heart disease; ERS, European Respiratory Society; ESC, European Society of Cardiology; PAH, pulmonary arterial hypertension

1. EISENMENGER'S SYNDROME[1]

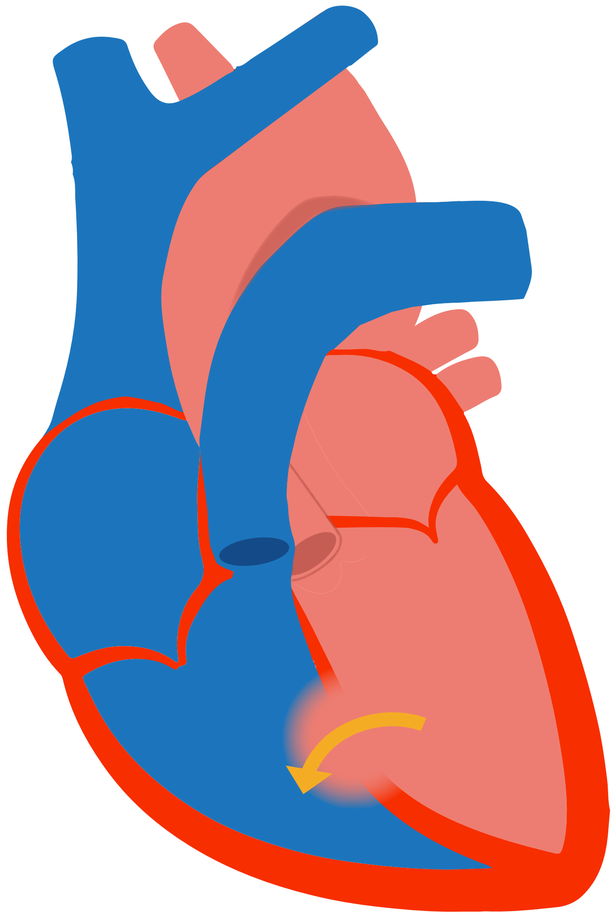


- Includes large defects that develop due to systemic-to-pulmonary shunts
- Progression to severe elevation of PVR
- Reversed or bidirectional shunting
- Cyanosis, erythrocytosis and multiple organ involvement
- PAH is present by definition[2]

PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance

References: 1. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119. **2.** Savale L, Manes A. *Eur Heart J Suppl* 2019; 21(Suppl K):K37–K45.

2. PAH ASSOCIATED WITH PREVALENT SYSTEMIC-TO-PULMONARY SHUNTS[1]

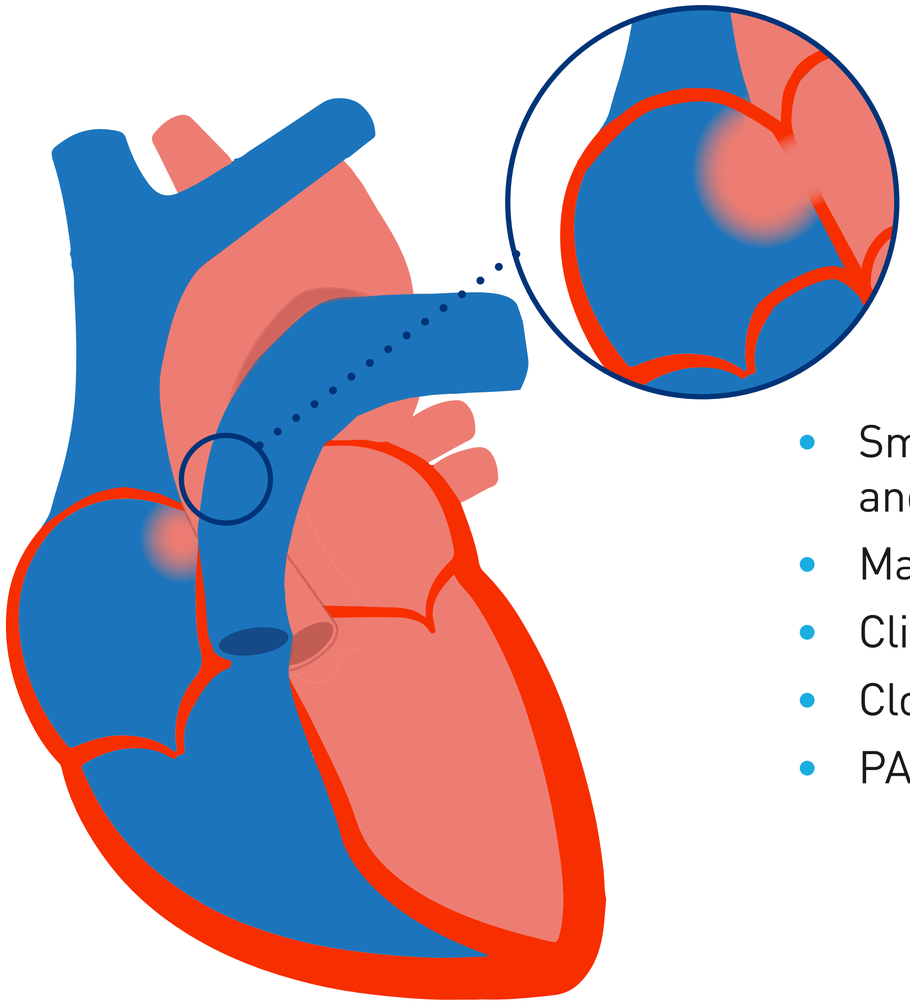


- Includes moderate-to-large defects
- Mild-to-moderate increase in PVR
- Systemic-to-pulmonary shunt is still present
- No cyanosis detectable at rest

PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance

References: 1. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119.

3. PAH WITH SMALL/COINCIDENTAL DEFECTS[1]

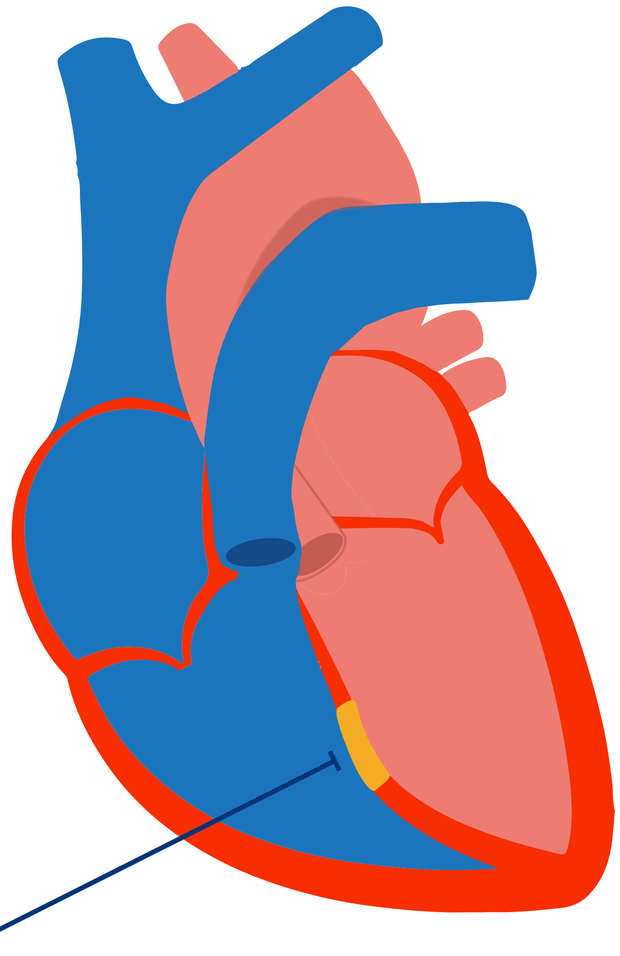


- Small defects (usually ASD <2 cm and VSD <1 cm)
- Marked elevation of PVR
- Clinical presentation similar to idiopathic PAH
- Closing the defects is contraindicated
- PAH is present by definition[2]

ASD, atrial septal defect; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; VSD, ventricular septal defect

References: 1. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119. **2.** Savale L, Manes A. *Eur Heart J Suppl* 2019; 21(Suppl K):K37–K45.

4. PAH AFTER DEFECT CORRECTION[1]



Corrected defect

- Defect is repaired
- PAH persists immediately after correction or recurs/develops months or years after defect closure in the absence of significant post-operative haemodynamic lesions

PAH, pulmonary arterial hypertension

References: 1. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119.

REFERENCES

1. Engelfriet PM *et al. Heart* 2007; 93(6):682–687.

2. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119.

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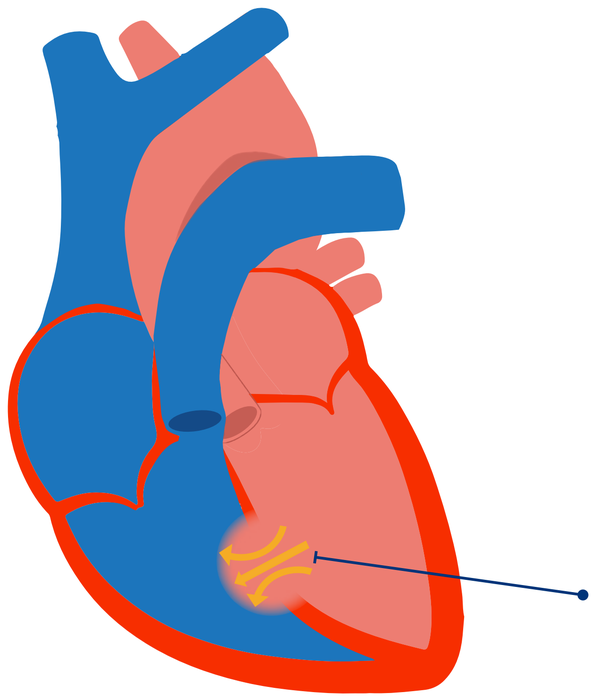
5. D'Alto M, Mahadevan VS. *Eur Respir Rev* 2012; 21(126):328–337.

PATIENTS WITH CORRECTED DEFECTS ARE STILL AT RISK OF DEVELOPING PAH[1]

Simple congenital heart defect | Corrected simple congenital heart defect



Adapted from Savale *et al.* 2019[3]

The majority of patients with CHD have septal defects, including simple defects such as ASD (15%) and VSD (36%)[2]

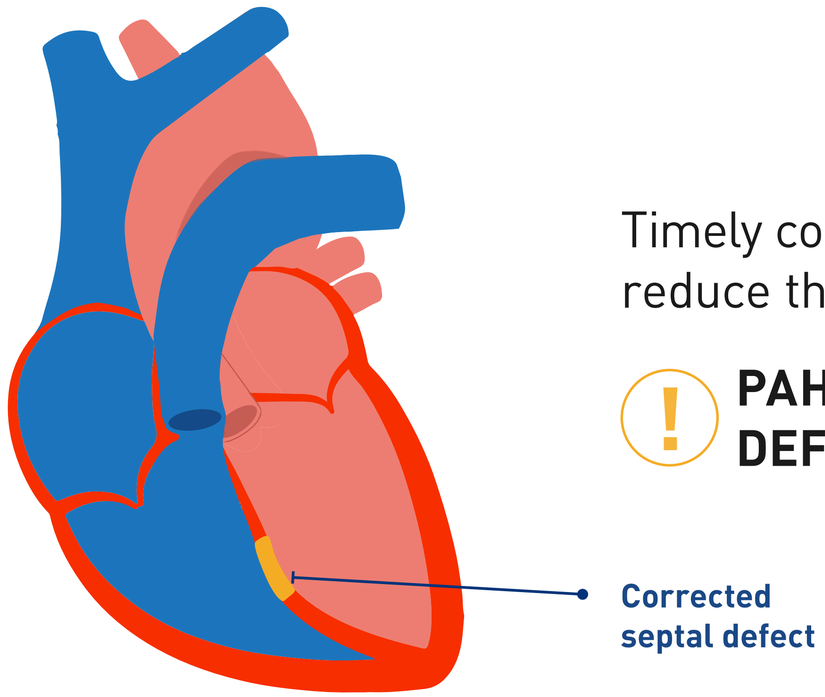
SINCE PAH CAN DEVELOP OVER TIME DESPITE SURGERY, PATIENTS WITH CHD NEED REGULAR, LONG-TERM SCREENING FOR PAH AFTER DEFECT CORRECTION[3,4]

ASD, atrial septal defect; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; VSD, ventricular septal defect

PATIENTS WITH CORRECTED DEFECTS ARE STILL AT RISK OF DEVELOPING PAH[1]

Simple congenital heart defect

Corrected simple congenital heart defect



Adapted from Savale *et al.* 2019[3]

Timely correction of these defects can reduce the risk of PAH[1,5]

PAH CAN STILL OCCUR AFTER DEFECT CORRECTION

SINCE PAH CAN DEVELOP OVER TIME DESPITE SURGERY, PATIENTS WITH CHD NEED REGULAR, LONG-TERM SCREENING FOR PAH AFTER DEFECT CORRECTION[3,4]

ASD, atrial septal defect; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; VSD, ventricular septal defect

REFERENCES

1. D'Alto M, Mahadevan VS. *Eur Respir Rev* 2012; 21(126):328–337.

2. Liu Y *et al. Int J Epidemiol* 2019; 48(2):455–463.

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5. van Riel A *et al. JACC* 2015; 66(9):1084–1085.

PAH ASSOCIATED WITH CORRECTED CHD IS INCREASING IN PREVALENCE[1]

Advances in the treatment of CHD over the past few decades have led to an increase in adult CHD survivors, who may then go on to develop PAH following defect correction.[1] The overall prevalence of PAH in patients with corrected simple defects, including ASD and VSD, ranges from 3% to 12%.*[2,3]

UP TO 12%

THE NUMBER OF PATIENTS WHO DEVELOP PAH AFTER CONGENITAL DEFECT CORRECTION IS INCREASING[1]

ASD, atrial septal defect; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; VSD, ventricular septal defect
*Data from adult patients with CHD in CONCOR, a Dutch registry (N=2,389),[2] and the Euro Heart survey database (N=1,877).[3]

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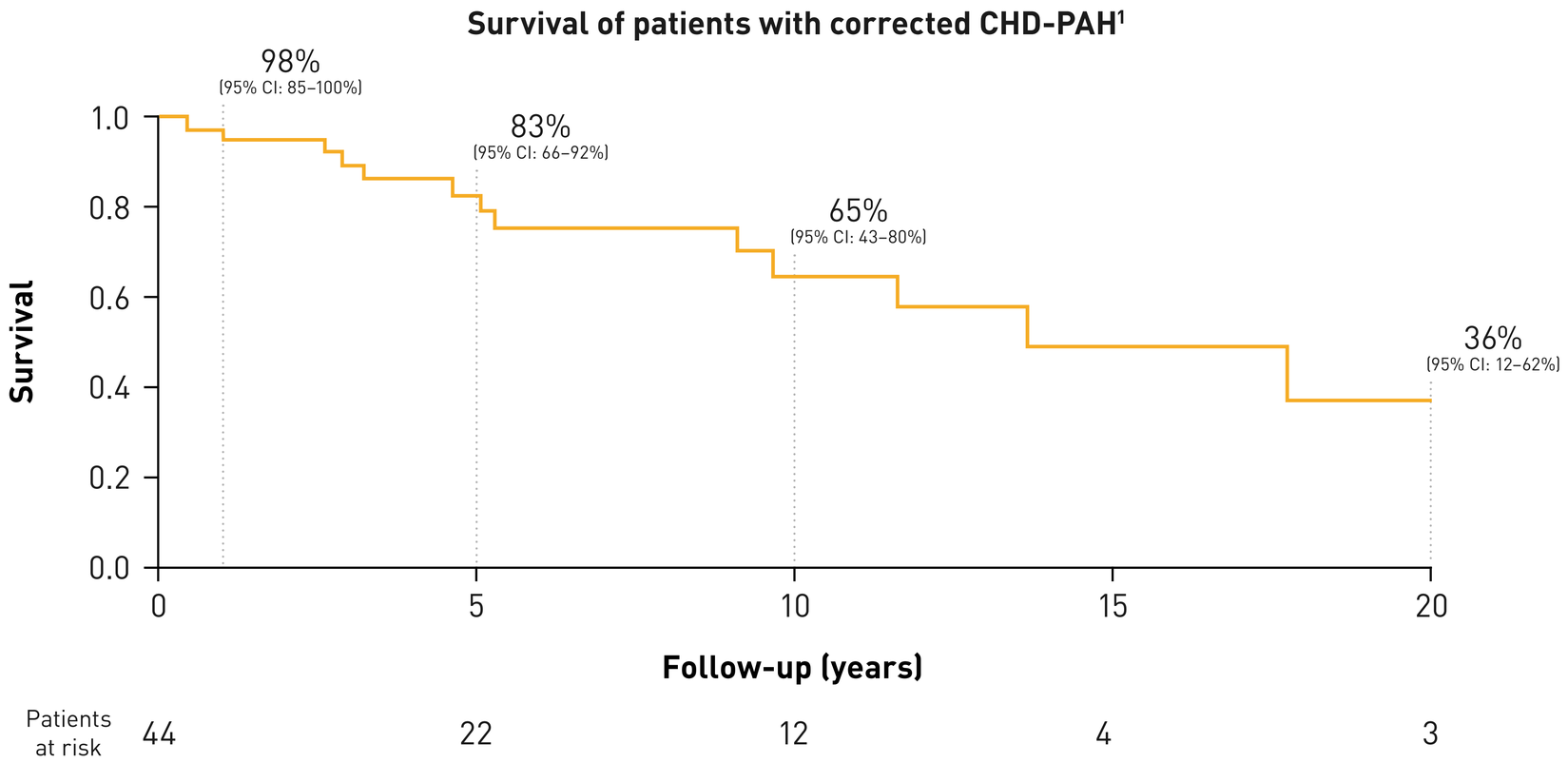
1. van Dissel A *et al. J Clin Med* 2017; 6(4):40.

2. Duffels MGJ *et al. Int J Cardiol* 2007; 120(2):198–204.

3. Engelfriet PM *et al. Heart* 2007; 93(6):682–687.

PATIENTS WITH CORRECTED CHD-PAH HAVE POOR OUTCOMES[1,2]

In patients with corrected CHD, development of PAH is associated with significant worsening in functional limitations and poor long-term survival.*[1,2]



Adapted from Manes *et al.* 2014[1]

MORE THAN 1 IN 3 PATIENTS WITH CORRECTED CHD-PAH DIE WITHIN 10 YEARS OF PAH DIAGNOSIS[1]

CHD, congenital heart disease; CI, confidence interval; PAH, pulmonary arterial hypertension
*Data from patients with CHD-PAH in an Italian database study (N=192)[1] and from patients with CHD in the Euro Heart survey database (N=1,877).[2]

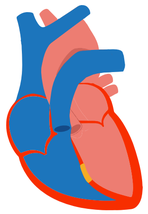
REFERENCES

1. Manes A *et al. Eur Heart J* 2014; 35(11):716–724.

2. Engelfriet PM *et al. Heart* 2007; 93(6):682–687.

ALL PATIENTS WITH CORRECTED CHD SHOULD BE PROACTIVELY SCREENED FOR PAH WITH ECHOCARDIOGRAPHY[1–5]

Regular screening of patients with CHD for PAH is **recommended in the 2015 ESC/ERS guidelines and the proceedings of the 2018 WSPH.***[1,2] If PAH is suspected, patients should be referred to a specialist PH centre for right heart catheterisation to establish the diagnosis.[1,2,4,5]



Defect correction

MONTHS → YEARS

3–6 months
Screening* for PAH after defect correction[2]

Regular screening
Screening* for PAH in the years after defect correction[2,3]

ECHO IN CHD-PAH +

PATIENT REFERRAL +

REGULAR SCREENING CAN HELP FACILITATE EARLY DIAGNOSIS AND THERAPEUTIC INTERVENTION FOR PATIENTS WITH CHD-PAH[3,6]

CHD, congenital heart disease; ECG, electrocardiography; ERS, European Respiratory Society; ESC, European Society of Cardiology; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WSPH, World Symposium on Pulmonary Hypertension
*Screening should include clinical, echocardiographic and ECG evaluation. Annual screening should be planned for corrected patients who presented with increased baseline pulmonary vascular resistance or with combinations of other predisposing factors.[2]

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3. Dimopoulos K *et al. J Am Coll Cardiol* 2018; 72(22):2778–2788.

4. Baumgartner H *et al. Eur Heart J* 2020; doi:10.1093/eurheartj/ehaa554.

5. Bhatt AB *et al. Circulation* 2015; 131(21):1884–1931.

6. Khou V *et al. Respirology* 2020; doi:10.1111/resp.13768.

SCREENING FOR PAH IN CHD USING ECHOCARDIOGRAPHY[1,2]

According to the 2015 ESC/ERS PH guidelines, the echocardiographic probability of PAH can be determined based on a number of specific signs;[1] however, these signs may not always apply to patients with CHD due to underlying anatomic and physiological factors.[2]

2015 ESC/ERS guidelines: Echocardiographic probability and signs suggestive of PAH*[1]

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'	Echocardiographic probablility of PH
≤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 outflow Doppler acceleration time <105 msec 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	

Adapted from Galiè *et al.* 2016[1]

AS ACHD IS A HETEROGENEOUS POPULATION, PROVIDING A STANDARDISED APPROACH FOR EACH INDIVIDUAL CASE IS IMPOSSIBLE. HOWEVER, THE GUIDELINE-RECOMMENDED ECHOCARDIOGRAPHIC SIGNS CAN HELP IDENTIFY PATIENTS WITH CHD WHO WOULD BENEFIT FROM RIGHT HEART CATHETERISATION TO CONFIRM PAH.

— CHAMPION Steering Committee expert opinion[2]

ACHD, adult congenital heart disease; CHD, congenital heart disease; ERS, European Respiratory Society; ESC, European Society of Cardiology; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension

*Echocardiographic signs from at least two different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of pulmonary hypertension.[1]

References: 1. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119. **2.** Dimopoulos K *et al. J Am Coll Cardiol* 2018; 72(22):2778–2788.

SUSPICION OF PAH IN CHD SHOULD TRIGGER FAST-TRACK REFERRAL TO A SPECIALIST PH CENTRE[1]

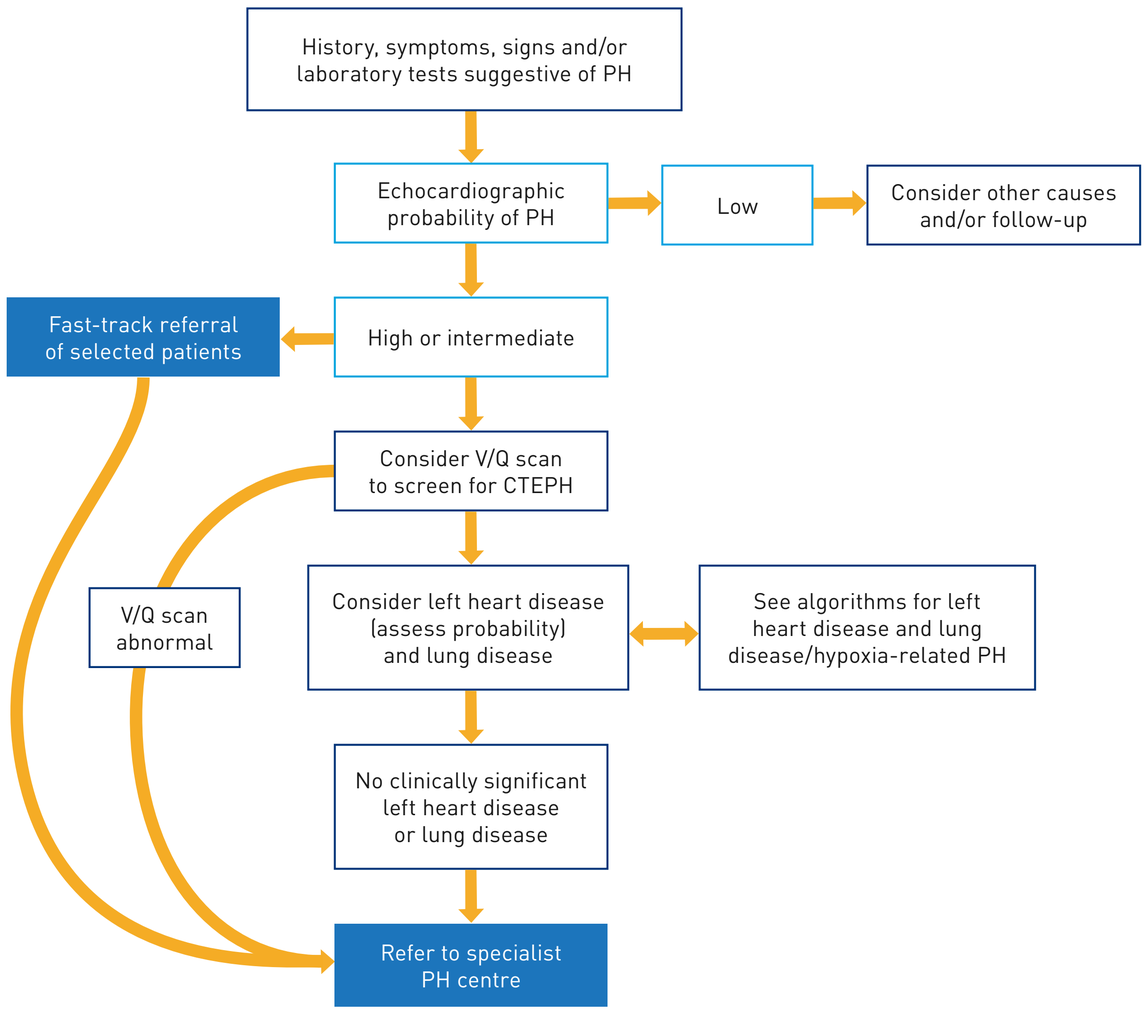
2018 WSPH algorithm for the diagnosis of PH[1]

ASSESS PROBABILITY OF PH

IDENTIFY HIGH-RISK PATIENTS

DIAGNOSE COMMON CAUSES OF PH

DIAGNOSE RARE CAUSES OF PH



Adapted from Frost *et al.* 2019[1]

CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; V/Q, ventilation/perfusion; WSPH, World Symposium on Pulmonary Hypertension

References: 1. Frost A *et al. Eur Respir J* 2019; 53(1):1801904.

ACHIEVING EARLY IDENTIFICATION AND TREATMENT OF PAH IN CHD CAN BE CHALLENGING[1–4]

Patients with CHD can experience a delay of almost 2 years between symptom onset and diagnosis of PAH, which is associated with poor survival outcomes.[5]

1. SIMPLE CHD DEFECT CORRECTION
2. REGULAR FOLLOW-UP (PULMONARY TESTING)
3. SCREENING FOR PAH WITH ECHOCARDIOGRAPHY
4. REFERRAL FOR RHC TO ESTABLISH PAH DIAGNOSIS
5. CONFIRMATION OF PAH AND TREATMENT INITIATION

Several barriers to early diagnosis and treatment of CHD-PAH exist:

- Patients are often first lost to follow-up during the transition from paediatric to adult services due to a lack of compliance or difficulty adjusting to an autonomous adult healthcare environment[2,6]
- A large proportion of adults with CHD fail to receive regular cardiac care following defect correction; they may be discharged or elect not to seek continued medical advice, and are lost to follow-up[1,2,7]
- Early PAH symptoms can be mild and non-specific, and other cardiopulmonary diseases are often considered before PAH[3]
- In older patients with CHD, challenging vascular access and reluctance to undergo diagnostic procedures can pose a barrier to assessment of PAH[4]

IDENTIFYING PAH AS EARLY AS POSSIBLE IN PATIENTS WITH CHD, THROUGH REGULAR FOLLOW-UP AND SCREENING, IS CRITICAL TO IMPROVING THEIR OUTCOMES[5,8,9]

CHD, congenital heart disease; CT, computerised tomography; MRI, magnetic resonance imaging; PAH, pulmonary arterial hypertension; RHC, right heart catheterisation; TRV, tricuspid regurgitation velocity

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5. CONFIRMATION OF PAH AND TREATMENT INITIATION

Recommendations to enable early diagnosis and treatment of CHD-PAH:

- In order to be transitioned effectively to adult care, patients should undergo regular follow-up during childhood and adolescence and receive transition support that continues into early adulthood[2,10]
- Regardless of age or success of repair, patients with corrected CHD lost to follow-up should be identified and referred back to specialist care for regular, long-term monitoring[1,2]
- To help detect PAH, patients with CHD should undergo routine screening for PAH with echocardiography, evaluating peak TRV and the presence of other signs suggestive of PAH[11]
- PAH can be investigated using a combination of non-invasive diagnostic procedures including echocardiography, cardiac MRI and CT scan[4,11]

IDENTIFYING PAH AS EARLY AS POSSIBLE IN PATIENTS WITH CHD, THROUGH REGULAR FOLLOW-UP AND SCREENING, IS CRITICAL TO IMPROVING THEIR OUTCOMES[5,8,9]

CHD, congenital heart disease; CT, computerised tomography; MRI, magnetic resonance imaging; PAH, pulmonary arterial hypertension; RHC, right heart catheterisation; TRV, tricuspid regurgitation velocity

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2. Mackie AS *et al. Circulation* 2009; 120(4):302–309.

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11. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119.

PAH THERAPIES CAN IMPROVE LONG-TERM OUTCOMES VS PLACEBO FOR PATIENTS WITH CORRECTED SIMPLE CHD-PAH*[1–4]

Find out how your patients could benefit from two targeted therapies in PAH:

START AHEAD | Opsumit® macitentan

ADD | Uptravi® selexipag

FOUNDATIONAL CHOICES

Patients diagnosed with WHO FC II–III PAH can be started on combination therapy with **OPSUMIT** ± PDE-5i/sGCs[5,6]

FIRST SIGN OF INTERMEDIATE RISK

If patients do not achieve a low-risk status at follow-up, PAH treatment can be intensified by adding **UPTRAVI**[5,7]

CHD, congenital heart disease; FC, functional class; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type-5 inhibitor; sGCs, soluble guanylate cyclase stimulator; WHO, World Health Organization
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1,3]

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2. Pulido T *et al. N Engl J Med* 2013; 369(9):809–818 (supplementary appendix).

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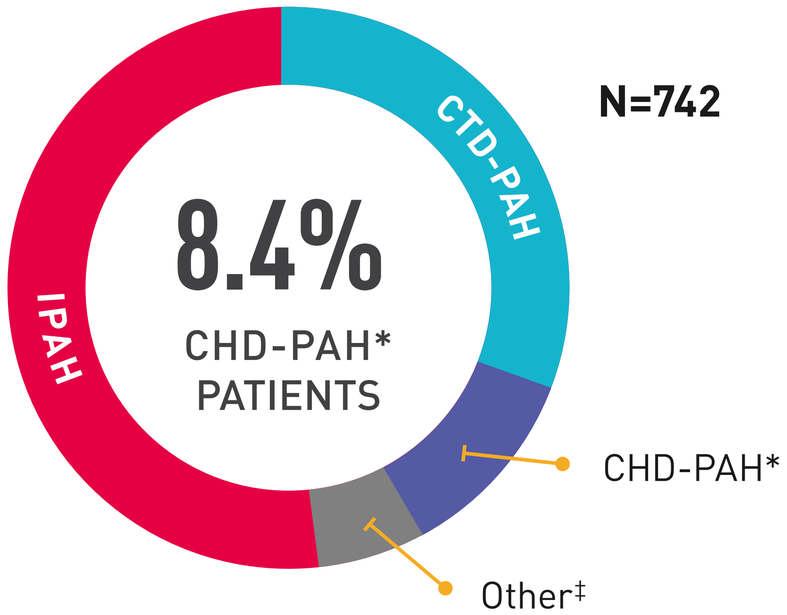
7. UPTRAVI SmPC, January 2021.
Available at: https://www.ema.europa.eu/en/documents/product-information/uptravi-epar-product-information_en.pdf (last accessed January 2021).

OPSUMIT SHOWS BENEFICIAL LONG-TERM OUTCOMES FOR PATIENTS WITH CHD-PAH*[1,2]

SERAPHIN study | Benefits in CHD-PAH

The SERAPHIN study assessed the efficacy and safety of OPSUMIT in a broad range of patients, including those with **corrected simple CHD-PAH,* who comprised 8.4% of the trial population.**[1]

Total SERAPHIN patient population by aetiology[1]



CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1]
‡Includes heritable PAH (2%), HIV-PAH (1%) and drug- or toxin-induced PAH (3%).[1]

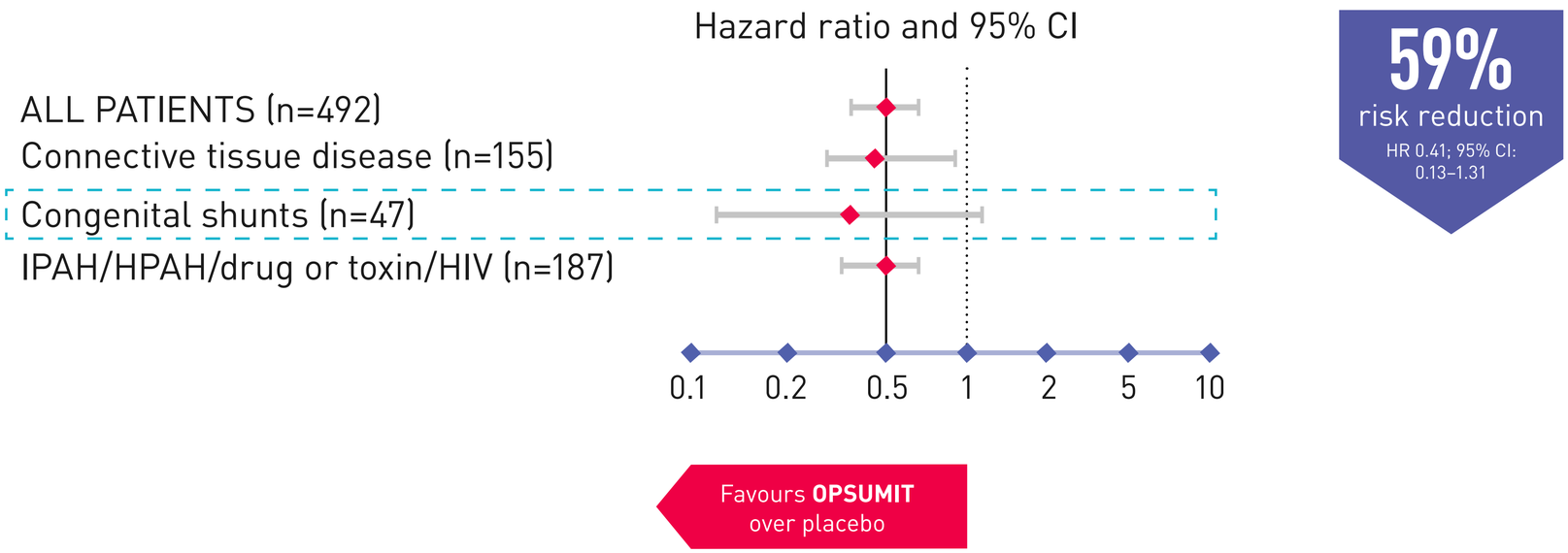
OPSUMIT SAFETY +

OPSUMIT SHOWS BENEFICIAL LONG-TERM OUTCOMES FOR PATIENTS WITH CHD-PAH*[1,2]

SERAPHIN study | **Benefits in CHD-PAH**

In the SERAPHIN study, treatment with OPSUMIT reduced the risk of a morbidity-mortality event‡ by 59% vs placebo in patients with CHD-PAH.*[2–4]

Primary endpoint of morbidity and mortality‡ by PAH aetiology[2–4]



Adapted from Pulido *et al.* 2013[2]

CHD, congenital heart disease; CI, confidence interval; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; HR, hazard ratio; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1]
‡Results were driven by a decrease in PAH worsening and do not apply to mortality on its own.[1]

OPSUMIT SAFETY +

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1. Pulido T *et al. N Engl J Med* 2013; 369(9):809–818.

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OPSUMIT SAFETY PROFILE[1]

Most frequent adverse events in the SERAPHIN study[1]

	OPSUMIT (n=242) (%)	PLACEBO (n=249) (%)
Worsening of PAH	**21.9**	**34.9**
Upper respiratory tract infection	**15.3**	**13.3**
Peripheral oedema	**18.2**	**18.1**
Nasopharyngitis	**14.0**	**10.4**
Right ventricular failure	**13.2**	**22.5**
Headache	**13.6**	**8.8**
Anaemia	**13.2**	**3.2**
Dizziness	**10.7**	**10.8**
Bronchitis	**11.6**	**5.6**
Dyspnoea	**7.4**	**8.8**
Cough	**8.7**	**12.0**
LFT (ALT/AST) >3x ULN	**3.4**	**4.5**
LFT (ALT/AST) >3x ULN and bilirubin >2x ULN	**1.7**	**1.7**
Haemoglobin decrease (% of patients ⩽8 g/dL)	**4.3**	**0.4**

Adapted from Pulido *et al.* 2013[1]

- Patients receiving OPSUMIT and placebo had a mean study treatment duration of 103.9 and 85.3 weeks, respectively[1]
- The incidence of peripheral oedema and elevated liver enzymes was similar for OPSUMIT and placebo[1]
- The overall incidence of treatment discontinuations due to adverse events with OPSUMIT was similar to placebo (10.7% and 12.4%, respectively)[1]

For full safety information, please consult the OPSUMIT Summary of Product Characteristics[2]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; PAH, pulmonary arterial hypertension; ULN, upper limit of normal

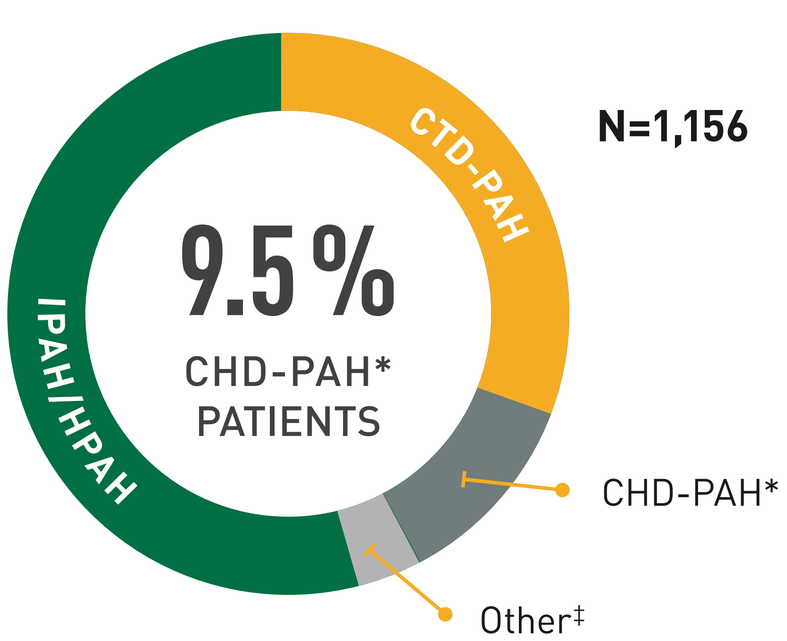
References: 1. Pulido T *et al. N Engl J Med* 2013; 369(9):809–818. **2.** OPSUMIT SmPC, April 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/opsumit-epar-product-information_en.pdf (last accessed January 2021).

ADDITION OF UPTRAVI CAN IMPROVE LONG-TERM OUTCOMES FOR PATIENTS WITH CHD-PAH*[1,2]

GRIPHON study | Benefits in CHD-PAH

The GRIPHON study assessed the efficacy and safety of UPTRAVI across a broad range of patients, and included the **largest population of patients with corrected simple CHD-PAH*** in a randomised controlled trial to date.[1,2]

Total GRIPHON patient population by aetiology[1]



CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1]
‡Includes HIV-PAH (1%) and drug- or toxin-induced PAH (2%).[1]

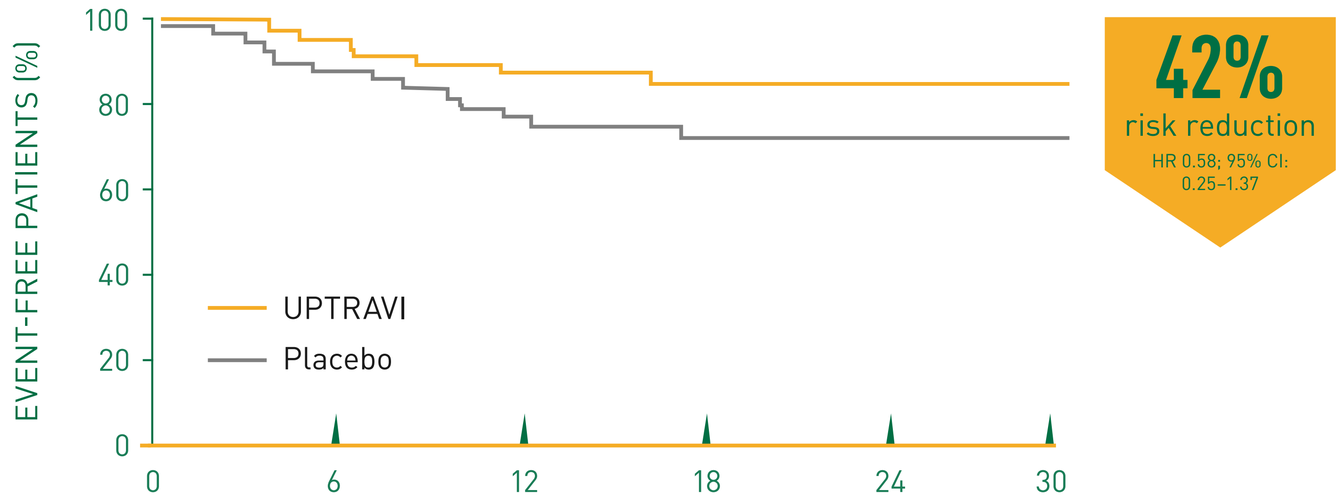
UPTRAVI SAFETY +

ADDITION OF UPTRAVI CAN IMPROVE LONG-TERM OUTCOMES FOR PATIENTS WITH CHD-PAH*[1,2]

GRIPHON study | **Benefits in CHD-PAH**

UPTRAVI improved long-term outcomes for patients with CHD-PAH* in the GRIPHON study, reducing the risk of a morbidity-mortality event‡ vs placebo by 42%.[2]

Time to first morbidity-mortality event‡ in patients with CHD-PAH* in GRIPHON[2]



Patients at risk						
UPTRAVI	60	53	43	29	20	12
Placebo	50	42	36	24	18	12

Adapted from Beghetti *et al.* 2019[2]

CHD, congenital heart disease; CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1]
‡Results were driven by a decrease in PAH worsening and do not apply to mortality on its own.[1]

UPTRAVI SAFETY +

REFERENCES

1. Sitbon O *et al. N Engl J Med* 2015; 373(26):2522–2533.

2. Beghetti M *et al. Eur J Heart Fail* 2019; 21(3):352–359.

UPTRAVI SAFETY PROFILE[1]

Common adverse reactions with ≥3% difference between UPTRAVI and placebo in the GRIPHON study*[1]

	UPTRAVI (n=575) (%)	PLACEBO (n=577) (%)
Headache	**65.2**	**32.8**
Diarrhoea	**42.4**	**19.1**
Jaw pain	**25.7**	**6.2**
Nausea	**33.6**	**18.5**
Myalgia	**16.0**	**5.9**
Vomiting	**18.1**	**8.5**
Pain in extremity	**16.9**	**8.0**
Flushing	**12.2**	**5.0**
Arthralgia	**10.8**	**7.6**
Anaemia	**8.3**	**5.4**

Adapted from Sitbon *et al.* 2015[1]

- Patients received UPTRAVI and placebo for a median duration of 70.7 and 63.7 weeks, respectively[1]
- The overall incidence of treatment discontinuations due to adverse events with UPTRAVI was similar to placebo (14.3% and 7.1%, respectively)[1]

IN PATIENTS WITH CORRECTED SIMPLE CHD-PAH,‡ THE SAFETY AND TOLERABILITY OF UPTRAVI WAS COMPARABLE TO THE OVERALL STUDY POPULATION AND THERE WERE NO NEW OR UNEXPECTED SAFETY FINDINGS[2]

For full safety information, please consult the UPTRAVI Summary of Product Characteristics[3]

CHD, congenital heart disease; PAH, pulmonary arterial hypertension
*Other common adverse reactions include: haemoglobin decrease, hyperthyroidism, hypotension, abdominal pain, decreased appetite, weight decrease, nasal congestion, pain, urticaria, erythema and a reduction in thyroid-stimulating hormone. Rare adverse reactions: sinus tachycardia and increased heart rate.[3]
‡PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[1]
References: 1. Sitbon O *et al. N Engl J Med* 2015; 373(26):2522–2533. **2.** Beghetti M *et al. Eur J Heart Fail* 2019; 21(3):352–359. **3.** UPTRAVI SmPC, January 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/uptravi-epar-product-information_en.pdf (last accessed January 2021).

HELP FACILITATE EARLY DIAGNOSIS AND TIMELY TREATMENT FOR YOUR PATIENTS WITH CHD-PAH AND IMPROVE THEIR LONG-TERM OUTCOMES

- PAH IS A SILENTLY PROGRESSIVE DISEASE[1] AND A COMMON COMPLICATION OF CHD[2]
- PATIENTS WITH CHD MAY DEVELOP PAH EVEN AFTER DEFECT CORRECTION,[3,4] WHICH IS ASSOCIATED WITH POOR LONG-TERM SURVIVAL[5]
- EARLY IDENTIFICATION OF PAH IS CRITICAL TO IMPROVING PATIENT OUTCOMES[6]
  - Regular screening for PAH using echocardiography is recommended for all patients with corrected CHD[3,7–9]
  - For patients with a suspicion of PAH, expedited referral to a specialist PH centre to confirm the diagnosis is advised[7]
- EARLY PAH TREATMENT WITH OPSUMIT AND UPTRAVI MAKES A DIFFERENCE
  - Proven to improve long-term outcomes vs placebo in a broad range of patients with PAH, including those with corrected simple CHD-PAH*[10–17]

CHD, congenital heart disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension
*PAH associated with corrected simple CHD (systemic-to-pulmonary shunts).[10,14]

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2. Engelfriet PM *et al. Heart* 2007; 93(6):682–687.

3. Galiè N *et al. Eur Heart J* 2016; 37(1):67–119.

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15. Coghlan JG *et al. Am J Cardiovasc Drugs* 2018; 18(1):37–47.

16. Beghetti M *et al. Eur J Heart Fail* 2019; 21(3):352–359.

17. Gaine S *et al. Eur Respir J* 2017; 50(2):1602493.