GENERAL UNIVERSITY HOSPITAL IN PRAGUE

FIRST FACULTY OF MEDICINE
Charles University

Plicní hypertenze u srdečního selhání a nová doporučení pro diagnostiku a léčbu plicní hypertenze

Aleš Linhart

Complex
CARDIO
VASCULAR
Center
GUH Prague

Deklarace konfliktu zájmů

.	Nemám konflikt zájmů	Mám konflikt zájmů	Specifikace konfliktu (vyjmenujte subjekty, firmy či institutce, se kterými Vaše spolupráce může vést ke konfliktu zájmů
Zaměstnanecký poměr	☑	☐	
Vlastník / akcionář	☑	☐	
Konzultant	☐	☑	Sanofi, Takeda, Boehringer Ingelheim, NovoNordisk, 4D genetics, Amicus Therapeutics,
Přednášková činnost	☐	☑	Sanofi, Takeda, Boehringer Ingelheim, NovoNordisk, Chiesi, Amicus Therapeutics, AOP health, Bayer, Servier, Novartis, Pfizer,
Člen poradních sborů (advisory boards)	☑	☐	Sanofi, Boehringer Ingelheim, NovoNordisk, 4D genetics, Amicus Therapeutics,
Podpora výzkumu / granty	☑	☐	
Jiné honoráře (např. za klinické studie či registry)	☑	☐	

Deklarace konfliktu zájmů

Expert	Type of Relationship with Industry
Humbert Marc	**2021** Financial Declaration Direct personal payment from healthcare industry: speaker fees, honoraria, consultancy, advisory board fees, investigator, committee member, etc.For yourself - Novartis : Asthma - Sanofi Aventis : Asthma - Astra Zeneca : Asthma, COPD - GlaxoSmithKline : Asthma, COPD - Chiesi Pharma : Pulmonary hypertension, asthma, COPD - Johnson & Johnson : Pulmonary hypertension: Bosentan, Macitentan, Epoprostenol, Selexipag - Bayer : Pulmonary hypertension: Riociguat - Merck Sharp & Dohme : Pulmonary hypertension: Riociguat - Altavant : Pulmonary hypertension: Rodatristat - Acceleron : Pulmonary hypertension: Sotatercept - Shou Ti : Pulmonary hypertension: translational research - Morphogenics : Pulmonary hypertension: translational research - Ferrer Internacional : Pulmonary hypertension: Treprostinil - AOP Orphan Pharmaceuticals : Pulmonary hypertension: Treprostinil Research funding from healthcare industry under your direct/personal responsibility (to department or institution).For yourself - Johnson & Johnson : Pulmonary hypertension translational research - Merck Sharp & Dohme : Pulmonary hypertension translational research - Acceleron : Pulmonary hypertension translational research - Shou Ti : Pulmonary hypertension translational research

Guidelines methodology

- Four questions that were considered highly important were formulated in the **PICO format**, and assessed with full systematic reviews and application of the Grading of Recommendations, Assessment, Development, and Evaluations (**GRADE**) approach and the Evidence to Decision (EtD) framework
- Eight questions that were considered of key importance (**key narrative questions**) were assessed with systematic literature searches and application of the EtD framework.
- The remaining topics of interest were assessed using the process commonly followed in ESC Guidelines.

Foreground (PICO) Questions

- **Population/Problem/Patient.** What is the problem to be addressed? ...
- **Intervention**. What is the relevant treatment or exposure? ...
- **Comparison**. What is the alternative to the intervention? (A different intervention? ...
- **Outcome**. What are the relevant effects? ...

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

GRADE strength and quality of evidence

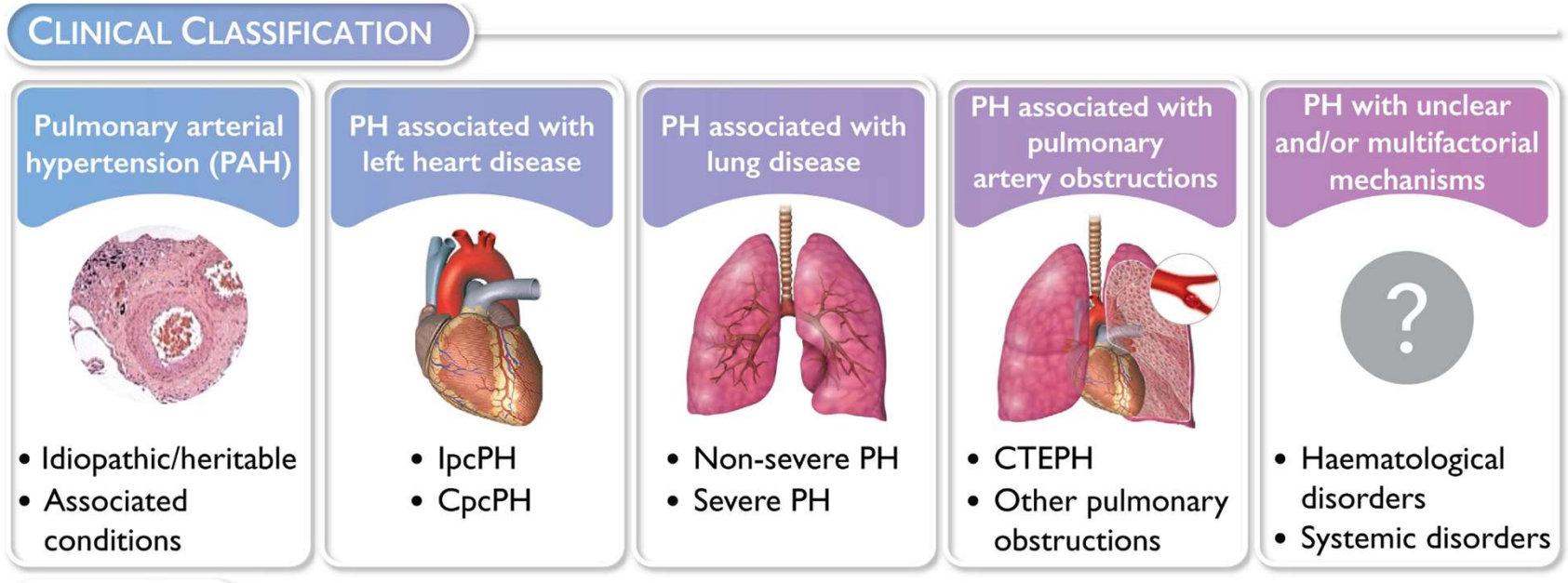
Recommendation strength	Rationale
Strong recommendation for	The panel is certain that the desirable outweigh the undesirable effects
Conditional recommendation for	The panel is less confident that the desirable outweigh the undesirable effects
Conditional recommendation against	The panel is less confident that the undesirable outweigh the desirable effects
Strong recommendation against	The panel is certain that the undesirable outweigh the desirable effects
No recommendation	The confidence in the results might be very low to make a recommendation, or the trade-offs between desirable and undesirable effects are finely balanced, or no data are available.

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Classification of PH

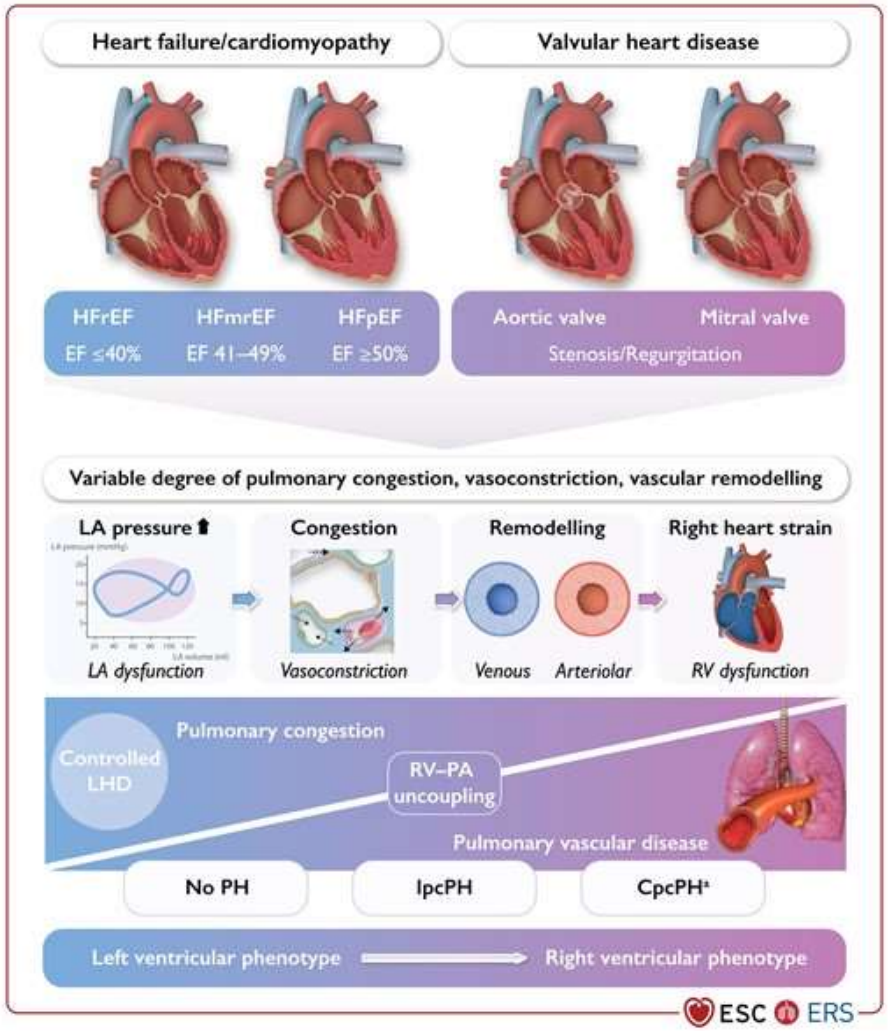
- **GROUP 1** Pulmonary arterial hypertension (PAH)
- **GROUP 2** PH associated with left heart disease
- **GROUP 3** PH associated with lung diseases and/or hypoxia
- **GROUP 4** PH associated with pulmonary artery obstructions
- **GROUP 5** PH with unclear and/or multifactorial mechanisms



Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

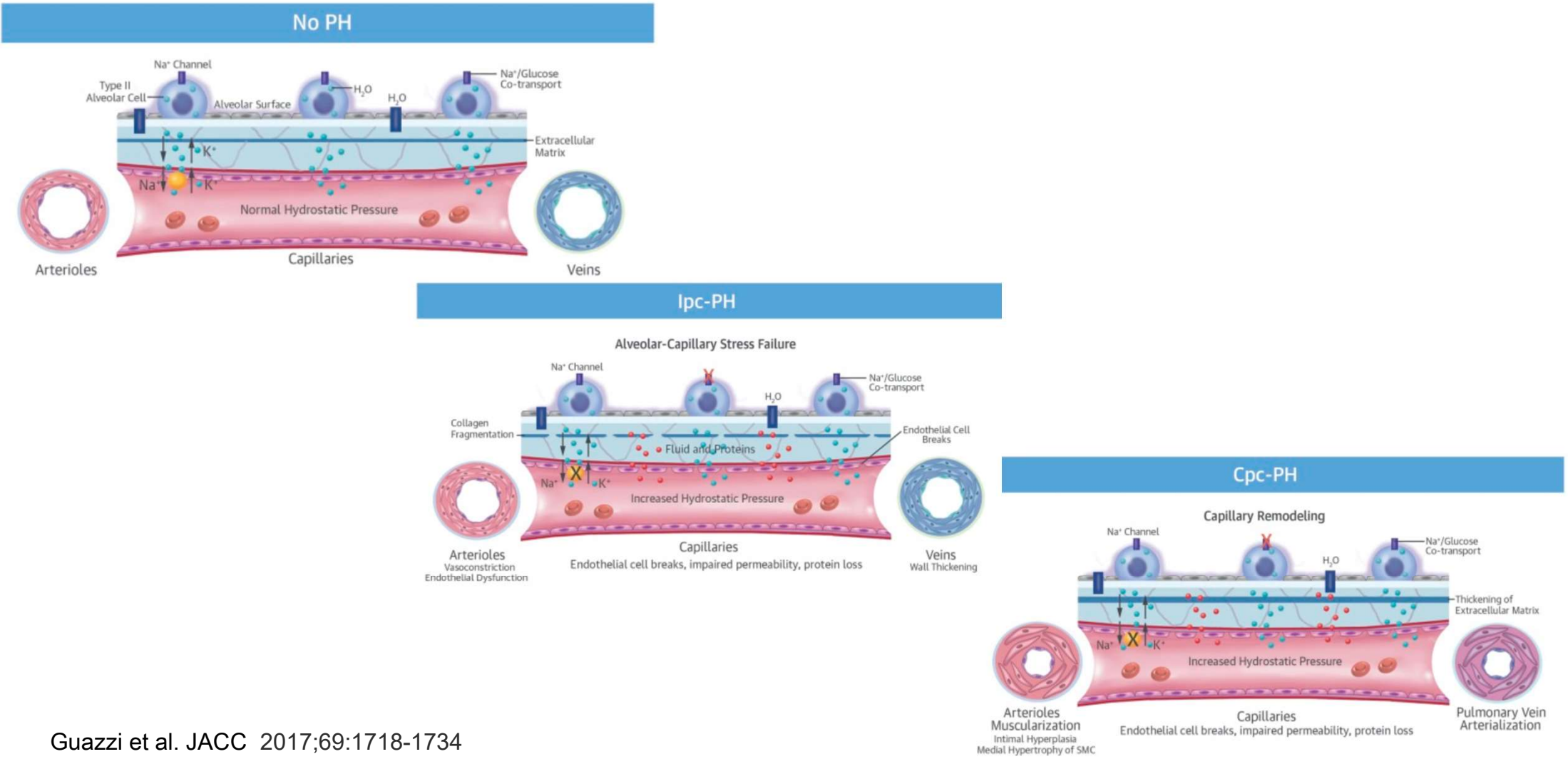
GROUP 2 PH associated with left heart disease

- **2.1 Heart failure:**
  - 2.1.1 with preserved ejection fraction
  - 2.1.2 with reduced or mildly reduced ejection fraction
- **2.2 Valvular heart disease**
- **2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH**



Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Progression from IpcPH to CpcPH



Guazzi et al. JACC 2017;69:1718-1734

Haemodynamic definitions of PH

Definition	Haemodynamic characteristics
PH	**mPAP >20 mmHg**
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg **PAWP >15 mmHg** **PVR ≤2 WU**
CpcPH	mPAP >20 mmHg **PAWP >15 mmHg** **PVR >2 WU**
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Why keeping PAWP at 15 mmHg

- Best threshold for PAWP discriminating pre- and post-capillary PH is contradictory.
- Although the upper limit of normal PAWP is considered to be 12 mmHg, previous ESC/ERS Guidelines suggest a higher threshold for the invasive diagnosis of heart failure (HF) with preserved ejection fraction (HFpEF) (PAWP ≥15 mmHg).
- Almost all studies of PAH have used the PAWP ≤15 mmHg threshold.
- Therefore, **it is recommended keeping PAWP ≤15 mmHg as the threshold** for pre-capillary PH, while acknowledging that any PAWP threshold is arbitrary and that the patient phenotype, risk factors, and echocardiographic findings, including left atrial (LA) volume, need to be considered when distinguishing pre- from post-capillary PH.

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Normal range of pulmonary pressures - metaanalysis

Data on 1,187 individuals from 47 studies in 13 countries were included.

P_{pa} mmHg	**14.0±3.3**
Systolic P_{pa} mmHg	20.8±4.4
Diastolic P_{pa} mmHg	8.8±3.0
P_{paw} mmHg	**8.0±2.9**
Heart rate min^{-1}	76±14
Cardiac output $L \cdot min^{-1}$	7.3±2.3
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	4.1±1.3
PVR $dyn \cdot s \cdot cm^{-5}$	74±30

Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J. 2009;34(4):888-894. doi:10.1183/09031936.00145608

Why DPG is no longer used?

2015

Definition	Characteristics[a]
PH	PAPm ≥25 mmHg
Pre-capillary PH	PAPm ≥25 mmHg PAWP ≤15 mmHg
Post-capillary PH	PAPm ≥25 mmHg PAWP >15 mmHg
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]

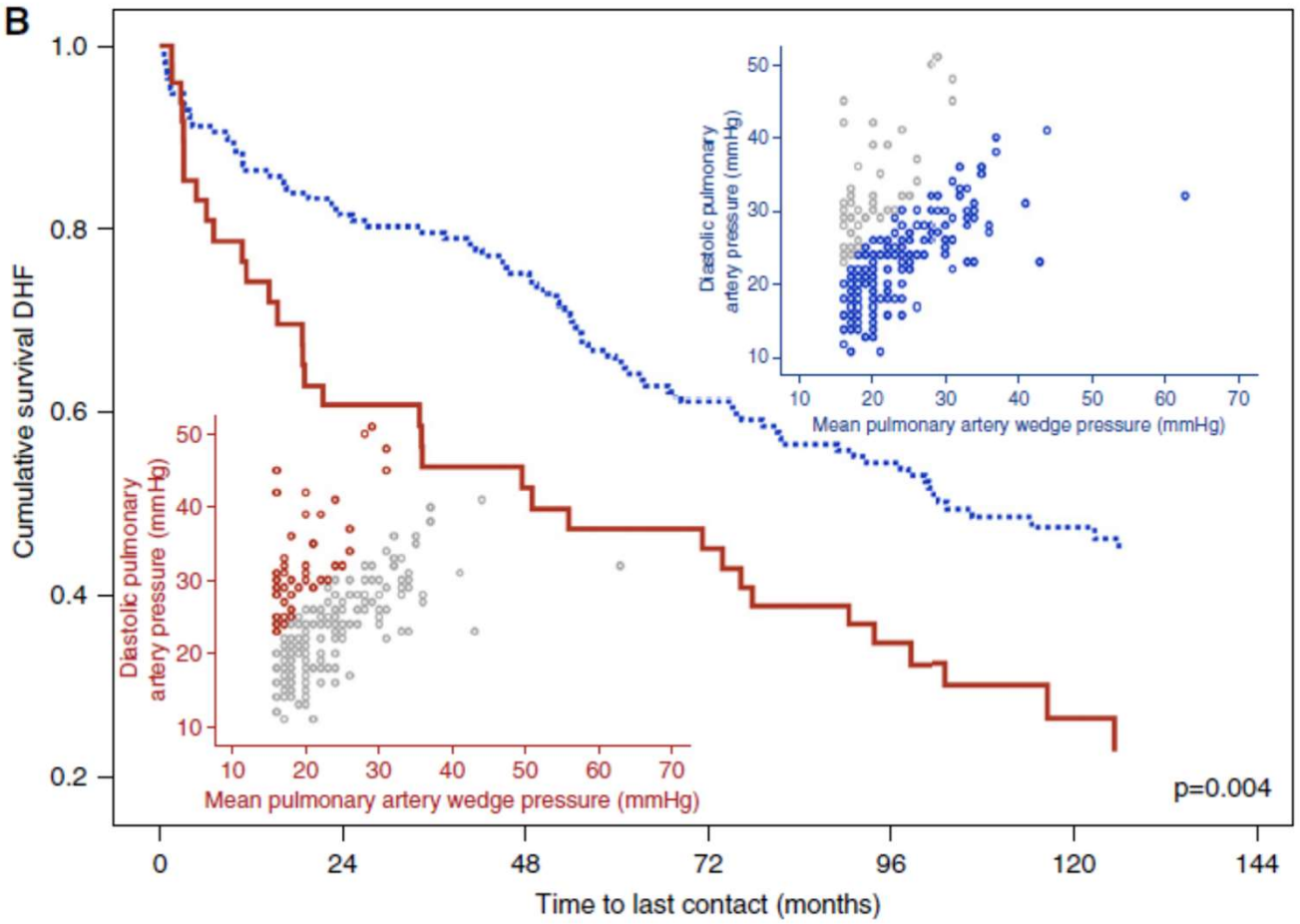
Galié et al. EHJ 2015

2022

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

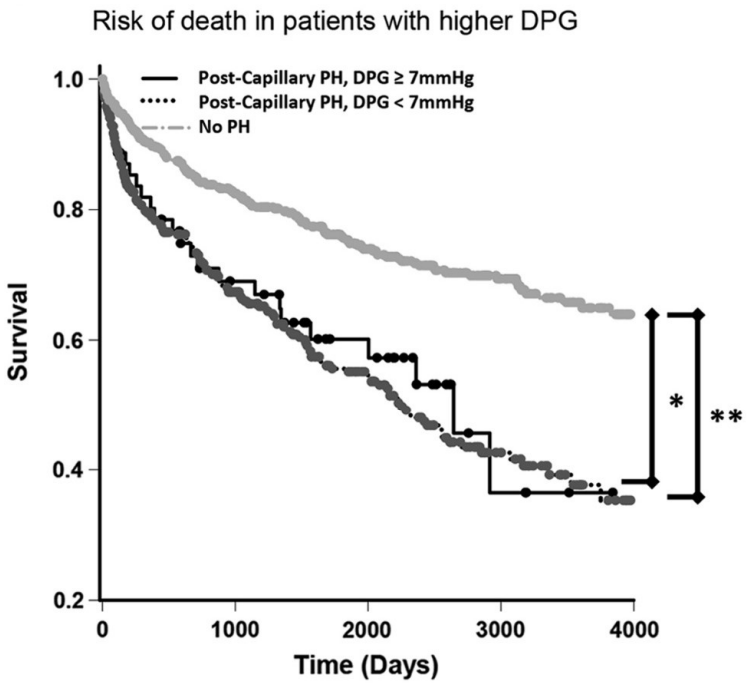
Humbert et al. EHJ 2022

Survival in HF-pEF patients accroding to DPG (< 7 mmHg vs. ≥ 7 mmHg)



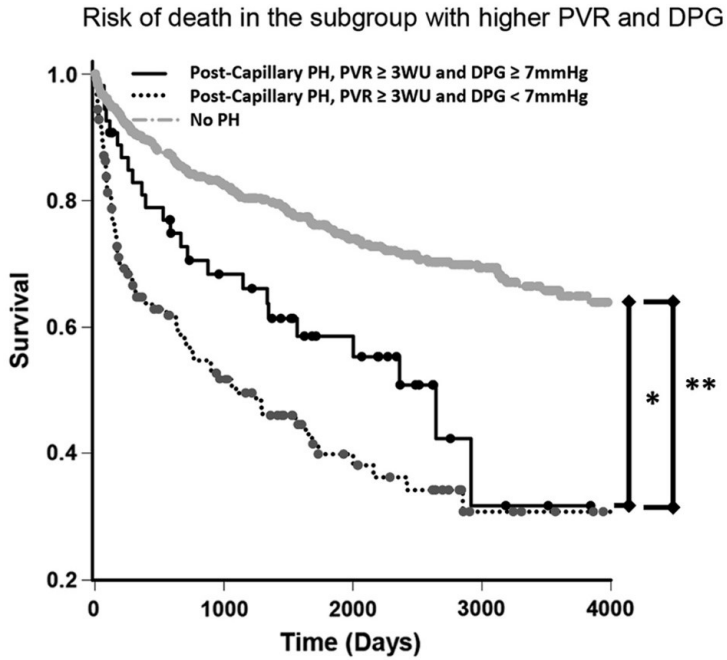
Gerges et al., Am J Respir Crit Care Med 2015;192:1234-1246

Why DPG is no longer used?



Number at risk

Low DPG	407	189	109	43	16
High DPG	62	34	21	5	0



Number at risk

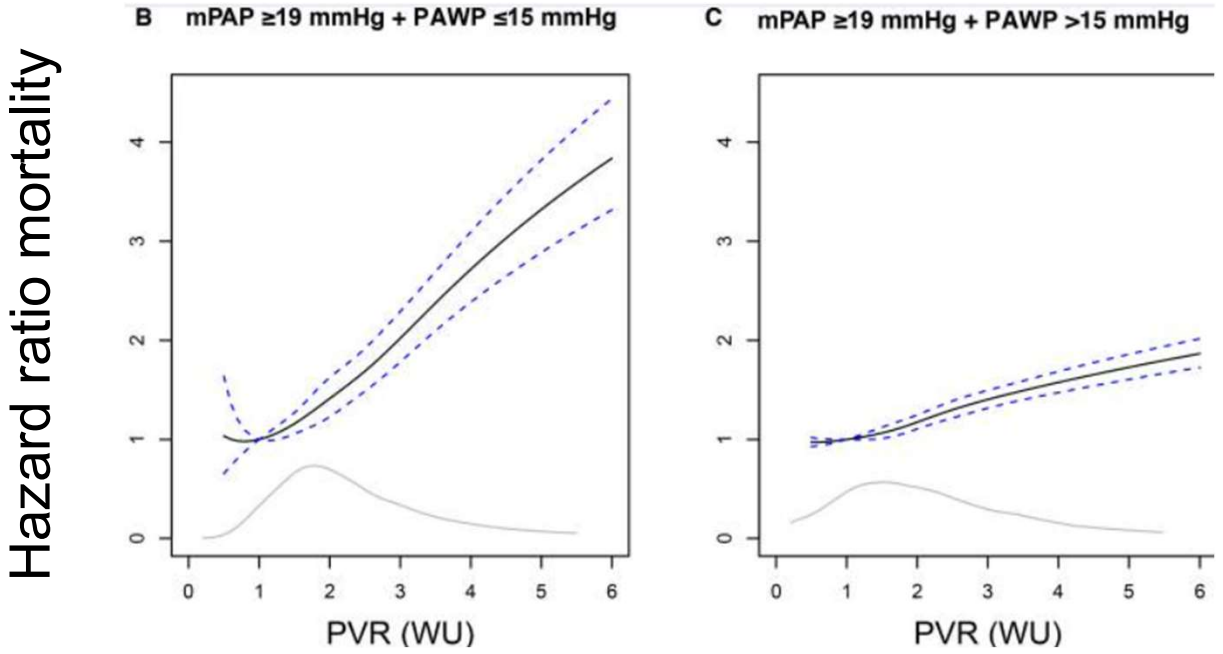
Low DPG	125	46	23	10	0
High DPG	54	30	18	4	0

Tampakakis E et al. J Am Coll Cardiol HF. 2015 Jan, 3 (1) 9–16

When to refer patients with LHD to PH center

Patients at risk for PH based on mean pulmonary artery pressure (mPAP) ≥19 mmHg (N=32,725 of 40,082 [81.6%]).

The all-cause mortality hazard for PVR was increased at ~2.2 WU compared to PVR=1.0 WU.



Based on available data, a PVR >5 WU may indicate a severe pre-capillary component, the presence of which may prompt physicians to refer patients to PH centres for specialized care.

Maron BA et al. Lancet Respir Med. 2020 Sep; 8(9): 873–884.

How many patients with LHD have PH

- HF-rEF : 40–72%
- HF-pEF: 36–83%

- Out fo these, ~20–30% of patients are categorized as having CpcPH.
- Valvular heart disease
  - Aortic stenosis 65%
  - Severe mitral valve stenosis – all develop PH
  - Severe mital valve regurgitation – large majority

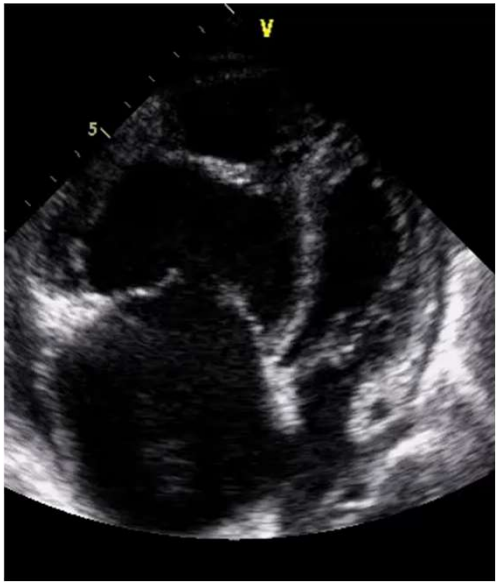
Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

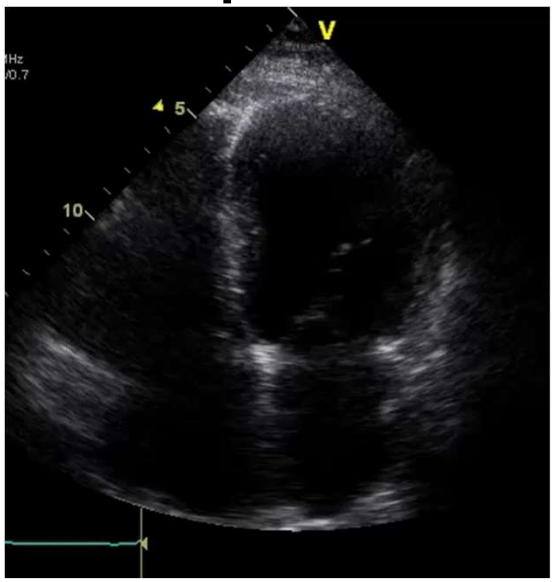
Phenotypic continuum

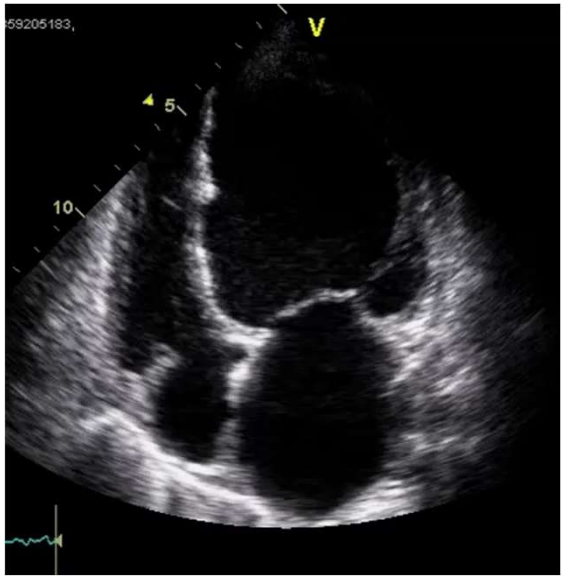
PAH
CTEPH

PAH / CTEPH?
PH in lung disease?
HF-pEF ?

HF-rEF







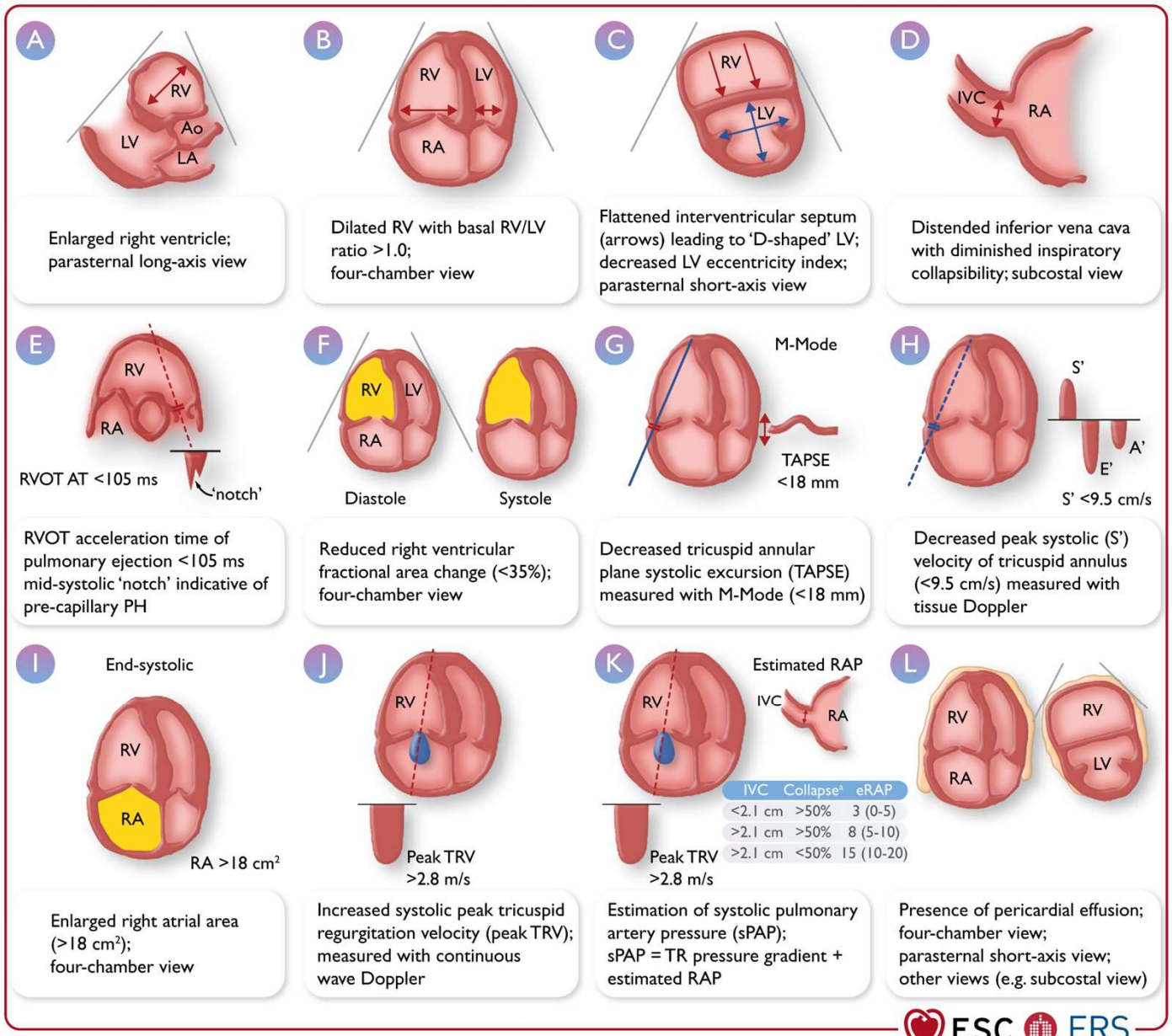
Precapillary

Postcapillary ?
Combined?
Precapillary ?

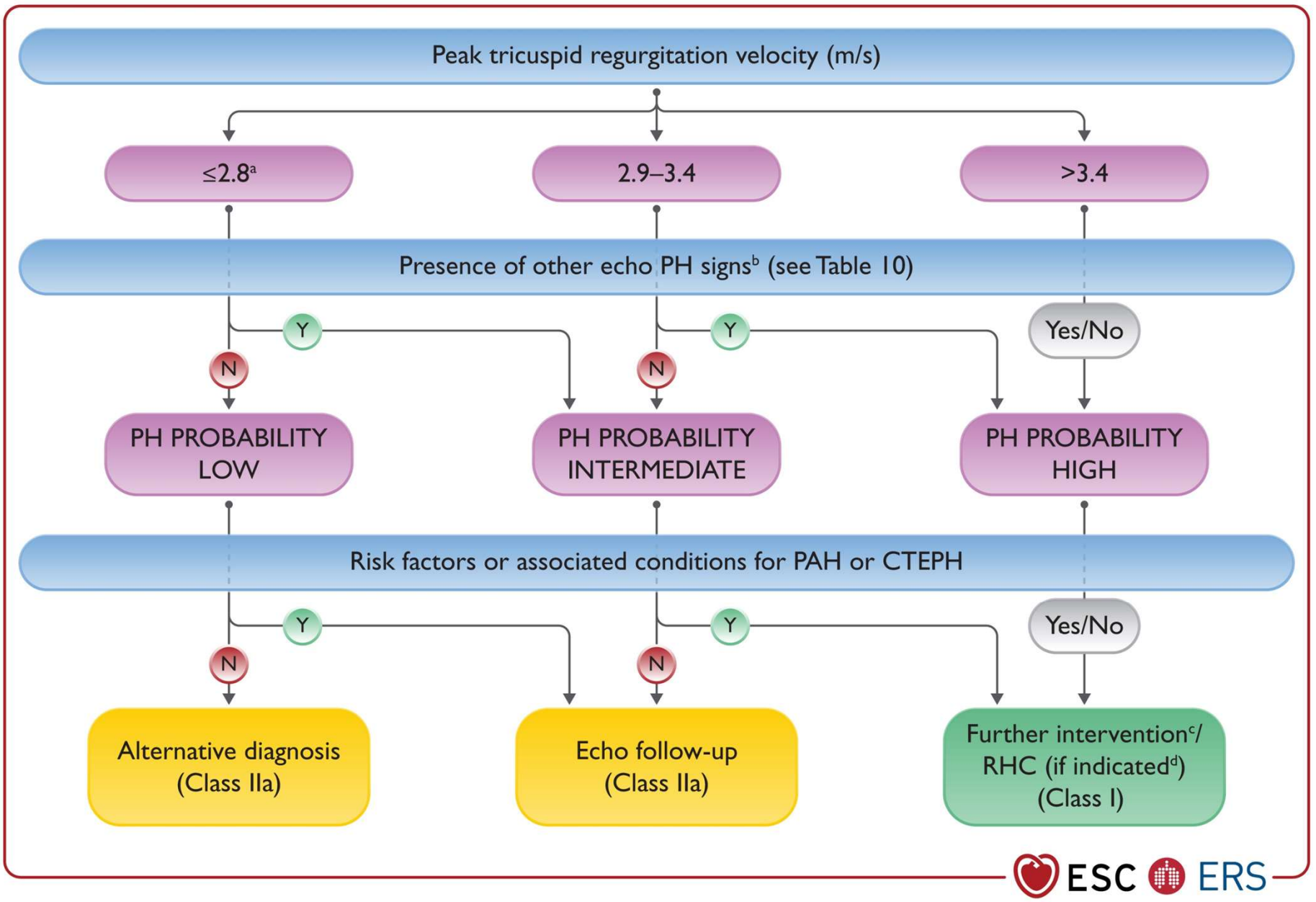
Postcapillary

RV phenotype ⟵ ⟶ **LV phenotype**

ECHOCARDIOGRAPHY


A
RV
Ao
LV
LA
Enlarged right ventricle; parasternal long-axis view
B
RV
LV
RA
Dilated RV with basal RV/LV ratio >1.0; four-chamber view
C
RV
LV
Flattened interventricular septum (arrows) leading to 'D-shaped' LV; decreased LV eccentricity index; parasternal short-axis view
D
IVC
RA
Distended inferior vena cava with diminished inspiratory collapsibility; subcostal view
E
RV
RA
RVOT AT <105 ms
'notch'
RVOT acceleration time of pulmonary ejection <105 ms mid-systolic 'notch' indicative of pre-capillary PH
F
RV
LV
RA
Diastole
Systole
Reduced right ventricular fractional area change (<35%); four-chamber view
G
M-Mode
TAPSE
<18 mm
Decreased tricuspid annular plane systolic excursion (TAPSE) measured with M-Mode (<18 mm)
H
S'
A'
E'
S' <9.5 cm/s
Decreased peak systolic (S') velocity of tricuspid annulus (<9.5 cm/s) measured with tissue Doppler
I
End-systolic
RV
RA
RA >18 cm²
Enlarged right atrial area (>18 cm²); four-chamber view
J
RV
Peak TRV
>2.8 m/s
Increased systolic peak tricuspid regurgitation velocity (peak TRV); measured with continuous wave Doppler
K
RV
Estimated RAP
IVC
RA
IVC Collapse[a] eRAP
<2.1 cm >50% 3 (0-5)
>2.1 cm >50% 8 (5-10)
>2.1 cm <50% 15 (10-20)
Peak TRV
>2.8 m/s
Estimation of systolic pulmonary artery pressure (sPAP); sPAP = TR pressure gradient + estimated RAP
L
RV
RA
RV
LV
Presence of pericardial effusion; four-chamber view; parasternal short-axis view; other views (e.g. subcostal view)
ESC ERS

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731



2.8 m/s
=
31 mmHg

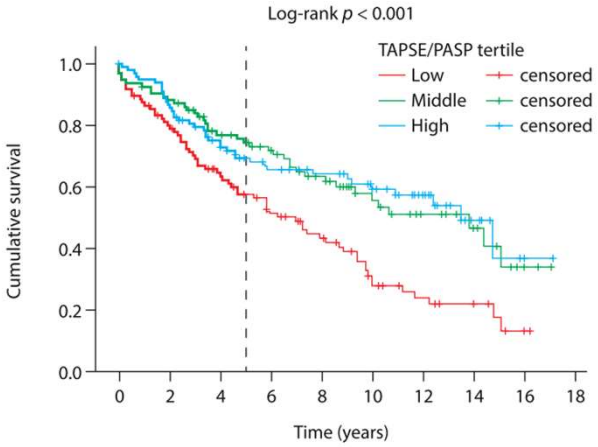
PASP vs. TRV

- Considering the **inaccuracies in estimating RAP** and the amplification of measurement errors by using derived variables, these guidelines **recommend using the peak TRV (and not the estimated sPAP)** as the key variable for assigning the echocardiographic probability of PH.
- **A peak TRV >2.8 m/s may suggest PH**; however, the presence or absence of PH cannot be reliably determined by TRV alone.
- **Lowering the TRV threshold in view of the revised haemodynamic definition of PH is not supported** by available data

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Prognostic stratification based on echo

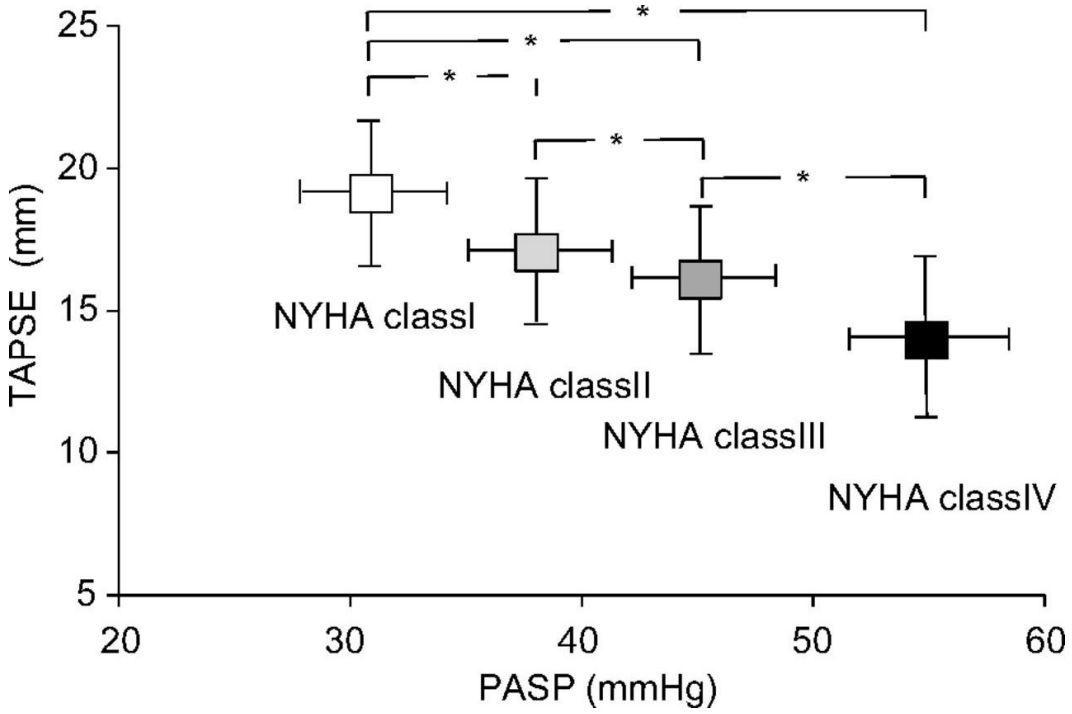
Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion

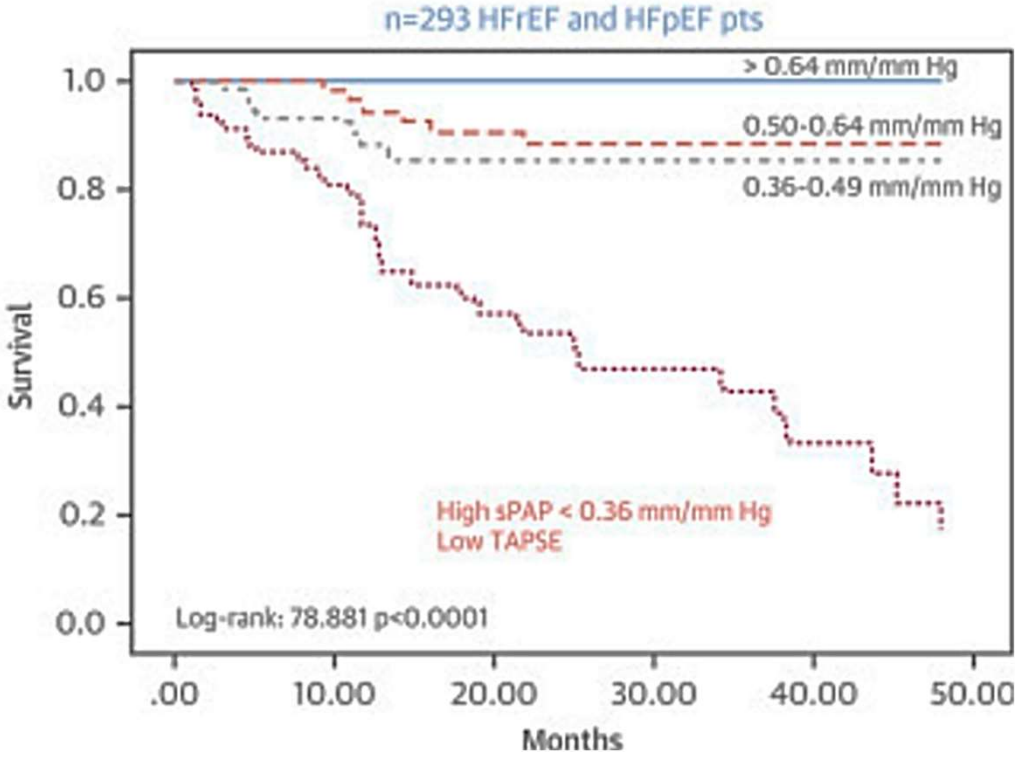


Number at risk	1 year	3 years	5 years
Low tertile	83	64	50
Middle tertile	93	81	63
High tertile	85	66	50

Humbert M. et al. Eur Heart J. 2022;43:3618–3731
Tello K et al. Int J Cardiol. 2018 Sep 1;266:229-235.

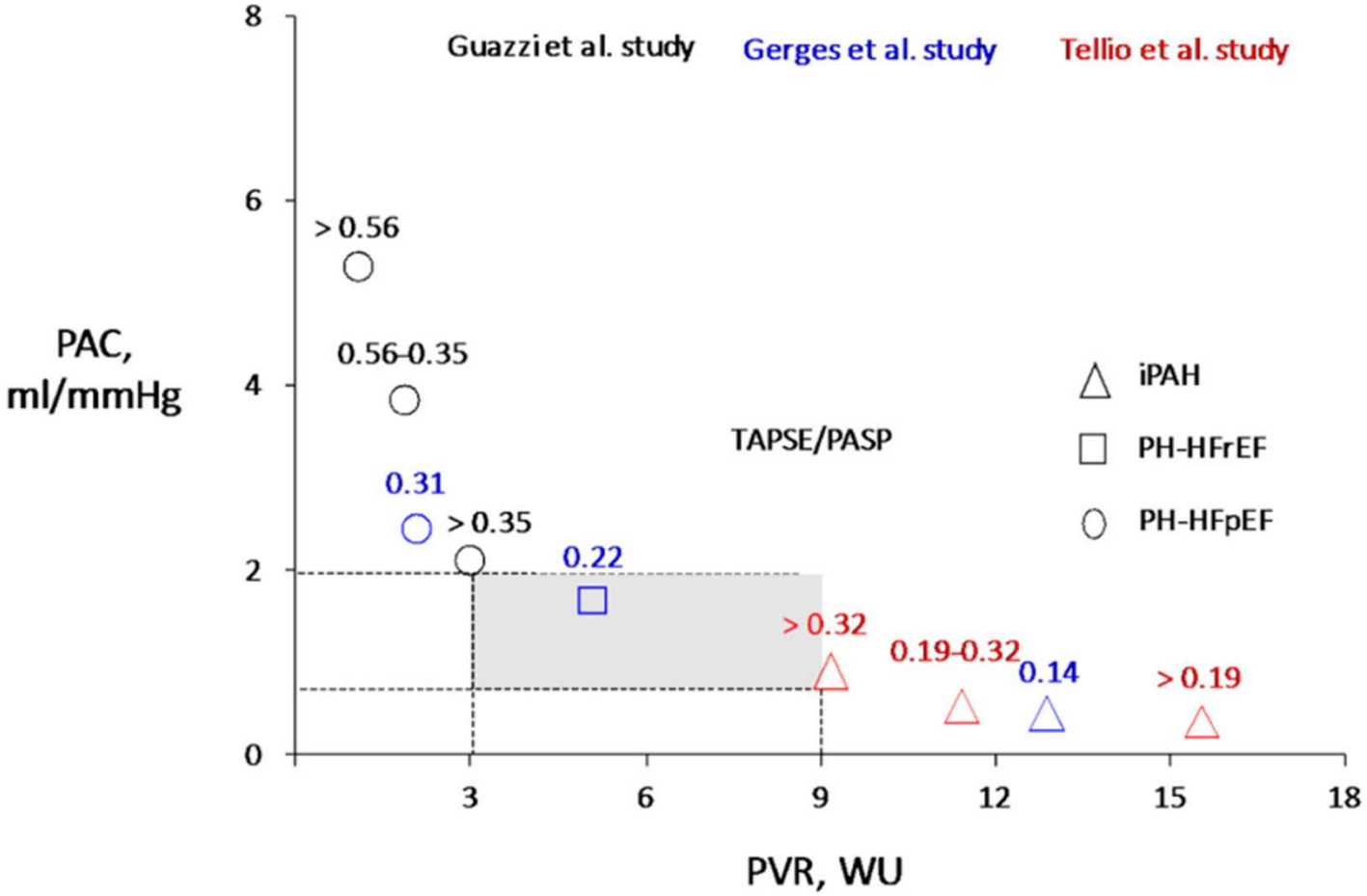
TAPSE/sPAP in Heart Failure





Guazzi et al. Am J Physiol Heart Circ Physiol305: H1373–H1381, 2013

Pulmonary arterial compliance and PVR – impact on TAPSE/sPAP

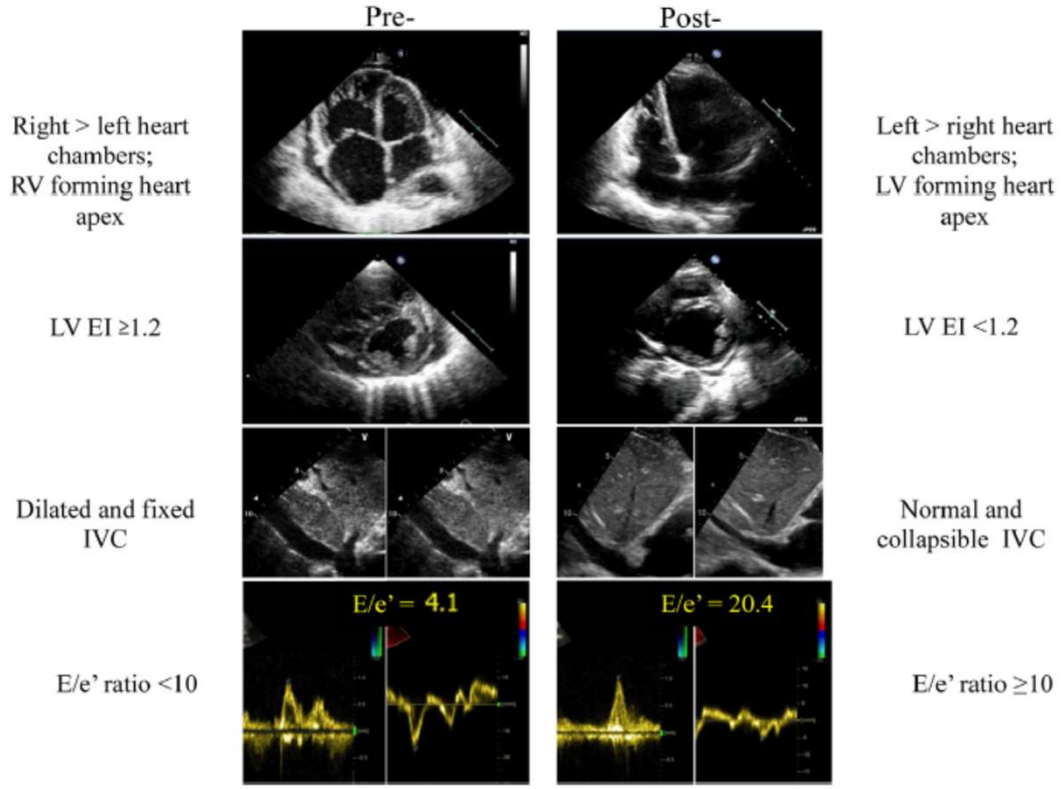


Guazzi et al. International Journal of Cardiology 266 (2018) 242–244

SCORING SYSTEMS

Scoring systems for prediction of pulmonary vascular disease

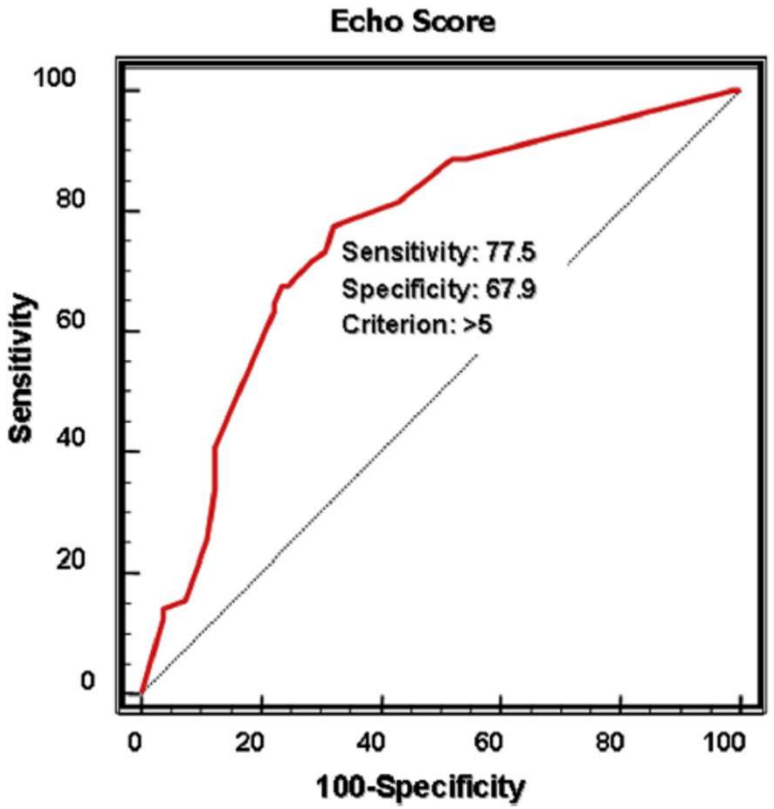
- n=152 echo and RHC within 1 hour
- precapillary hypertension (PCWP≤ 15 mmHg)



D´Alto et al. J Am Soc Echocardiogr 2015;28:108-15

Scoring systems for prediction of pulmonary vascular disease

- right vs. left heart chamber dimensions (LA + LV < RA + RV),
- RV forming the heart apex
- LV eccentricity index (EI) (>1.2 or ≤1.2)
- pericardial effusion
- systolic notch on RVOT flow
- IVC diameter (≤20 or >20 mm) and collapsibility (≤ 50% or >50%)
- E/e´ ratio (≤ 10 or >10)
- moderate to severe mitral or aortic valve disease.



D´Alto et al. J Am Soc Echocardiogr 2015;28:108-15

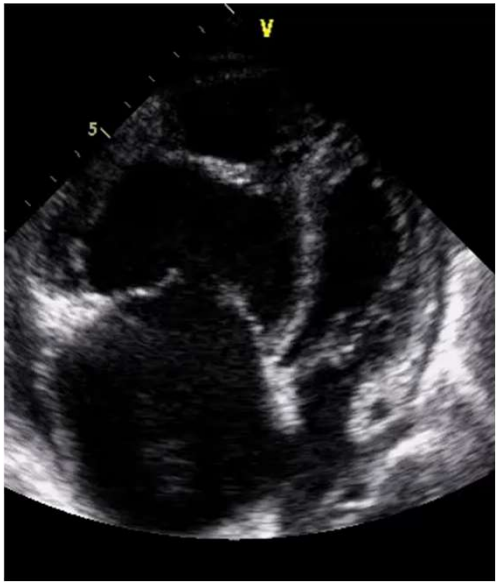
Probability of PH due to LHD

Feature	PH-LHD unlikely	Intermediate probability	PH-LHD likely
Age	<60 years	60–70 years	>70 years
Obesity, hypertension, dyslipidaemia, glucose intolerance/diabetes	No factors	1–2 factors	>2 factors
Presence of known LHD	No	Yes	Yes
Previous cardiac intervention	No	No	Yes
Atrial fibrillation	No	Paroxysmal	Permanent/persistent
Structural LHD	No	No	Present
ECG	Normal or signs of RV strain	Mild LVH	LBBB or LVH
Echocardiography	No LA dilation E/e′ <13	No LA dilation Grade <2 mitral flow	LA dilation (LAVI >34 mL/m^2) LVH Grade >2 mitral flow
CPET	High VE/VCO$_2$ slope No EOV	Elevated VE/VCO$_2$ slope EOV	Mildly elevated VE/VCO$_2$ slope EOV
cMRI	No left heart abnormalities		LVH LA dilation (strain or LA/RA >1)

Humbert M. et al. *European Heart Journal*, 2022;43:3618–3731

Who may benefit from RHC

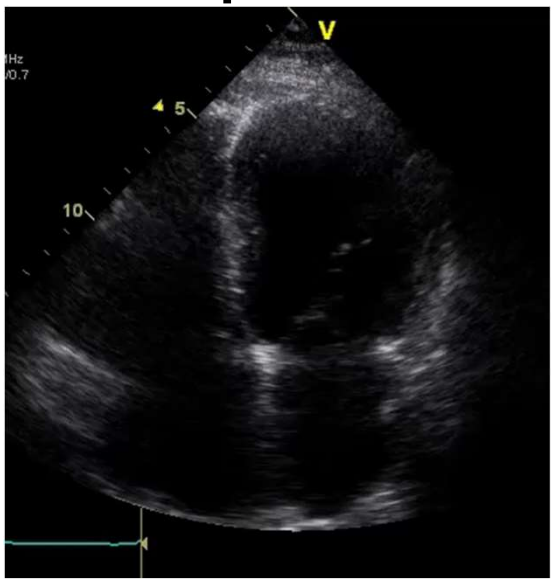
PAH
CTEPH



Precapillary

Yes – to confirm the diagnosis + lead the Rx

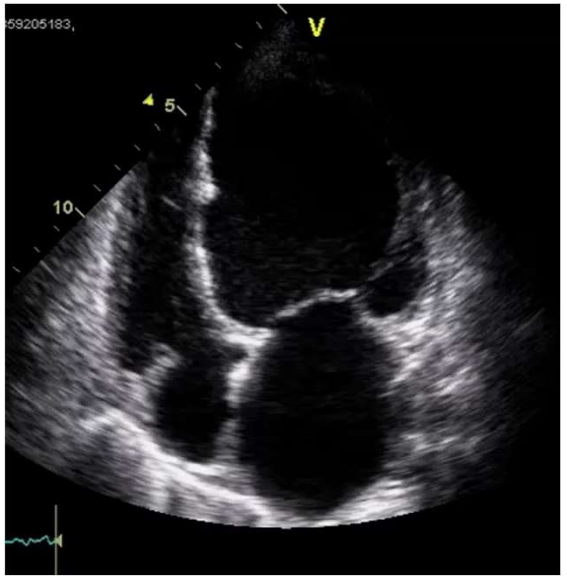
PAH / CTEPH?
PH in lung disease?
HF-pEF ?



Postcapillary ?
Combined?
Precapillary ?

Yes – if in doubt - to confirm the diagnosis

HF-rEF



Postcapillary

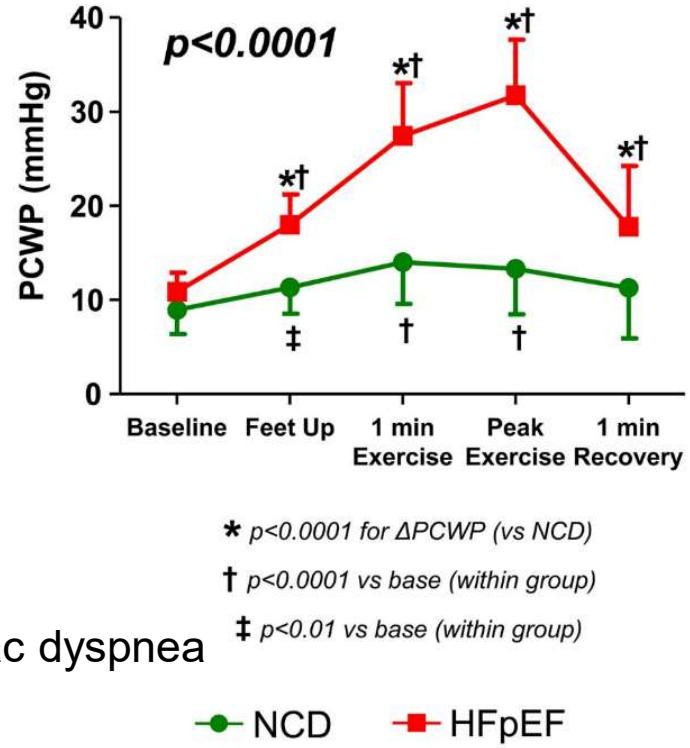
Yes – if HTx is considered

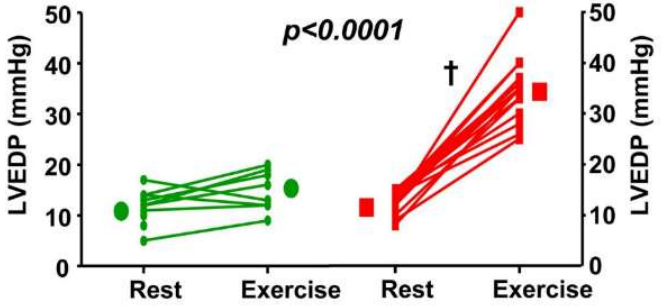
Imaging: General University Hospital, Prague, CZ

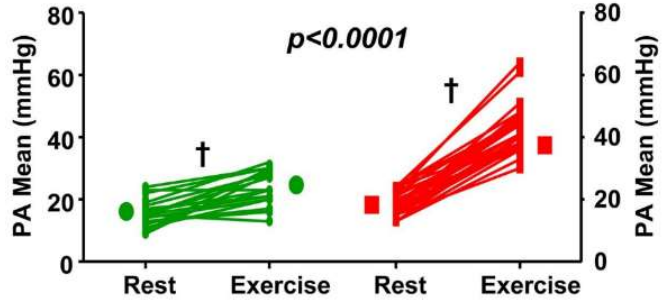
Stress RHC – PAWP ≥ 25 mmHg

55 subjects with exercise-induced dyspnea,
PAPM < 25 mmHg and PAWP < 15 mmHg at rest, normal BNP

Exercise rise in PAWP > 25 mmHg = HF-pEF







NCD= non-cardiac dyspnea

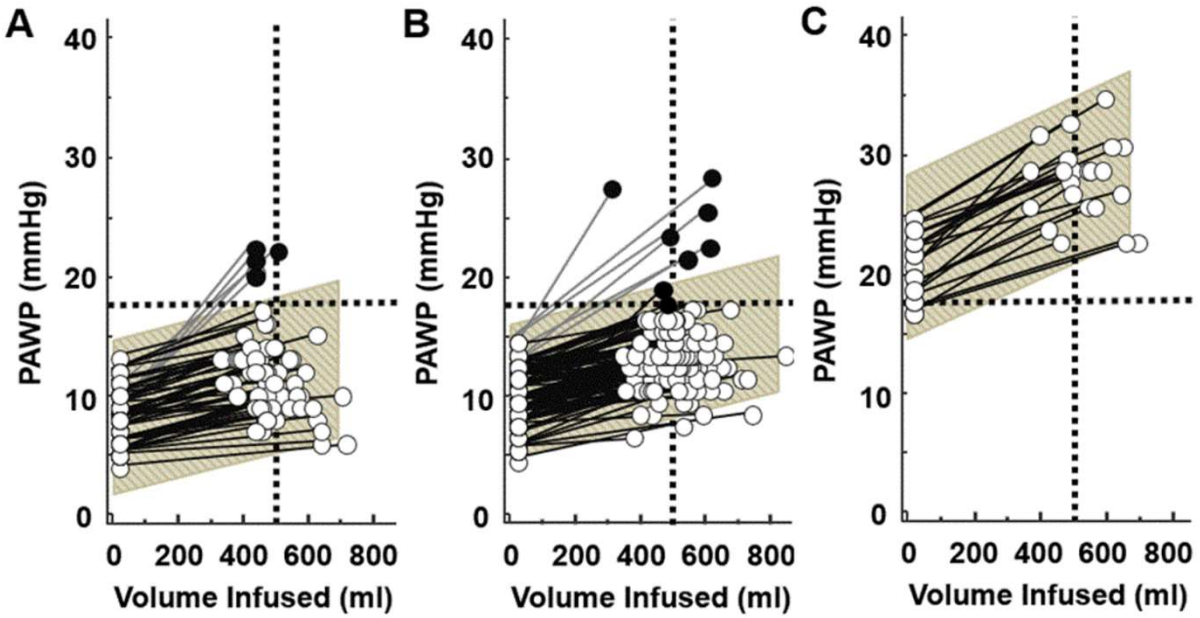
Borlaug BA et al. Circulation: Heart Failure. 2010;3:588-595

Volume challenge to diagnose HF-pEF

- (A) no pulmonary hypertension controls,
- (B) patients with precapillary pulmonary hypertension
- (C) patients with post-capillary pulmonary hypertension

rapidly infused saline
7 ml/kg

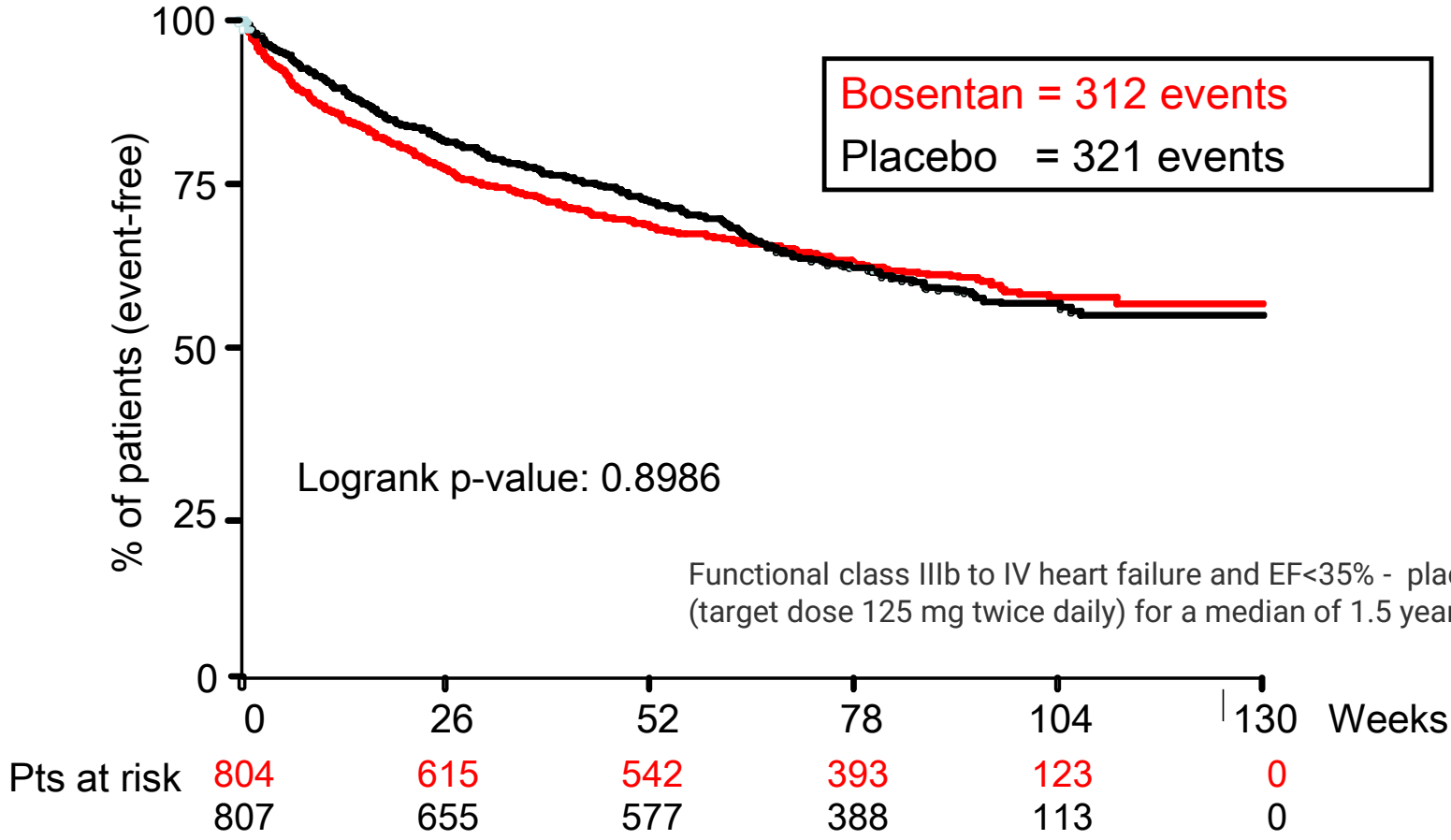
Cut-off PCW > 18
mmHg



D´Alto M et al. Chest. 2017 Jan;151(1):119-126.

TREATMENT

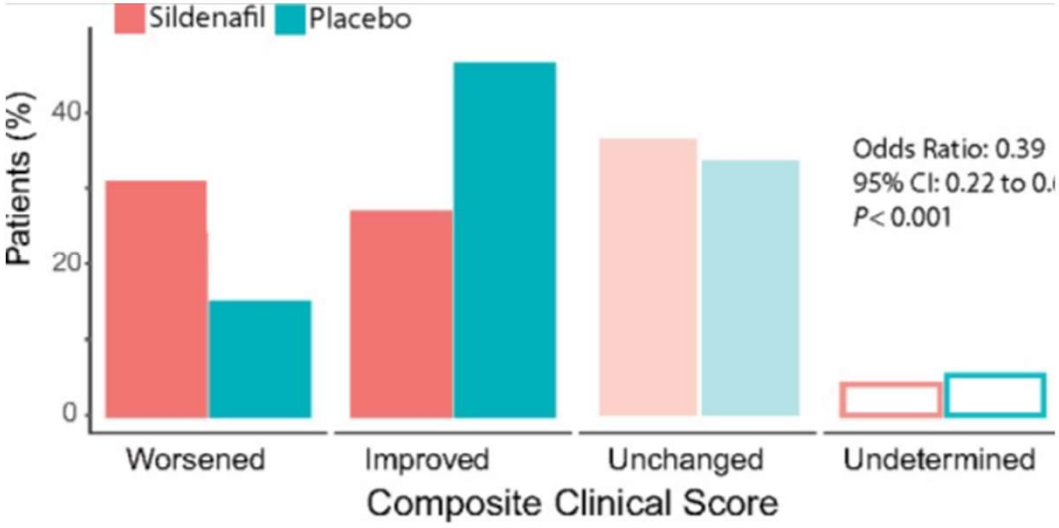
ENABLE: Death or hospitalization for heart failure

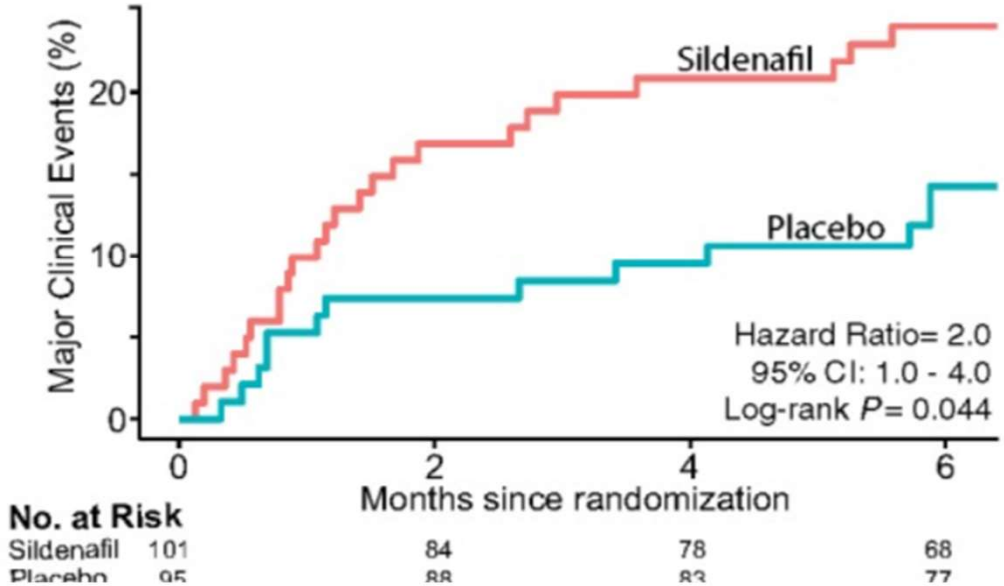


Functional class IIIb to IV heart failure and EF<35% - placebo or bosentan (target dose 125 mg twice daily) for a median of 1.5 years.

Packer M et al. J Am Coll Cardiol HF. 2017 May, 5 (5) 317–326

SIOVAC - Sildenafil to improve PH in aortic stenosis patients after replacement / repair





Bermejo J et al. Eur Heart J. 2018 Apr 14;39(15):1255-1264.

Recommendations for LHD PH

Recommendations	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH	IIb	C
Drugs approved for PAH are not recommended in PH-LHD	III	A

GRADE recommendations - sildenafil

	Recommendation			
	GRADE			
Recommendations	**Quality of evidence**	**Strength of recommendation**	**Class**[a]	**Level**[b]
No recommendation can be given for or against the use of PDE5is in patients with HFpEF and combined post- and pre-capillary PH	Low	None	–	–
The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	**III**	**C**

Conclusions

- **Left heart Disease is the most frequent cause of PH**
- **Despite modification of definition PAWP of 15 mmHg stays unchanged to define postcapillary PH**
- **Definition of CpcPH is using PVR of >2 WU instead of DPG**
- **Specific therapy of PH using drugs indicated in PAH is recommended neither in IpcPH nor in CpcPH**
- **TAPSE/sPAP – stressed out as an important prognostic measure (? thresholds, validation?)**

Thanks for your attention !

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