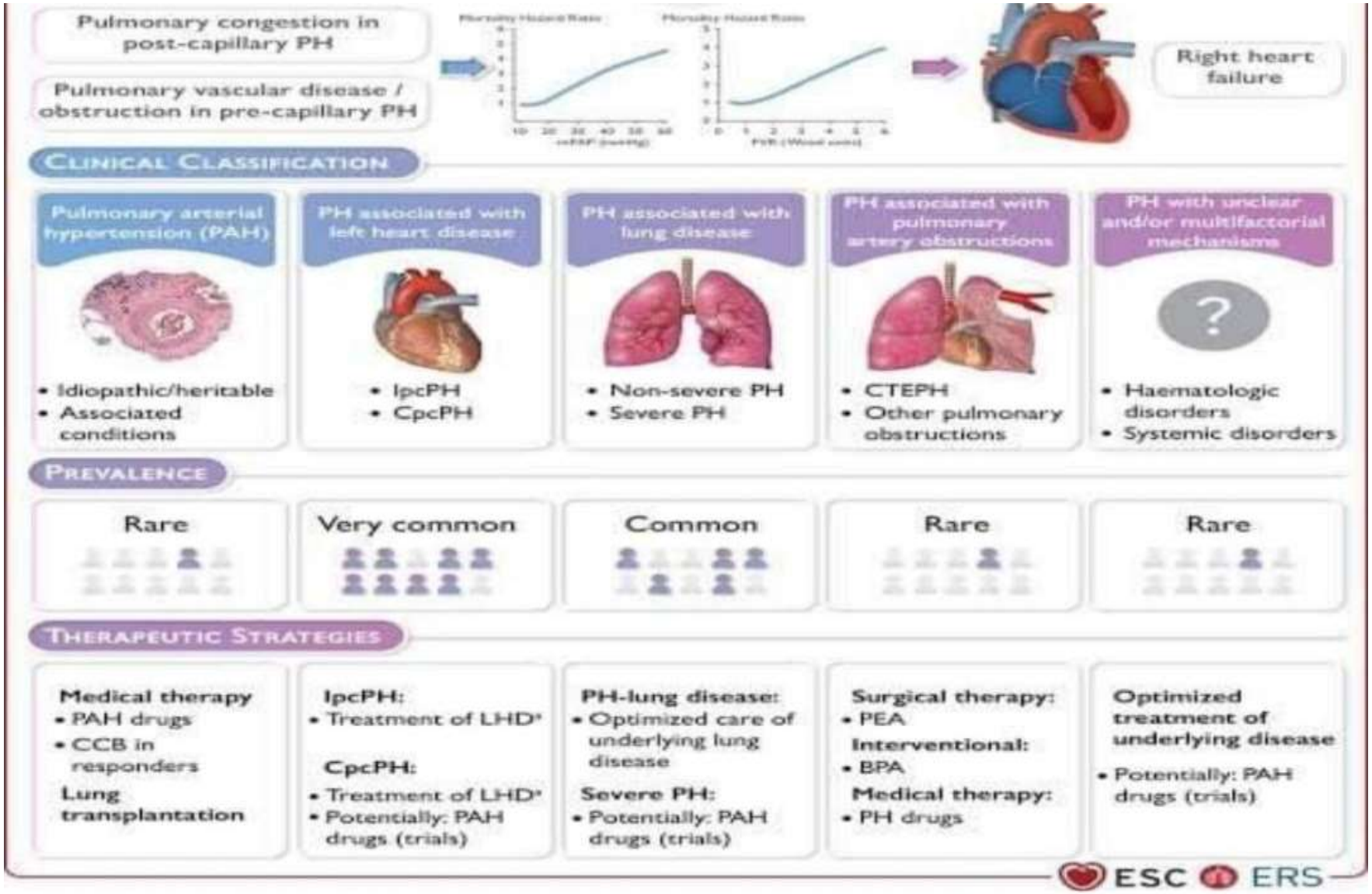
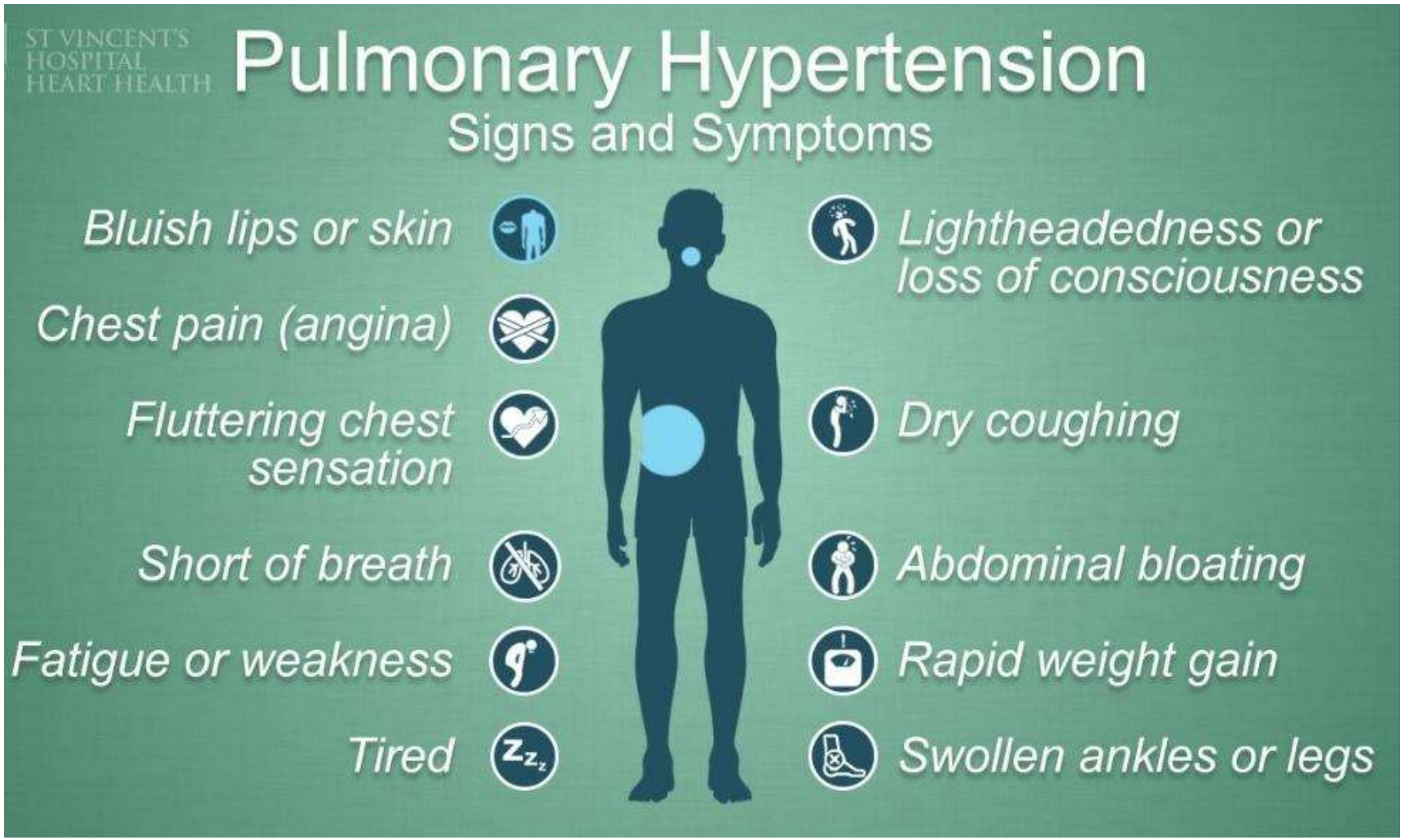
PAH treatment & mortality

Prof. **Marijan Bosevski,** MD, PhD, FESC

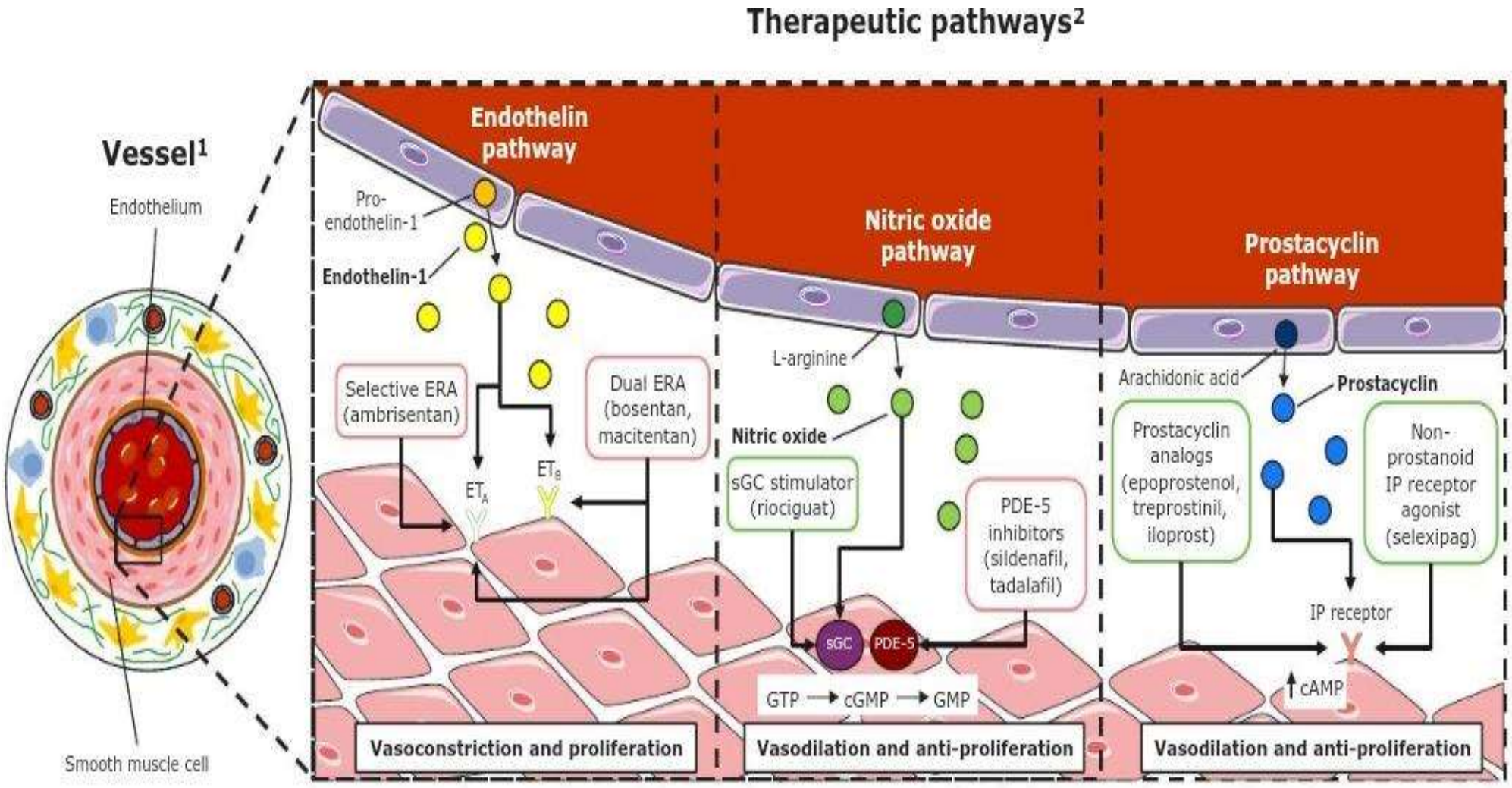
PAH definition and clasification



Recognize PAH and its deterioration



Th is available to target 3 pathways involved in PAH



cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanidine monophosphate; ERA: endothelin receptor antagonist; ET: endothelin; GMP: guanidine monophosphate; GTP: guanidine triphosphate; IP: prostacyclin; PAH: pulmonary arterial hypertension; PDE: phosphodiesterase; sGC: soluble guanylate cyclase.

1. Adapted from Pugliese S, *et al. Am J Physiol Lung Cell Mol Physiol* 2015; 308:L229-52; 2. Lau EMT, *et al. Nat Rev Cardiol* 2017; 14:603-14.

Efficacy of drug monotherapy, for PAH (Group 1)

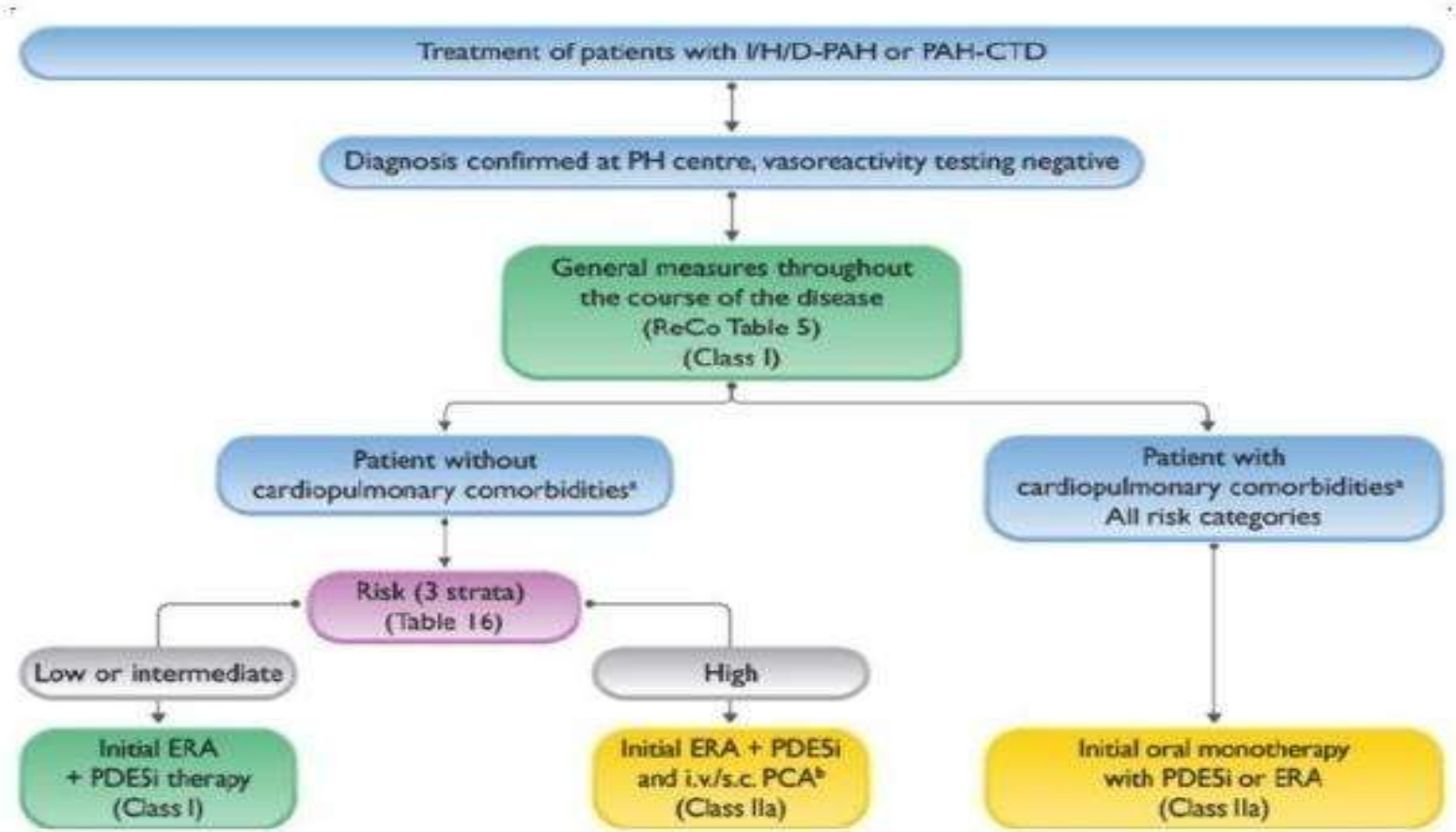
Recommendations			Class - Level					
Measure/treatment			WHO-FC II		WHO-FC III		WHO-FC IV	
Calcium channel blockers			I	C	I	C	-	-
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C
	Bosentan		I	A	I	A	IIb	C
	Macitentan[d]		I	B	I	B	IIb	C
Phosphodiesterase type-5 inhibitors	Sildenafil		I	A	I	A	IIb	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.

ERS RESPIRATORY SOCIETY

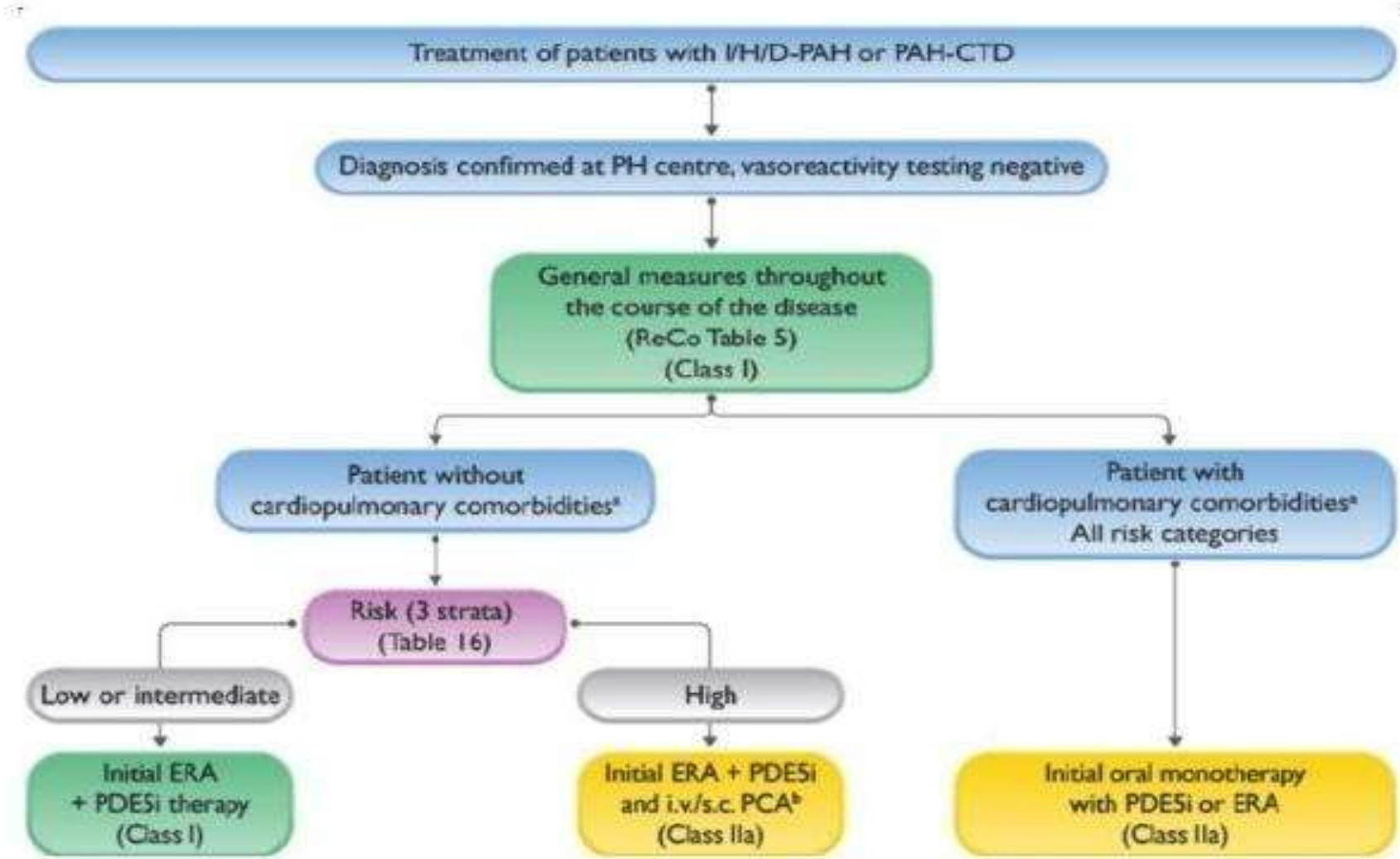
EUROPEAN SOCIETY OF CARDIOLOGY®

Treatment in PAH is lead by disease severity and risk of dying



DLCO: Lung diffusion capacity for carbon monoxide; ERA: endothelin receptor antagonist; I/H/D-PAH: idiopathic, heritable, or drug-associated pulmonary arterial hypertension; I.v.: intravenous; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; PCA: prostacyclin analogue; PDE5I: phosphodiesterase 5 inhibitor; PH: pulmonary hypertension; PRA: prostacyclin receptor agonist; ReCo: recommendation; s.c.: subcutaneous; sGCs: soluble guanylate cyclase stimulator. [a]Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild

3-strata risk assessment at diagnosis



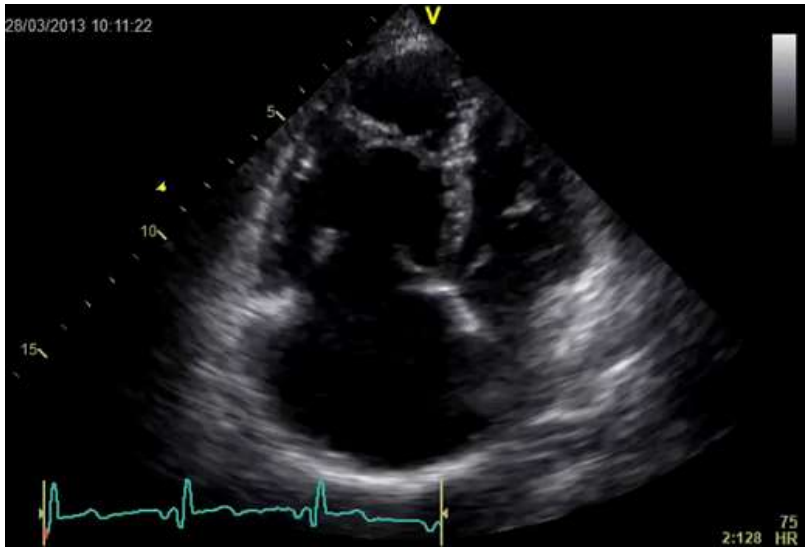
DLCO: Lung diffusion capacity for carbon monoxide; ERA: endothelin receptor antagonist; I/H/D-PAH: idiopathic, heritable, or drug-associated pulmonary arterial hypertension; I.v.: intravenous; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; PCA: prostacyclin analogue; PDE5I: phosphodiesterase 5 inhibitor; PH: pulmonary hypertension; PRA: prostacyclin receptor agonist; ReCo: recommendation; s.c.: subcutaneous; sGCs: soluble guanylate cyclase stimulator. [a]Cardiopulmonary comorbidities are conditions associated with an increased risk of left ventricular diastolic dysfunction, and include obesity, hypertension, diabetes mellitus, and coronary heart disease; pulmonary comorbidities may include signs of mild

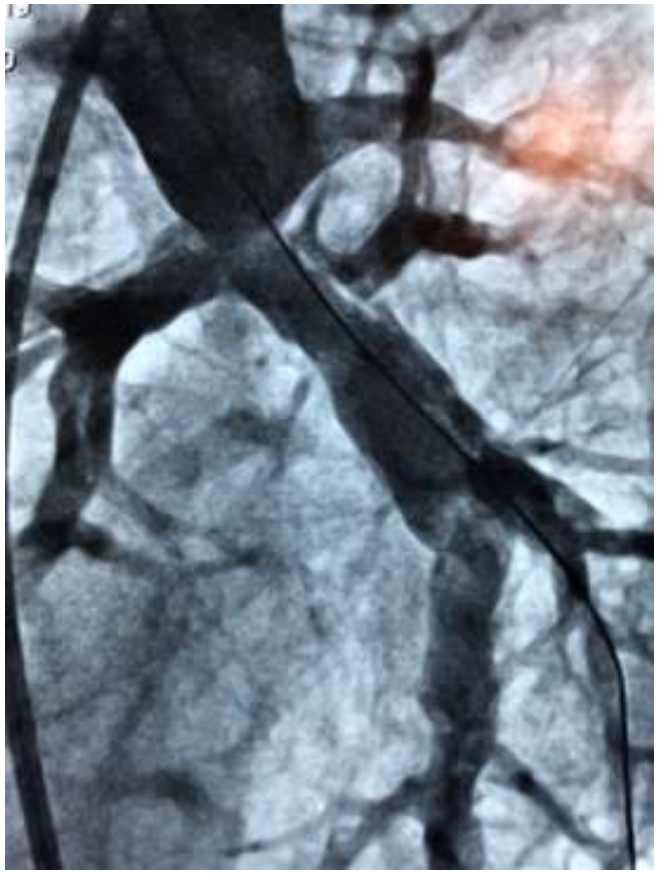
Three recent studies have validated the ERS/ESC risk score

	Swedish	COMPERA	French
Number of patients at baseline	500	1588	1017
Number of patients at FUP	383	1094	1017
Associated PAH included	yes	yes	no
Definition of low risk	Avg score <1.5	Avg score <1.5	3-4 of 4 low-risk criteria
1-year mortality % by risk group	1-7-26	2.2-9.9-21.2	1-na-13-30
% low risk at baseline	23	12.3	17
% low risk at FUP	29	24	41.5
Initial combination therapy, % of patients	12	17	48
Initial monotherapy, % of patients	86	83	52

Kylhammar D, et al. Eur Heart J. 2017 Jun 1 [Epub ahead of print]. Hoeper et al. Eur Resp J 2017 Aug 3;50(2). Boucly A, et al. Eur Resp J 2017: Aug 3;50(2).:D73–81.

WHO, BNP, 6MWD are the basis
But imaging is crucial when added



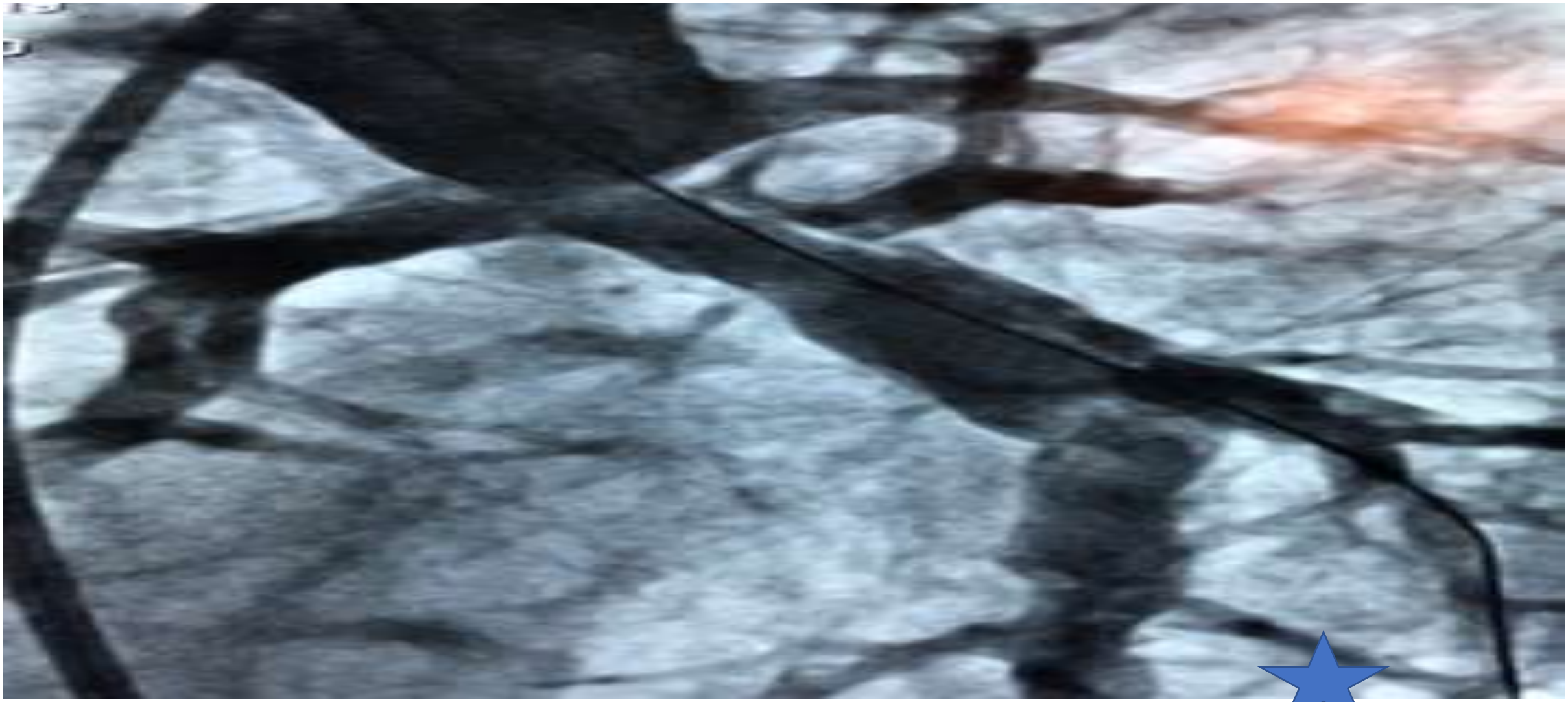


Additional echocardiographic signs suggestive of pulmonary hypertension

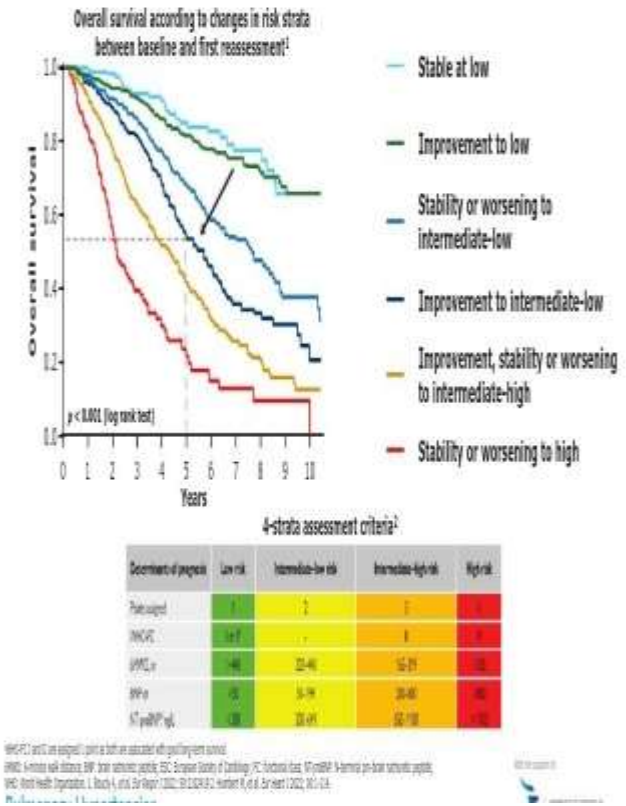
A: The ventricles	B: Pulmonary artery	C: Inferior vena cava and RA
RV/LV basal diameter/area ratio >1.0	RVOT AT <105 ms and/or mid-systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
TAPSE/sPAP ratio <0.55 mm/mmHg	PA diameter > AR diameter PA diameter >25 mm	

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

Faith in intermediate risk pts

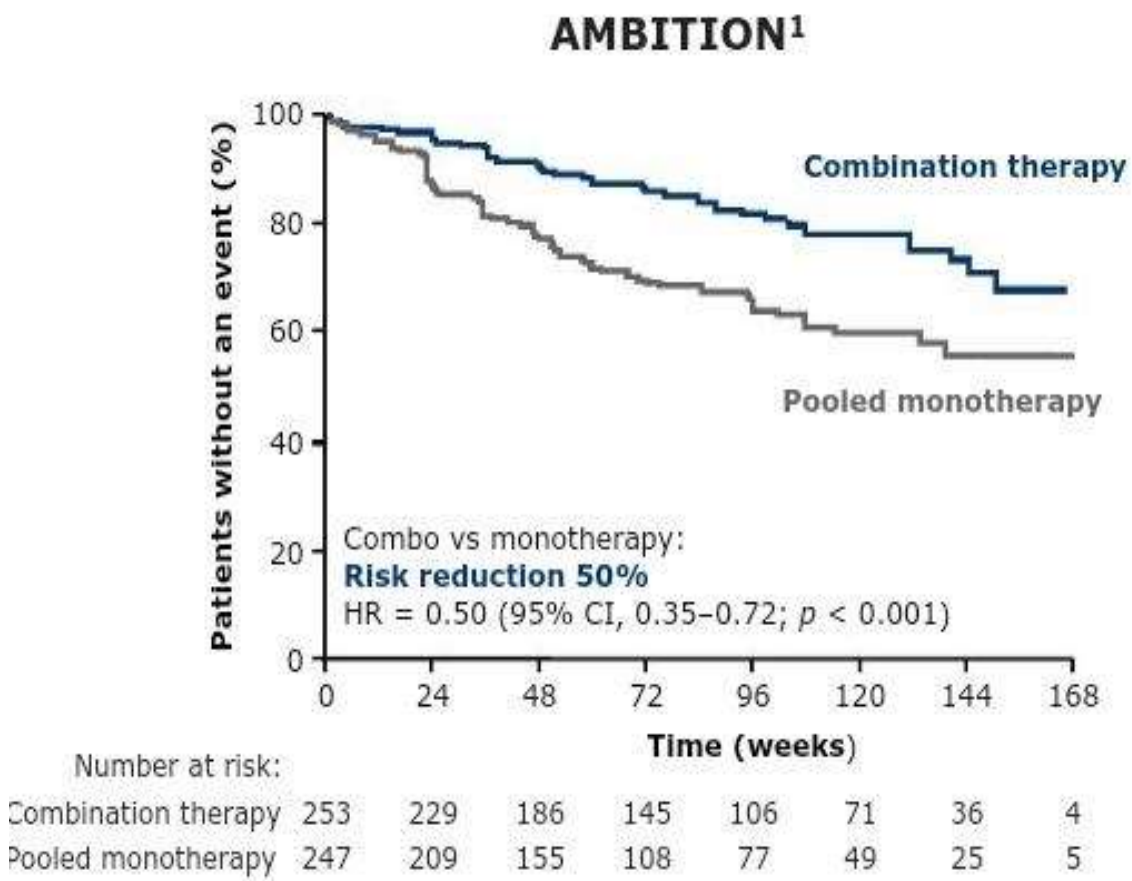


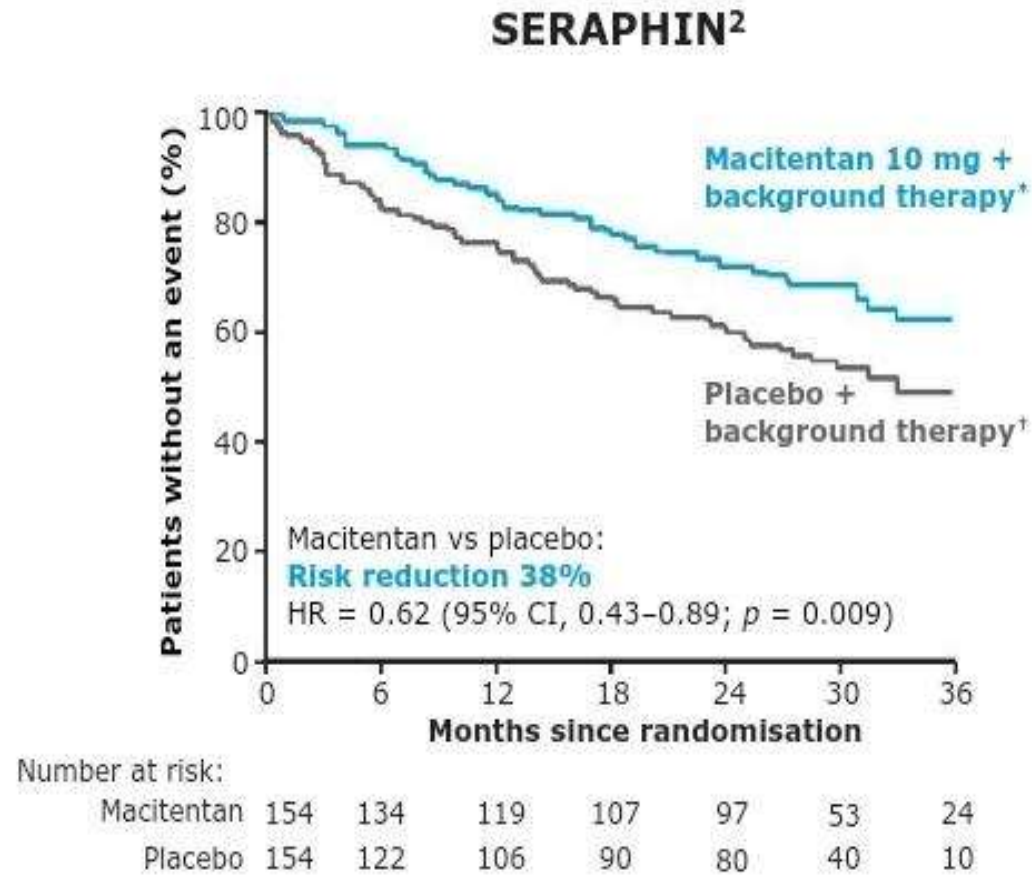
Risk strata applicable in Euro & Asian population



Double Th and survival

Th in intermediate-low risk pts





What is new (21)

Treatment of non-vasoreactive patients with IPAH, HPAH, or DPAH who present without cardiopulmonary comorbidities			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be consideredc	**IIa**
		In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, addition of selexipag should be considered	**IIa**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (22)

Treatment of non-vasoreactive patients with IPAH, HPAH, or DPAH who present without cardiopulmonary comorbidities (continued)			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
	↓	In patients with IPAH/HPAH/DPAH who present at intermediate-high or high risk of death while receiving ERA/PDE5i therapy, addition of i.v./s.c. prostacyclin analogues and referral for lung transplantation evaluation should be considered	**IIa**
		In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered	**IIb**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (21)

Treatment of non-vasoreactive patients with IPAH, HPAH, or DPAH who present without cardiopulmonary comorbidities			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		In patients with IPAH/HPAH/DPAH who present at high risk of death, initial combination therapy with a PDE5i, an ERA, and i.v./s.c. prostacyclin analogues should be consideredc	**IIa**
		In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, addition of selexipag should be considered	**IIa**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (22)

Treatment of non-vasoreactive patients with IPAH, HPAH, or DPAH who present without cardiopulmonary comorbidities (continued)			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		In patients with IPAH/HPAH/DPAH who present at intermediate-high or high risk of death while receiving ERA/PDE5i therapy, addition of i.v./s.c. prostacyclin analogues and referral for lung transplantation evaluation should be considered	**IIa**
		In patients with IPAH/HPAH/DPAH who present at intermediate-low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to riociguat may be considered	**IIb**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (23)

Initial oral drug combination therapy for patients with IPAH, HPAH, or DPAH without cardiopulmonary comorbidities			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
Ambrisentan + tadalafil	**I**	Initial combination therapy with ambrisentan and tadalafil is recommended	**I**
		Initial combination therapy with macitentan and tadalafil is recommended	**I**
Other ERA + PDE-5i	**IIa**	Initial combination therapy with other ERAs and PDE5is should be considered	**IIa**
		Initial combination therapy with macitentan and tadalafil and selexipag is not recommended	**III**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (24)

Sequential drug combination therapy for patients with IPAH, HPAH, or DPAH			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		It is recommended to base treatment escalations on risk assessment and general treatment strategies (see treatment algorithm)	I
Macitentan added to sildenafil	I	Addition of macitentan to PDE5is or oral/inhaled prostacyclin analogues is recommended to reduce the risk of morbidity/mortality events	I
		Addition of oral treprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity/mortality events	I

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (25)

Sequential drug combination therapy for patients with IPAH, HPAH, or DPAH (continued)			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
Bosentan added to sildenafil	**IIb**	Addition of bosentan to sildenafil is not recommended to reduce the risk of morbidity/mortality events	**III**
Riociguat added to bosentan	**I**	Addition of riociguat to bosentan should be considered to improve exercise capacity	**IIa**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (26)

Treatment of non-vasoreactive patients with IPAH, HPAH, or DPAH who present with cardiopulmonary comorbidities			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		In patients with IPAH/HPAH/DPAH and cardiopulmonary comorbidities, initial monotherapy with a PDE5i or an ERA should be considered	**IIa**
		In patients with IPAH/HPAH/DPAH with cardiopulmonary comorbidities who present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medications may be considered on an individual basis	**IIb**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

What is new (27)

Efficacy of intensive care management for PAH			
2015 Guidelines	**Class**	**2022 Guidelines**	**Class**
		When managing patients with right heart failure in the ICU, it is recommended to involve physicians with expertise, to treat causative factors, and to use supportive measures including inotropes and vasopressors, fluid management, and PAH drugs as appropriate	**I**
		Mechanical circulatory support may be an option for selected patients as bridge to transplantation or to recovery, and interhospital transfer should be considered if such resources are not available on site	**IIa**

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac237 and *European Respiratory Journal*; 2022 – doi: 10.1183/13993003.00879-2022)

When prioritize transplantation & balloon angioplasty

Conclusions

Comprehensive 3-strata risk ass at Dg and 4-strata at follow up

Initial dual oral th (combo) for interm to low risk pts

Intensify th in those who not each low risk

Triple th (PGE) for interm-high to high risk pts

Future directions

National Society of Cardiology of N. Macedonia

2. VESSELS SEMINAR

29-31.03.2024
DoubleTree by Hilton
Skopje, N. Macedonia