Update moderne PAH-Therapie

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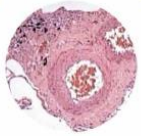
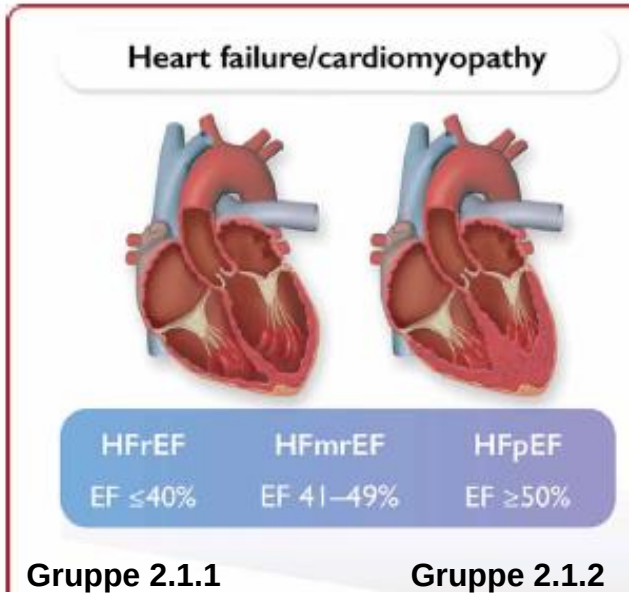
Pulmonary arterial hypertension (PAH)	PH associated with left heart disease	PH associated with lung disease	PH associated with pulmonary artery obstructions	PH with unclear and/or multifactorial mechanisms
				
• Idiopathic/heritable • Associated conditions	• IpcPH • CpcPH	• Non-severe PH • Severe PH	• CTEPH • Other pulmonary obstructions	• Haematologic disorders • Systemic disorders
Prevalence				
Rare	Very common	Common	Rare	Rare
Therapeutic Strategies				
Medical therapy • PAH drugs • CCB in responders **Lung transplantation**	**IpcPH:** • Treatment of LHD[a] **CpcPH:** • Treatment of LHD[a] • Potentially: PAH drugs (trials)	**PH-lung disease:** • Optimized care of underlying lung disease **Severe PH:** • Potentially: PAH drugs (trials)	**Surgical therapy:** • PEA **Interventional:** • BPA **Medical therapy:** • PH drugs	**Optimized treatment of underlying disease** • Potentially: PAH drugs (trials)

GRUPPE 2.1



Gruppe 2.1.1 **Gruppe 2.1.2**

SGLT2-Hemmer

Empagliflozin
Jardiance©

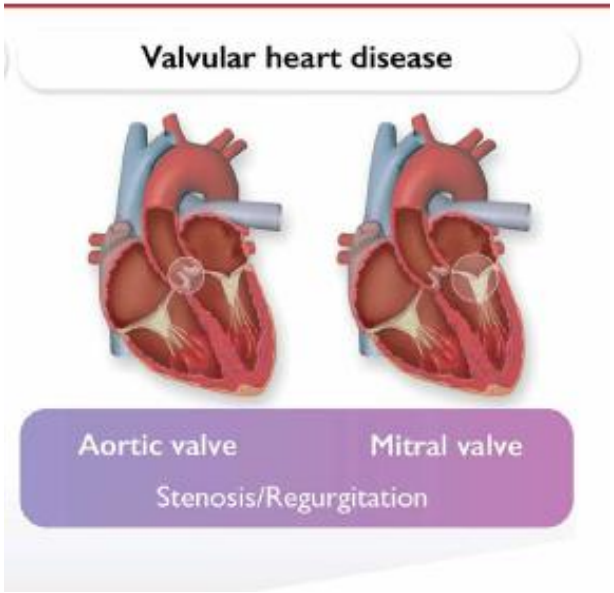
Anker et al N Engl J Med 2021; 385:1451-1461

HFpEF mit kombiniert post/präkap. PH (**CpcPH)**:

Positive Effekte bei PDE5-Hemmer Sildenafil

Lewis GD, et al. Circulation 2007; 116: 1555–1562.
Dumitrescu Det al. Int J Cardiol 2012; 154: 205–206.
Wu X et al. Eur J Heart Fail 2014; 16: 444–453.

GRUPPE 2.2



PH Persistenz häufig, höhere Mortalität
PH-spez. Therapie mit negativem Outcome

Bermejo J et al Eur Heart J 2018; 39: 1255–1264.

GRUPPE 3

PH Gruppe 3.1
Obstruktive Lungen-KH
COPD

COPD + «out-of-proportion» severe PH (WU >5)
Pos. Effekte bei PDE5-Hemmer Sildenafil

Vitulo P et al. J Heart LungTransplant 2017; 36: 166–174.

Studie laufend am KSSG (PH-COPD)
mit inhalativer PH-spez. Therapie

PH Gruppe 3.2
Restriktive Lungen-KH

Falls interstitielle Lungenerkrankung mit PH
(unabhängig vom Schweregrad)
Treprostinil inhalativ (in CH nicht verfügbar)
Idiopathische Lungenfibrose
Evtl. pos. Effekte bei PDE5-Hemmer Sildenafil

INCREASE Waxman A et al N Engl J Med 2021; 384: 325–334.
Behr J et al Lancet Respir Med. 2021 Apr;9(4):e38. PMID: 32822614.
Pitre et al Pulm Pharmacol Ther 2022 Jun;73-74:102128

GRUPPE 3

PH Gruppe 3.4 Hypoventilation

Alte Klassifikation ESC 2015: 3.4 Sleep-disordered Breathing, 3.5 Alveoläre Hypoventilation
→ Schlafapnoe alleine erklärt PH nicht !

Zusammenfassung - Abklärungen im PH Zentrum / Studien

- ✓ **Gruppe 2.1 HFpEF wenn kombiniert post- und präkapilläre PH**

CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU

- ✓ **Gruppe 3 - Präkapilläre PH wenn schwergradig (WU>5) oder ILD/IPF**

NEU 2022……

General measures for patients with pulmonary hypertension

Avoid pregnancy
I C

Sars-Cov2

Influenza and pneumococcal immunisation
according to STIKO
I C

Psychological counselling
Frequent depression, anxiety disorders
I C

Supervised exercise training
IIa B to I A

Supplemental oxygen (during air travel and at altitudes >1500 metres above sea level)
IIa C

Regional anaesthesia
should be preferred over general anaesthesia whenever possible
IIa C

International Journal of Cardiology 2018 272, 30-36DOI: (10.1016/j.ijcard.2018.08.085)

Supportive therapy

Diuretic administration
loop diuretics,
aldosterone antagonists
IIa B

Long-term oxygen therapy
Saturation <90%;
PaO_2 <8 kPa
(60 mmHg)
I C

Anticoagulation
INR 2-3
CTEPH
Check IPAH/HPAH/DPAH
Not generally in APAH
IIb C

Iron deficiency correction

IIb C

!

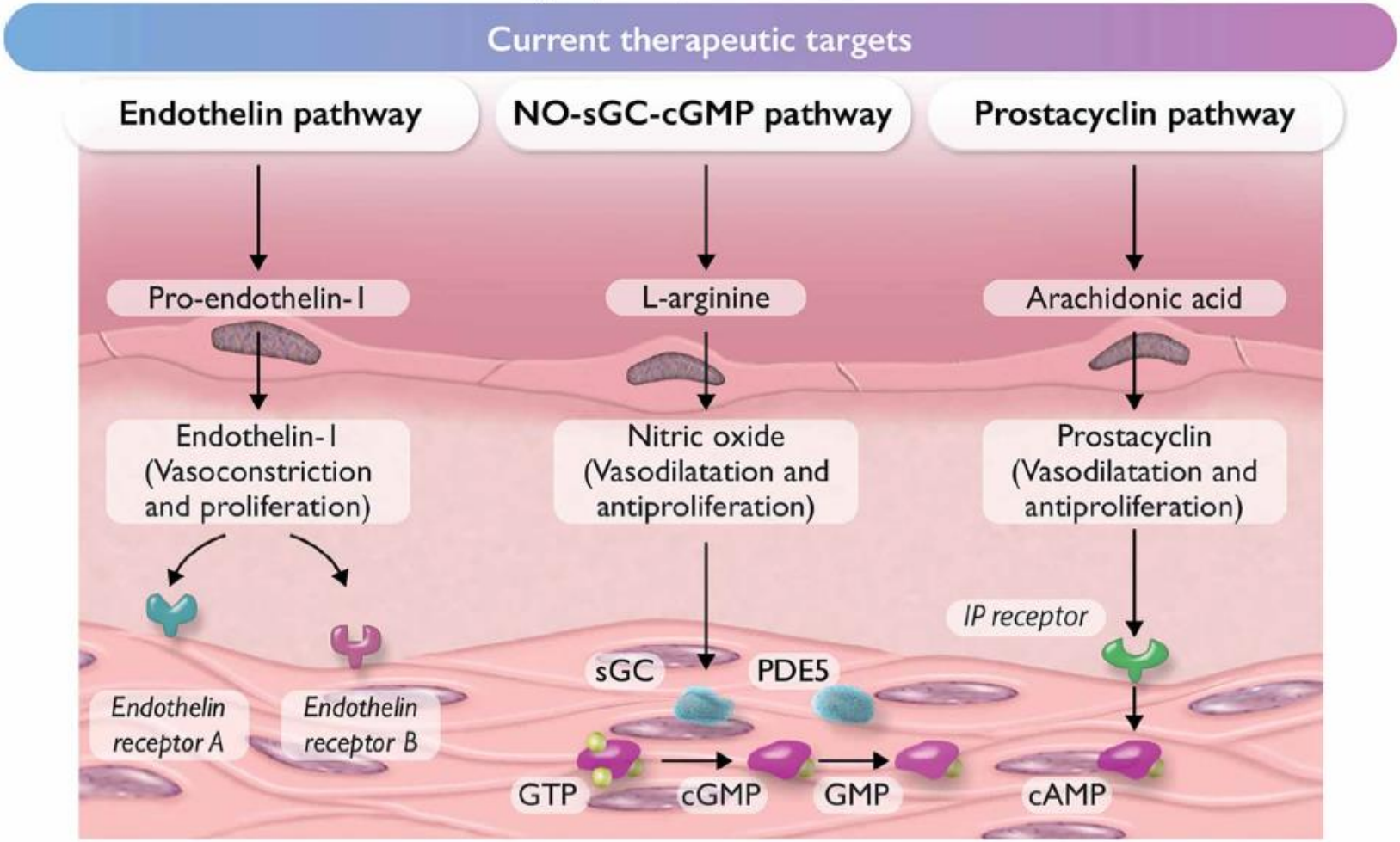
Use of ACE inhibitors, AT_1-antagonists, β-blockers, ivabradine only if specifically indicated, e.g., comorbidity
III C

Treatment of arrhythmias
Electrical cardioversion /ablation for atrial fibrillation
IIa C

+ ARNIs + SGLT2-Inhib.

International Journal of Cardiology 2018 272, 30-36DOI: (10.1016/j.ijcard.2018.08.085)

PH-spezifische Therapie – 3 Pathways


Current therapeutic targets
Endothelin pathway
NO-sGC-cGMP pathway
Prostacyclin pathway
Pro-endothelin-1
L-arginine
Arachidonic acid
Endothelin-1 (Vasoconstriction and proliferation)
Nitric oxide (Vasodilatation and antiproliferation)
Prostacyclin (Vasodilatation and antiproliferation)
IP receptor
sGC
PDE5
Endothelin receptor A
Endothelin receptor B
GTP
cGMP
GMP
cAMP

PH-spezifische Therapie - Übersicht

Endothelinrezeptorantagonisten

Bosentan (Tracleer®)
Ambrisentan (Volibris®)
Macitentan (Opsumit®)

Phosphodiesterase-Hemmer

Sildenafil PAH
Tadalafil (Adcirca®)

Guanylatzyklase-Stimulator

Riociguat (Adempas®)

Prostazykline / Prostazyklin-Rez. – Agonisten

Treprostinil (Remodulin®) s.c. oder i.v.
Selexipag (Uptravi®) p.o.

Humbert M et al, Circulation. 2014;130:2189–2208

Besonderheiten der Vasodilatativa

Nebenwirkungen häufig

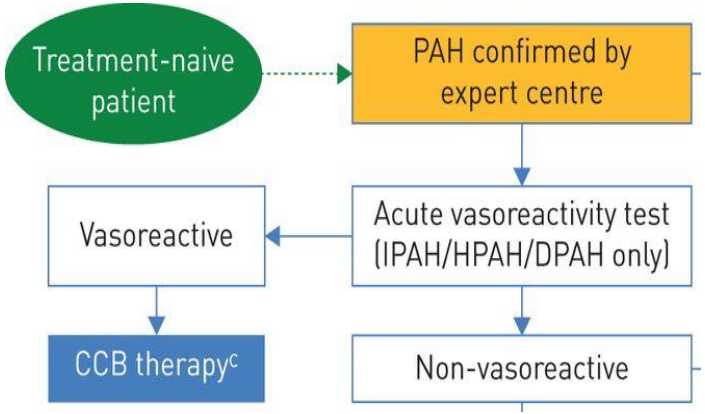
- Hypotonie (Blutdruckwerte <100mmHg syst. «normal»)
- Schwindel, Kopfschmerzen
- Hepatotoxizität (Endothelin-Antagonisten)
- Teratogen (Endothelin-Antagonisten, Riociguat) → sichere Verhütungsmethoden!
- Hypermenorrhoe (PDE5-Hemmer)
- Flush, Schmerzen, Diarrhoe (Prostazykline)

Titration/Stopp

- Dosistitration über mehrere Wochen (Riociguat, Prostazykline/Prostazyklin-Agonisten)
- S.c. / I.v. Gabe oder via Pumpe (Prostazyklinen)

➔ kein abruptes Absetzen! Re-Titration notwendig

CALCIUM-Kanalblocker



- NUR bei positivem Vasoreaktivitätstest im Rechtsherzkatheter
- Sehr selten, <10% der Gruppe 1-PH
- Nifedipin, Diltiazem, Amlodipin

Galié et al. ERJ 2018

Mit Komorbiditäten

Mit erhöhtem Risiko für HFpEF

- Adipositas, Art. Hypertonie, Diabetes, KHK

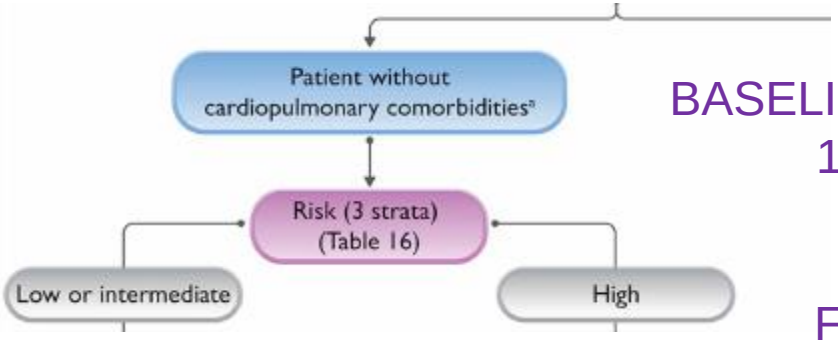
Mit leichter parenchymatöser Lungenkrankheit

- DLCO <45%

MONOTHERAPIE

Kein Risiko-Assessment

PAH ohne Komorbiditäten: RISK ASSESSMENT

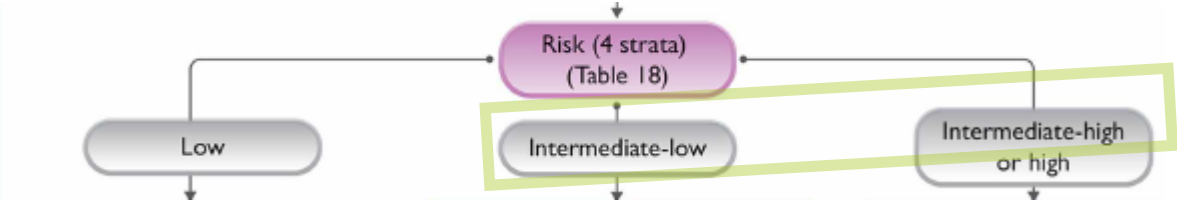


BASELINE:

1. Low 2. Intermediate 3. High

FOLLOW-UP

1. Low 2. ***Intermediate-low &***
3***. Intermediate-high*** 4. High



ESC Guidelines 2022

Baseline 3 – Strata - Modell

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
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
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ⩾2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Follow Up → 4-Strata

Prognostische Faktoren	Tiefes Risko	Intermediär-tiefes Risiko	Intermediär-hohes Risiko	Hohes Risiko
Punktevergabe	1	2	3	4
WHO funktionelle Klasse	I oder II	–	III	IV
6MWD	> 440 m	320–440 m	165–319 m	< 165 m
BNP/ NT-pro-BNP	< 50 ng/l < 300 ng/l	50–199 ng/l 300–649 ng/l	200–800 ng/l 650–1100 ng/l	> 800 ng/l > 1100 ng/l

Anmerkung: Das Risiko wird kalkuliert aus der (aufgerundeten) Summe aller Punkte geteilt durch die Anzahl an Variablen.

TABLE 17 Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

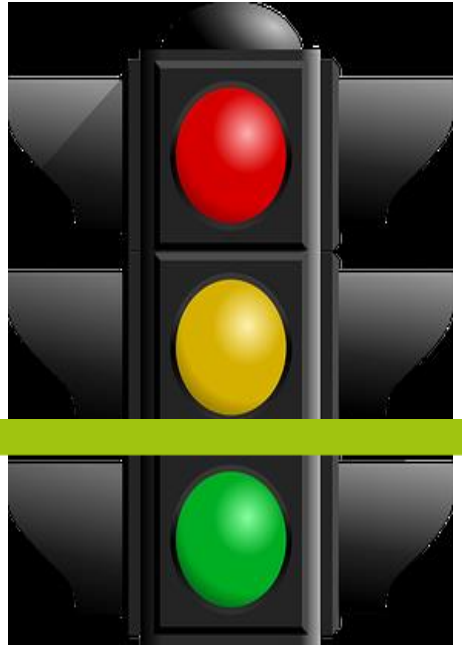
	At baseline	3–6 months after changes in therapy[a]	Every 3–6 months in stable patients[a]	In case of clinical worsening
Medical assessment (including WHO-FC)				
6MWT				
Blood test (including NT-proBNP)[b,c]				
ECG				
Echocardiography or cMRI				
ABG or pulse oximetry[d]				
Disease-specific HR-QoL				
CPET				
RHC				

Green: is indicated; yellow: should be considered; orange: may be considered

MORTALITÄT & TREAT to TARGET

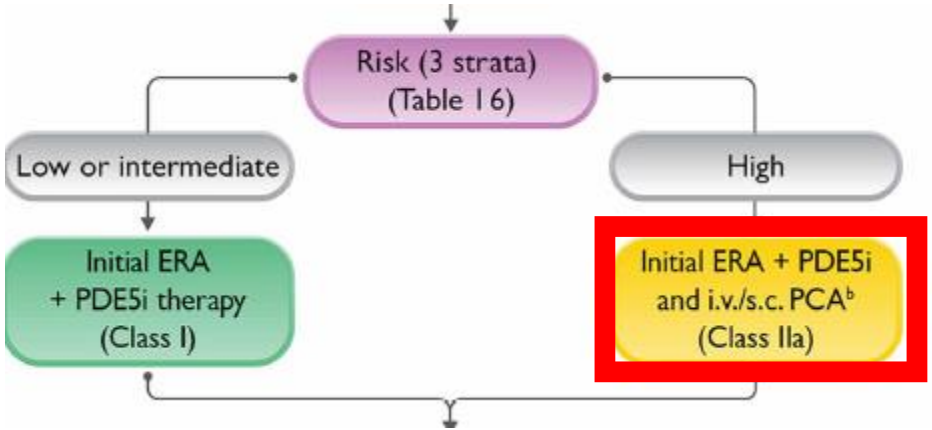
HIGH RISK
***>20%* 1-Jahres-Mortalität**

MEDIUM RISK
5-*20*% 1-Jahres-Mortalität

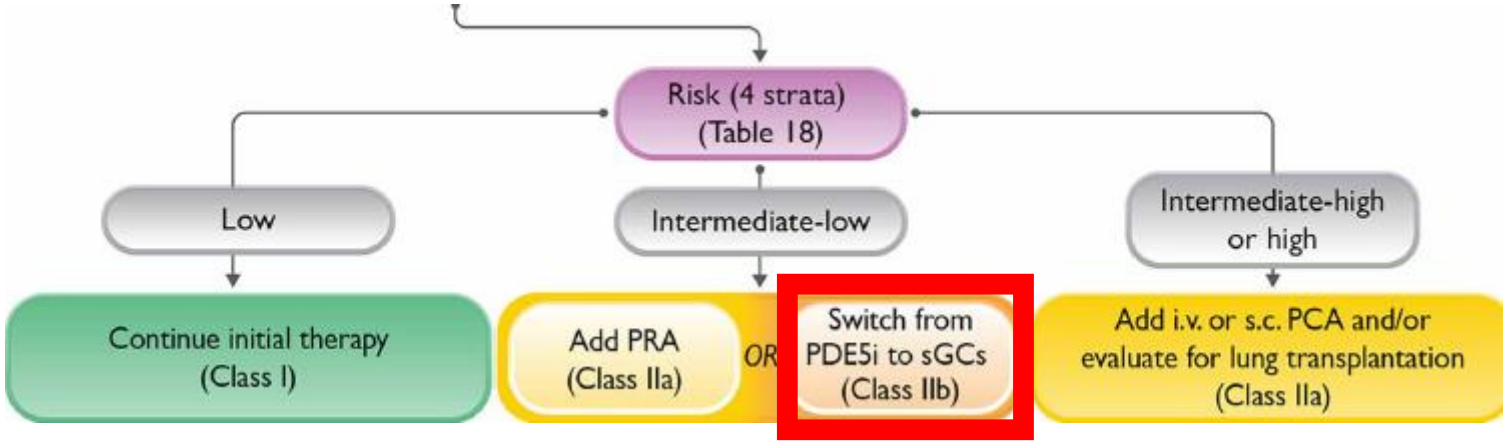


LOW RISK
<5% 1-Jahres-Mortalität

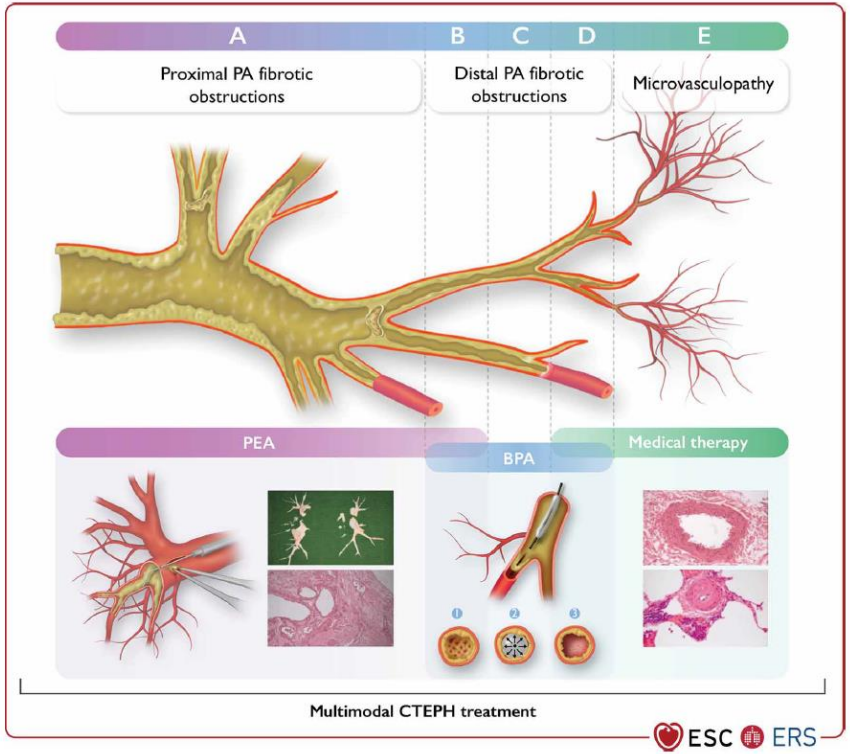
PAH– Therapieschema initial



PAH– Therapieschema Follow-UP



Interventionen / Operation – Gruppe 4



<u>Swiss CTEPH-Board</u>
virtuelle Besprechung von Patientenfällen
USZ; CHUV
alle 1-2 Monate

PH-Medikation:
Riociguat, s.c. Treprostinil, Macitentan

Lebenslange orale Antikoagulation (DOAK)

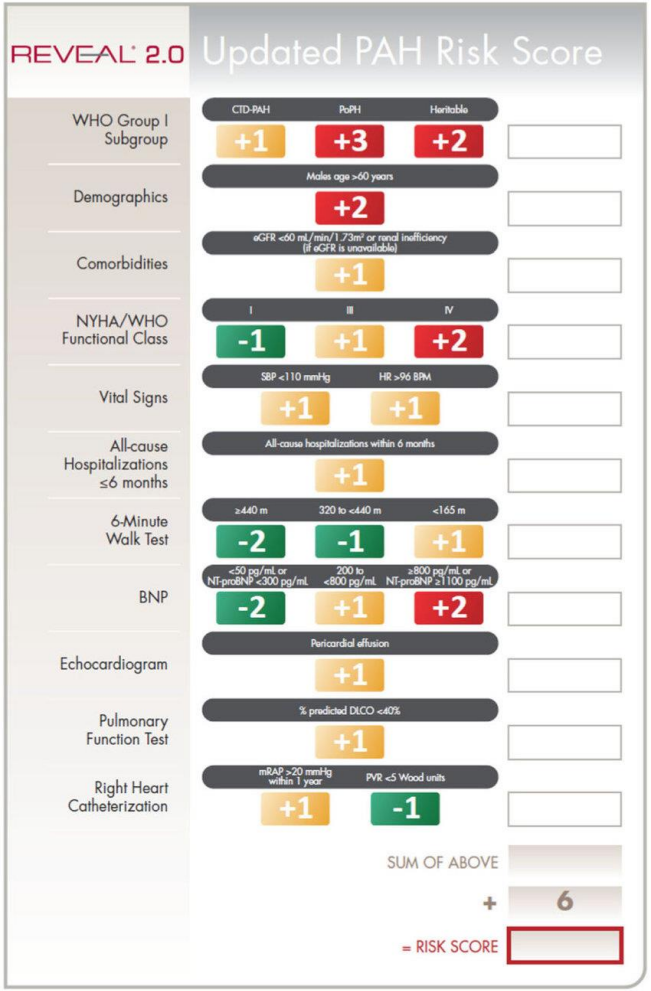
Lungentransplantation

Bei fortgeschrittener pulmonaler Hypertonie

Frühzeitig Zuweisung

- wenn Kombi-Therapie ungenügend; Reveal>7

Abklärung und Nachbetreuung (prä- und post-LuTpl) am KSSG möglich



Zukünftige Therapien

- **Sotatercept:** Wirkmechanismus via TGF-beta, positive RCT Studien

  Humbert et al N Engl J Med 2021; 384:1204-1215

  Hoeper et al N Engl J Med 2023; 388:1478-1490

- **Ralinepag:** Prostazyklin-Rez. Agonist, positive RCT Studie, Phase 3 ausstehend
- **Diverse inhalative Medikamente für Gruppe 1, Gruppe 3…**

PAH-Board am KSSG

1x/Monat virtuell (Skype) montags 17-18 Uhr

Reguläre Teilnehmer: Kardio/Rheuma/Pneumo

Patientenkollektiv: (V.a.) pulmonal-arterielle Hypertonie, unklare/multifaktorieller PH-Gruppe, chronisch thrombembolische PH

Anmeldung: intern → PMS – Module – Board-Anmeldung

extern → lungenzentrum@kssg.ch

PH-Links- und Vorträge

- **PH-Biennale am KSSG (2024)**
- **Kardiovaskuläres Manual KSSG**
- **ESC Guidelines 2022 (Pocket, App)**

Take-Home Message

- **Spezifische PAH-Therapie v.a. für Gruppe 1 und 4; Gruppe 2 und 3 Grunderkrankung (Studien/PHCenter wenn «out-of-proportion»)**
- **Beginn Standard dual, bei Komorbiditäten Mono; High-Risk = Triple-Therapie**
- **Low Risk : Klinik + 6MGT + BNP/NT-proBNP**