Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-349 Sotatercept

Stand: März 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Sotatercept
zur Behandlung der pulmonal arteriellen Hypertonie (PAH)

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Als nicht-medikamentöse Behandlungen kommen grundsätzlich infrage: • Lungen- oder Herz-Lungen-Transplantation • physiotherapeutische Maßnahmen i.S. der Heilmittel-RL (Physikalische Therapie z.B. Krankengymnastik, Übungsbehandlung, Atemtherapie)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Verfahren der frühen Nutzenbewertung nach § 35a SGB V</u> • *Riociguat (Beschluss vom 03.09.2020)* • *Macitentan (Beschluss vom 6. April 2017)* • *Selexipag (Beschluss vom 15. Dezember 2016)*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Sotatercept	Geplantes Anwendungsgebiet laut Beratungsanforderung: "zur Behandlung der Pulmonal Arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit WHO Funktionsklasse II und III"
Endothelin-Rezeptor-Antagonisten (ERA):	
Macitentan C02KX04 Opsumit®	Opsumit®, als Monotherapie oder in Kombination, ist indiziert für die Langzeitbehandlung der pulmonal arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit funktioneller WHO-/NYHA-Klasse II bis III. Die Wirksamkeit wurde bei Patienten mit PAH nachgewiesen, einschließlich idiopathischer und erblicher PAH, PAH in Assoziation mit Bindegewebserkrankungen sowie PAH in Assoziation mit korrigierten einfachen angeborenen Herzfehlern.
Bosentan C02KX01 Bosentan Heumann®	Behandlung der pulmonal arteriellen Hypertonie (PAH) zur Verbesserung der körperlichen Belastbarkeit und Symptomen bei Patienten mit der funktionellen WHO-/NYHA-Klasse III. Die Wirksamkeit wurde nachgewiesen bei: – Primärer (idiopathischer und erblicher) pulmonal arterieller Hypertonie – Sekundärer pulmonal arterieller Hypertonie in Assoziation mit Sklerodermie ohne signifikante interstitielle Lungenerkrankung – Pulmonal arterieller Hypertonie in Assoziation mit kongenitalen Herzfehlern und Eisenmenger-Physiologie. Verbesserungen des Krankheitsbildes wurden ebenso bei Patienten mit PAH der funktionellen WHO-Funktionsklasse II gezeigt.
Ambrisentan C02KX02 Volibris®	Volibris® ist zur Behandlung von erwachsenen Patienten mit pulmonal arterieller Hypertonie (PAH) der WHO-Funktionsklassen II und III indiziert, einschließlich der Anwendung in der Kombinationstherapie (siehe Abschnitt 5.1). Die Wirksamkeit wurde bei idiopathischer PAH (IPAH) und PAH assoziiert mit einer Bindegewebserkrankung nachgewiesen.
Phosphodiesterase-Typ-5 (PDE5)-Inhibitoren:	
Sildenafil G04BE03 Revatio®	Behandlung von erwachsenen Patienten mit pulmonaler arterieller Hypertonie (PAH) der WHO-Funktionsklassen II und III zur Verbes-serung der körperlichen Leistungsfähigkeit. Die Wirksamkeit konnte nachgewiesen werden bei primärer PAH und bei pulmonaler Hypertonie in Verbindung mit einer Bindegewebskrankheit.

Tadalafil G04BE08 Adcirca®	Adcirca® ist angezeigt zur Behandlung der pulmonalen arteriellen Hypertonie (PAH) der WHO-Funktionsklasse II und III zur Verbesserung der körperlichen Leistungsfähigkeit bei Erwachsenen. Die Wirksamkeit wurde gezeigt bei idiopathischer PAH (IPAH) und bei PAH aufgrund einer Kollagenose.
Prostazyklin-Analoga:	
Iloprost B01AC11 Ventavis®	Behandlung erwachsener Patienten mit primärer pulmonaler Hypertonie im funktionellen Schweregrad NYHA III zur Verbesserung der körperlichen Leistungsfähigkeit und der Symptomatik.
Treprostinil B01AC21 Remodulin®	Behandlung von idiopathischer oder familiärer pulmonal-arterieller Hypertonie (PAH) zur Verbesserung der Belastbarkeit und zur Milderung der Krankheitssymptome bei Patienten mit New York Heart Association(NYHA)-Funktionsklasse III.
Epoprostenol B01AC09 Epoprostenol-Rotexmedica®	Epoprostenol-Rotexmedica® ist indiziert zur Behandlung pulmonaler arterielle Hypertonie (PAH) (idiopathische oder vererbbare PAH und mit Bindegewebserkrankungen assoziierte PAH) bei Patienten mit Symptomen der WHO Funktionsklasse III – IV zur Verbesserung der körperlichen Belastungsfähigkeit (siehe Abschnitt 5.1).
Selektive Prostacyclin (IP)-Rezeptor-Agonisten	
Selexipag B01AC27 Uptravi®	Uptravi® ist indiziert für die Langzeitbehandlung der pulmonal arteriellen Hypertonie (PAH) bei erwachsenen Patienten der WHO-Funktionsklasse (WHO-FC) II bis III entweder als Kombinationstherapie bei Patienten, deren Erkrankung mit einem Endothelin-Rezeptor-Antagonisten (ERA) und/oder einem Phosphodiesterase-5(PDE-5)-Inhibitor unzureichend kontrolliert ist oder als Monotherapie bei Patienten, die für diese Therapien nicht infrage kommen. Die Wirksamkeit wurde bei PAH, einschließlich idiopathischer und erblicher PAH, PAH in Assoziation mit Bindegewebserkrankungen und PAH in Assoziation mit korrigierten einfachen angeborenen Herzfehlern nachgewiesen (siehe Abschnitt 5.1).
Stimulator der löslichen Guanylatyclase	
Riociguat C02KX05 Adempas®	Adempas, als Monotherapie oder in Kombination mit Endothelin-Rezeptorantagonisten, ist indiziert für die Behandlung erwachsener Patienten mit pulmonal arterieller Hypertonie (PAH) der WHO-Funktionsklassen (FK) II bis III zur Verbesserung der körperlichen Leistungsfähigkeit. Die Wirksamkeit wurde in einer PAH-Population einschließlich Ätiologien einer idiopa-thischen oder hereditären PAH oder einer mit einer Bindegewebserkrankung assoziierten PAH nachgewiesen (siehe Abschnitt 5.1).

Quellen: AMIS-Datenbank, Fachinformationen (Stand März 2023)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-349 (Sotatercept)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Februar 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CTEPH	chronic thromboembolic disease
ERA	endothelin receptor antagonists
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
mPAP	mean pulmonary artery pressure
NICE	National Institute for Health and Care Excellence
NYHA	or New Yor Heart Association
OR	Odds Ratio
PAH	pulmonary arterial hypertension
PDE5	Phosphodiesterase 5 inhibitors
PVR	pulmonary vascular resistance
RR	Relatives Risiko
sGC	Soluble guanylate cyclase
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WHO-FC	WHO-Functional Class
6MWD	Six-minute walk distance (6MWD) test

1 Indikation

Behandlung der Pulmonal Arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit WHO Funktionsklasse II und III.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Pulmonal-arterielle Hypertonie* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.ecosia.org/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 03.01.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 846 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Barnes H et al., 2019 [1].

Phosphodiesterase 5 inhibitors for pulmonary hypertension

Zielsetzung

To determine the efficacy of PDE5 inhibitors for pulmonary hypertension in adults and children.

Methodik

Population:

- any individual with a diagnosis of pulmonary hypertension from any cause who required medical treatment for their condition.

Intervention:

- PDE-5 inhibitors

Population:

[...] any individual with a diagnosis of pulmonary hypertension from any cause who required medical treatment for their condition.

1. Comparison 1 specifically assesses the effects of PDE5 inhibitors compared to placebo on Group 1 PAH, confirmed as a mean pulmonary artery pressure ≥ 25 mmHg by right-heart catheterisation.
2. Comparison 2 compares PDE5 inhibitors with placebo in PAH participants on combination therapy.
3. Comparison 3 compares PDE5 inhibitors to ERAs in PAH participants.
4. Comparison 4 includes group 2 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and left-heart disease, as defined by the authors.
5. Comparison 5 includes group 3 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and lung disease, as defined by the authors.
6. Comparison 6 included group 4 pulmonary hypertension participants with a diagnosis of pulmonary hypertension and chronic thromboembolic disease (CTEPH), as defined by the authors.
7. Comparison 7 included mixed group 2 to 5 pulmonary hypertension participants with a diagnosis of pulmonary hypertension as defined by the authors.

Intervention und Komparator:

[…] studies comparing any type of PDE5 inhibitors by any route of administration with placebo or any other treatment used for pulmonary hypertension.

Primäre Endpunkte:

- Change in WHO functional class
- Six-minute walk distance (6MWD)
- Mortality

Sekundäre Endpunkte:

- Haemodynamic parameters, including change in mean pulmonary artery pressure, change in cardiac output, cardiac index
- Exercise capacity other than six-minute walk distance
- Quality of life / health status, by any validated scale
- Dyspnoea score, including visual analogue scale or Borg scale
- Hospitalisation / intervention
- Adverse events

Recherche/Suchzeitraum:

[…] searches of the following databases up to 26 September 2018:

1. The Cochrane Airways Group Register of Trials,
2. Cochrane Central Register of Controlled Trials (CENTRAL) through the Cochrane Register of Studies Online,
3. MEDLINE (Ovid) 1950 to 26 September 2018,
4. Embase (Ovid) 1974 to 26 September 2018,
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov,
6. World Health Organization International Clinical Trials Registry Platform.

[…] searched for handsearched conference abstracts and grey literature through the CENTRAL database.

Qualitätsbewertung der Studien:

Cochrane 'Risk of bias' assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Nineteen trials included group 1 PAH participants (Albini 2017; Bharani 2003; Bharani 2007; Boonstra 2005; Galiè 2005a; Galiè 2009; Galiè 2015; Inversen 2009 (specifically Eisenmenger's syndrome); Jing 2011; Mazzanti 2013; Mukhopadhyay 2011; (Barst 2012; Palii 2014 – specifically children with PAH); Sastry 2004; Simonneau 2008; Singh 2006; Vizza 2017a; Wilkins 2005; Zhuang 2014).
- All studies were randomised […].
- Eleven trials in PAH patients compared a PDE5 inhibitor to placebo: seven trials compared sildenafil to placebo, three compared tadalafil to placebo, and one compared vardenafil to placebo.
- Four studies compared PDE5 inhibitors to placebo, whilst on additional combination therapy (all as add-on therapy), and four studies compared PDE5 inhibitors to endothelin receptor antagonists.

Charakteristika der Population:

Most trials recruited participants with WHO functional class II and III.

Qualität der Studien: (⇨ Anhang Abbildung 1)

There are sufficient trials of high quality in the use of PDE5 inhibitors compared to placebo for group 1 PAH. Most trials had a low risk of bias and the direction of effect was consistent across studies.

Studienergebnisse:

Tabelle 1: Summary of findings for the main comparison. Group 1 Pulmonary arterial hypertension – PDE5I compared to placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PDE5I				
Improvement in WHO functional class	61 per 1000	358 per 1000 (204 to 549)	OR 8.59 (3.95 to 18.72)	282 (4 RCTs)	⊕⊕⊕⊕ HIGH	-
Six-minute walk distance	Ranges from 170 - 319 m[a]	MD 48 metres higher (40 higher to 56 higher)	-	880 (8 RCTs)	⊕⊕⊕◯[b] MODERATE	6MWD in PAH MCID is 41 metres
Mortality	41 per 1000	9 per 1000 (3 to 28)	OR 0.22 (0.07 to 0.68)	1119 (8 RCTs)	⊕⊕⊕⊕ HIGH	-
Quality of life SF-36: (scores 1 to 100, higher scores indicate better QoL) EQ-5D questionnaire: (higher scores indicate worse QoL) CHFQ: (lower scores indicate worse QoL)	Galiè 2005a found a statistically significant improvement in all SF-36 domains for sildenafil-treated participants, and when compared to placebo in physical functioning (P < 0.001), general health (P < 0.001), and vitality (P < 0.05). There was also a statistically significant improvement in placebo-treated participants in the physical functioning domain. Galiè 2005a found statistically significant improvements for the EQ-5D current health status (P < 0.01) and utility index (P < 0.01). Sastry 2004 found a statistically significant difference for the CHFQ fatigue domain (sildenafil post-treatment score 22.33, SD 4.82 compared to placebo post-treatment score 20.67, SD 5.19; P = 0.04), and a non-statistically significant difference in the emotional function domain (sildenafil post-treatment score 37.33, SD 9.3, compared to placebo post-treatment score 34.71, SD 10.91; P = 0.06), favouring sildenafil compared with placebo.			163 (2 RCTs)	-	Data considered too heterogeneous to meta-analyse
PAP	-	MD 6.43 mmHg lower (8.13 lower to 4.74 lower)	-	453 (6 RCTs)	⊕⊕⊕◯[b] MODERATE	The higher the mean PAP, the worse the PH

RAP	-	MD 1.35 mmHg lower (2.34 lower to 0.36 lower)	-	341 (3 RCTs)	⊕⊕⊕⊕ HIGH	The higher the RAP, the worse the PH
Cardiac index	-	MD 0.28L/min/m² higher (0.16 higher to 0.4 higher)	-	239 (4 RCTs)	⊕⊕⊕◯[b] MODERATE	The lower the cardiac index, the worse the PH
PVR	-	MD 4.74 WU lower (6.13 lower to 3.35 lower)	-	266 (3 RCTs))	⊕⊕⊕⊕ HIGH	The higher the PVR. the worse the PH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **EQ-5D**: EuroQoL 5D; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PAP**: pulmonary arterial pressure; **PDE-5I:** phosphodiesterase-5 inhibitor; **PH**: pulmonary hypertension; **PVR**: pulmonary vascular resistance; **RAP**: right atrial pressure; **RCT**: randomised controlled trials; **SD**: standard deviation; **SF-36**: Medical Outcomes Study 36-item short form; **WU**: woods units; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Post-treatment values for participants in the placebo group were presented in two studies only; the remaining included studies presented a mean difference only.
[b]Downgraded due to imprecision owing to significantly high heterogeneity, although the direction of effect is consistent.

Tabelle 2: Summary of findings 2. Group 1 Pulmonary arterial hypertension – PDE5I compared to placebo, on combination therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo, on combination therapy	Risk with PDE5I				
Improvement in WHO functional class	263 per 1000	300 per 1000 (191 to 437)	OR 1.20 (0.66 to 2.17)	227 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Six-minute walk distance	Ranges from 341 - 377 m[b]	MD 20 metres higher (9 higher to 30 higher)	-	509 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	6MWD in PAH MCID is 41 metres
Mortality	32 per 1000	9 per 1000 (2 to 34)	OR 0.26 (0.07 to 1.06)	492 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]	-
Quality of life physical functioning on SF-36 (higher scores indicate better quality of life)	0.3 (4.7 higher to 4.1 higher)	7.8 (3.6 higher to 12.1 higher)	-	267 (1 RCT)	⊕⊕⊕⊖ MODERATE[d]	-
PAP	-	MD 4.58 mmHg lower (6.14 lower to 3.01 lower)	-	387 (2 RCTs)	⊕⊕⊕⊕ HIGH	The higher the PAP, the worse the pulmonary hypertension
Cardiac output	-	MD 0.87 L/min higher (0.53 higher to 1.21 higher)	-	310 (3 RCTs)	⊕⊕⊕⊕ HIGH	The lower the cardiac output, the worse the pulmonary hypertension

PVR	-	SMD 0.48 lower (0.72 lower to 0.25 lower)	-	303 (3 RCTs)	~~⊕⊕⊕⊕~~ HIGH	The higher the PVR, the worse the pulmonary hypertension

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **MCID:** minimal clinically important difference; **MD:** mean difference; **OR:** odds ratio; **PAP:** pulmonary arterial pressure; **PDE-5I:** phosphodiesterase-5 inhibitor; **PVR:** pulmonary vascular resistance; **RCT:** randomised controlled trials; **SMD:** standardised mean difference; **WHO:** World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded due to imprecision owing to small participant numbers and inconsistent direction of effect.
[b]Range of baseline values, as studies only presented mean difference values for analysis.
[c]Downgraded due to imprecision as the confidence interval crosses the line of no difference.
[d]Downgraded due to imprecision owing to small participant numbers in one trial.

Tabelle 3: Summary of findings 3. Group 1 Pulmonary arterial hypertension – PDE5I compared to ERA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with ERA	Risk with PDE5I				
Improvement in WHO functional class	339 per 1000	325 per 1000 (220 to 450)	OR 0.94 (0.55 to 1.60)	244 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	-
Six-minute walk distance	Ranges from 290 - 354 m[b]	MD 49 higher (4 higher to 95 higher)	-	36 (2 RCTs)	⊕⊕⊖⊖ LOW[c]	6MWD in PAH MCID is 41 metres
Mortality	14 per 1000	45 per 1000 (11 to 167)	OR 3.19 (0.74 to 13.64)	272 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
Quality of life Kansas City Cardiomyopathy Quality-of-Life questionnaire (higher scores indicate better quality of life)	-	MD 22 higher (9 higher to 35 higher)	-	25 (1 RCT)	⊕⊕⊖⊖ LOW[c]	-
PAP	-	MD 7.00 mmHg lower (4.82 lower to 18.82 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The higher the mean PAP, the worse the PH
RAP	-	MD 2 mmHg higher (2.14 lower to 6.14 higher)	-	11 (1 RCT)	⊕⊕⊖⊖ LOW[d]	The higher the RAP, the worse the PH

Cardiac index	-	MD 0 L/min/m² higher (0.49 lower to 0.49 higher)	-	11 (1 RCT)	⊕⊖⊖⊖ LOW[d]	The lower the cardiac index, the worse the PH
PVR	-	MD 0 WU lower (1.93 lower to 1.93 higher)	-	11 (1 RCT)	⊕⊖⊖⊖ LOW[d]	The higher the PVR. the worse the PH

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** Confidence interval; **MCID:** minimal clinically important difference; **MD**: mean difference; **OR:** odds ratio; **PDE-5I:** phosphodiesterase-5 inhibitor; **RCT**: randomised controlled trials; **WHO**: World Health Organization

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded once due to imprecision.
[b]Range of baseline values, as studies only presented mean difference values for analysis.
[c]Downgraded twice due to imprecision and small participant numbers.
[d]Downgraded twice due to very small participant numbers and high risk of bias.

Anmerkung/Fazit der Autoren

- Data from this review suggest a benefit for the use of PDE5 inhibitors in group 1 PAH, for improvement in WHO functional class, reduction in clinical worsening and improvement in haemodynamics, six-minute walk distance, quality of life, and mortality.
- Sildenafil, tadalafil and vardenafil are all efficacious in this clinical setting.
- Clinicians may wish consider the side-effect profile for each drug when choosing which to prescribe to an individual patient.
- This review suggests that a PDE5 inhibitor may be better than an ERA for six-minute walk distance and quality of life, but that there appears to be no difference in WHO functional class or mortality. These conclusions are limited by the small number of trials.

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Barnes H et al., 2019 [2].

Prostacyclin for pulmonary arterial hypertension

Zielsetzung

To determine the efficacy and safety of prostacyclin, prostacyclin analogues or prostacyclin receptor agonists, compared to placebo or any other treatment, for pulmonary arterial hypertension (PAH) in adults and children.

Methodik

Population:

[...] any individual with a diagnosis of World Health Organization (WHO) Group 1 pulmonary hypertension, referred to as pulmonary arterial hypertension (PAH), as per the present definition of a mean pulmonary arterial pressure (mPAP) higher than 25 mmHg by right heart catheterisation.

Intervention und Komparator:

[…] studies comparing any type of prostacyclin treatment by any route of administration with placebo or any other treatment for at least six weeks. This included […] prostaglandins, enoprostenol, iloprost, beraprost, treprostinil, prostacyclin receptor agonist and selexipag, via the intravenous, subcutaneous, inhaled, and oral route.

Primäre Endpunkte:

- Change in WHO or New York Heart Association (NYHA) functional class
- Six-minute walk distance (6MWD) test
- Mortality

Sekundäre Endpunkte:

- Cardiopulmonary haemodynamics: including mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), cardiac index, cardiac output, systemic arterial oxygen saturation and systemic oxygen transport
- Exercise capacity tests other than 6MWD test
- Symptom scales: Borg dyspnoea score, dyspnoea-fatigue ratings
- Quality of life
- Clinical worsening
- Adverse events
- Cost analysis

Recherche/Suchzeitraum:

[…] searches of the following databases up to 16 September 2018.

1. Cochrane Airways Register of Trials through the Cochrane Register of Studies (CRS Web)
2. Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies (CRS Web),
3. MEDLINE Ovid SP 1946 to 16 September 2018
4. Embase Ovid SP 1974 to 16 September 2018

In addition, we searched the CENTRAL database in the Cochrane Library for conference abstracts and grey literature. […] We also searched the following trial registries for additional trials for inclusion and for additional data for included trials:

1. US National Institutes of Health Ongoing Trial Register ClinicalTrials.gov
2. World Health Organization (WHO) International Clinical Trials Registry Platform

Qualitätsbewertung der Studien:

Cochrane's tool for assessment of risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- […] included 17 trials with 3765 participants in the final meta-analysis. All included studies were randomised, parallel-group trials involving people with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) (confirmed on right heart catheterisation).
- Fifteen trials compared a prostacyclin analogue with placebo / conventional treatment, and two trials compared selexipag (an oral selective IP prostacyclin receptor agonist) to placebo.

Charakteristika der Population:

Most (80%) participants were functional class III, and 10% were functional class II and 10% functional class IV.

Qualität der Studien: (⇨ Anhang Abbildung 2)

Studienergebnisse:

Tabelle 4: Summary of findings for the main comparison. Prostacyclin compared to control for pulmonary arterial hypertension

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with control	Risk with prostacyclin				
Improvement in WHO functional class Mean follow-up 16 weeks	Study population 116 per 1000	239 per 1000 (185 to 304)	OR 2.39 (1.72 to 3.32)	1066 (8 RCTs)	⊕⊕⊕⊖ Moderate[1]	
6MWD Mean follow-up 15 weeks	The mean 6MWD was 257 m*	MD 19.50 m higher (14.82 higher to 24.19 higher)	-	2283 (13 RCTs)	⊕⊕⊖⊖ Low[1,2]	6MWD in PAH MCID is 41 m
Mortality Mean follow-up 15 weeks	Study population 39 per 1000	24 per 1000 (15 to 37)	OR 0.60 (0.38 to 0.94)	2554 (15 RCTs)	⊕⊕⊕⊖ Moderate[1]	
mPAP (the higher the mPAP, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mPAP ranged from 56 to 66 mmHg#	MD 3.60 mmHg lower (4.73 lower to 2.48 lower)	-	1132 (8 RCTs)	⊕⊕⊖⊖ Low[1,2]	
PVR (the higher the PVR, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean PVR ranged from 26 to 29 units/m²#	MD 2.81 WU lower (3.80 lower to 1.82 lower)	-	658 (7 RCTs)	⊕⊕⊕⊖ Moderate[1]	

Cardiac index (the lower the cardiac index, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean cardiac index ranged from 2 to 2.4 L/min/m$^{2\#}$	MD 0.31 L/min/m 2 higher (0.23 higher to 0.38 higher)	-	868 (6 RCTs)	⊕⊕⊖⊖ Low[1,2]	
RAP (the lower the RAP, the worse the pulmonary hypertension) Mean follow-up 11 weeks	The mean RAP ranged from 8 to 13 mmHg[#]	MD 1.90 mmHg lower (2.58 lower to 1.22 lower)	-	1060 (6 RCTs)	⊕⊕⊕⊖ Moderate[1]	The higher the RAP, the worse the pulmonary hypertension
Dyspnoea (lower scores indicates more severe breathlessness) Mean follow-up 17 weeks	-	SMD 0.21 lower (0.32 lower to 0.11 lower)	-	1521 (8 RCTs)	⊕⊕⊖⊖ Low[1,2]	Using an illustrative SD, this converts to a difference of 0.64 units on the Borg scale. MCID in PAH is 0.9 units
Quality of life Mean follow-up 12 weeks	-	SMD 0.28 better (0.04 better to 0.42 better)	-	271 (3 RCTs)	⊕⊕⊕⊖ Moderate[1]	
Headache[+] Mean follow-up 12 weeks	277 per 1000	529 per 1000 (95% CI 501 to 593)	3.16 (2.62 to 3.80)	2351 (12 RCTs)	⊕⊕⊕⊖ Moderate[2]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** confidence interval; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio; **PAH:** pulmonary arterial hypertension; **mPAP:** mean pulmonary arterial pressure; **PVR:** pulmonary vascular resistance; **RAP:** right atrial pressure; **RCT:** randomised controlled trials; **SD:** standard deviation; **SMD:** standardised mean difference; **WHO:** World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded due to the risk of bias with open-label studies.
[2]Downgraded due to imprecision owing to significantly high heterogeneity, although the direction of effect is consistent.
*based on only one study which published placebo data; all other studies reported a mean difference between groups.
#based on baseline data; all other studies reported a mean difference between groups.
+This was chosen as the most commonly experienced adverse event.

Tabelle 5: Summary of findings 2. Selexipag compared to placebo for pulmonary arterial hypertension

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with placebo	Risk with selexipag				
Improvement in WHO functional class Mean follow-up 17 weeks	Study population 100 per 1000	152 per 1000 (19 to 635)	OR 1.61 (0.17 to 15.63)	43 (1 RCT)	⊕⊕⊕⊖ Moderate[1]	
6MWD Mean follow-up 40 weeks	The mean 6MWD ranged from 348 to 396 m	MD 12.62 m higher (1.90 higher to 23.34 higher)	-	1199 (2 RCTs)	⊕⊕⊕⊕ High	6MWD in PAH MCID is 41 m
Mortality Mean follow-up 40 weeks	Study population 30 per 1000	48 per 1000 (27 to 84)	**Risk difference** 0.02 (-0.00 to 0.04)	1199 (2 RCTs)	⊕⊕⊕⊖ Moderate[1]	
mPAP the higher the mPAP, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mPAP was 60 mmHg	MD 7.4 mmHg lower (15.9 lower to 1.1 higher)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	
PVR Mean follow-up 17 weeks	The mean PVR was 1687 dyn/sec/m²	MD 33 dyn/sec/m² lower (47 lower to 19 lower)	-	43 (1 RCT)	⊕⊕⊕⊖ Moderate[2]	

Cardiac index (the lower the cardiac index, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mean cardiac index was 2.3 L/min/m²	MD 0.5 L/min/m² higher (0.13 higher to 0.87 higher)	-	43 (1 RCT)	⊖⊖⊖⊖ Moderate[2]	
RAP (the lower the RAP, the worse the pulmonary hypertension) Mean follow-up 17 weeks	The mean RAP was 8.3 mmHg	MD 3.2 mmHg higher (0.8 higher to 5.6 higher)	-	43 (1 RCT)	⊖⊖⊖⊖ Moderate[2]	
Dyspnoea (lower scores indicates more severe breathlessness) Mean follow-up 17 weeks	-	MD 0.1 lower (1.4 lower to 1.2 higher)	-	43 (1 RCT)	⊖⊖⊖⊖ Moderate[1]	MCID in PAH is 0.9 units
Headache[+] Mean follow-up 40 weeks	Study population		3.91 (3.07 to 4.98)	1199 (2 RCTs)	⊖⊖⊖⊖ High	
	325 per 1000	653 per 1000				

[*] **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

6MWD: six-minute walk distance; **CI:** confidence interval; **MCID:** minimum clinically important difference; **MD:** mean difference; **OR:** odds ratio; **PAH:** pulmonary arterial hypertension; **mPAP:** mean pulmonary arterial pressure; **PVR:** pulmonary vascular resistance; **RAP:** right atrial pressure; **RCT:** randomised controlled trials; **RR:** risk ratio; **SD:** standard deviation; **WHO:** World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

[1]Downgraded due to imprecision with confidence intervals including no difference.
[2]Downgraded due to imprecision owing to small participant numbers in one trial.
[+]This was chosen as the most commonly experienced adverse event.

Anmerkung/Fazit der Autoren

This review demonstrates clinical and statistical benefit for the use of prostacyclin compared to control in terms of improved functional class, six-minute walk distance (6MWD), mortality, symptoms scores, and cardiopulmonary haemodynamics, (low- to moderate-certainty evidence) but at a cost of increased risk of adverse events. There is a statistical benefit for the use of 6MWD, haemodynamics, and avoidance of clinical worsening using selexipag, however the clinical significance remains uncertain.

Liu C et al., 2021 [5].

Endothelin receptor antagonists for pulmonary arterial hypertension

Zielsetzung

To evaluate the efficacy of endothelin receptor antagonists (ERAs) in pulmonary arterial hypertension.

Methodik

Population:

- We included trials involving adults and children (≥ 2 years) with PAH. The diagnosis of PAH should have been made according to European Respiratory Society/European Society of Cardiology/World component of their syndrome were available.

Intervention:

- We considered trials in which participants took an ERA alone or in combination against any comparator.
- We included the following co-interventions.
  - Phosphodiesterase type 5 (PDE5) inhibitors
  - Soluble guanylate cyclase (sGC)
  - Prostanoids
  - Nitrates
  - Calcium channel blockers
  - Non-pulmonary hypertension-specific medications including diuretics, anticoagulants, and oxygen

Komparator:

- Comparison 1: Placebo
- Comparison 2: Sildenafil (PDE5-Inhibitor)

Endpunkte:

- Exercise capacity (as measured by a six-minute walk distance (6MWD)).
- World Health Organization (WHO) functional class or New Yor Heart Association (NYHA) functional class (WHO/NYHA).
- Borg dyspnoea scores and dyspnoea-fatigue ratings.
- Mortality

Recherche/Suchzeitraum:

- 04.November.2020 durchgeführt
- CENTRAL, Medline, Ovid, Embase, clinicaltrials.gov, WHO Clinical Trials Registry Platform

Qualitätsbewertung der Studien:

- RoB2

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 RCTs were identified, One radomised head-to-head study

Charakteristika der Population:

- 13 trials recruited participants with idoiopathic PAH
- Two trials Eisenmenger Syndrome
- One study investegated the effect of macitentan on participants with portopulmonary hypertension
- One study systemic sclerosis with mildly elevated mean pulmonary arterial pressure

Qualität der Studien:

- Siehe Abbildung 3 im Anhang

Studienergebnisse:

- Change from baseline in 6MWD

Tabelle 1 Summary of findings 1. Endothelin receptor antagonists compared to placebo for pulmonary arterial hypertension

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with endothelin receptor antagonists				
Change from baseline in 6MWD (m) **mean duration of study 16.3 weeks**	The weighted mean change on control was −4.56 m.	MD 25.06 higher (17.13 higher to 32.99 higher)	-	2739 (14 RCTs)	⊕⊕⊕⊖ Moderate[1]	Higher is better for 6MWD.
Proportion of participants with improved functional class **mean duration of study 16.8 weeks**	175 per 1000	230 per 1000 (197 to 264)	OR 1.41 (1.16 to 1.70)	3060 (15 RCTs)	⊕⊕⊕⊖ Moderate[1]	Participants with high OR are more likely to achieve functional improvement.
Change from baseline in BDI **mean duration of study 14.3 weeks**	The weighted mean change on control was 0.25 higher.	MD 0.43 lower (0.90 lower to 0.04 higher)	-	788 (7 RCTs)	⊕⊕⊖⊖Low[2]	Symptoms are worse with higher score of BDI.
Mortality **mean duration of study 30.2 weeks**	73 per 1000	58 per 1000 (44 to 78)	OR 0.78 (0.58 to 1.07)	2889 (12 RCTs)	⊕⊕⊖⊖ Low[3]	Participants with lower OR are less likely to die.
Change from baseline in mean PAP (mmHg) **mean duration of study 17.1 weeks**	The weighted mean change on control was 0.53 higher.	MD 4.65 lower (6.05 lower to 3.26 lower)	-	729 (8 RCTs)	⊕⊕⊕⊖ Moderate[4]	Participants are worse with higher pulmonary artery pressure.

Anmerkung/Fazit der Autoren

For people with pulmonary arterial hypertension with WHO functional class II and III, endothelin receptor antagonists probably increase exercise capacity, improve WHO functional class, prevent WHO functional class deterioration, result in favourable changes in cardiopulmonary haemodynamic variables compared with placebo. However, they are less effective in reducing dyspnoea and mortality.The efficacy data were strongest in those with idiopathic pulmonary hypertension. The irreversible liver failure caused by sitaxsentan and its withdrawal from global markets emphasise the importance of hepatic monitoring in people treated with ERAs. The question of the effects of ERAs on pulmonary arterial hypertension has now likely been answered. The combined use of ERAs and phosphodiesterase inhibitors may provide more benefit in pulmonary arterial hypertension; however, this needs to be confirmed in future studies.

3.2 Systematische Reviews

Es konnte kein Systematischer Review identifiziert werden.

3.3 Leitlinien

Klinger JR et al., 2019 [4].

American College of Chest Physicians (CHEST)

Therapy for pulmonary arterial hypertension in adults – update of the CHEST guideline and expert panel report

Fragestellungen

For adult patients with PAH, what are the comparative effectiveness and safety of (1) mono- or combination pharmacotherapies using calcium channel blockers, prostanoids, endothelin antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, or orally active prostacyclin derivatives and prostacyclin receptor agonists; (2) cardiopulmonary rehabilitation; (3) palliative care; (4) supportive care; and (5) preventive care on intermediate-term and long-term patient outcomes?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt, trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft teilweise zu (Literaturrecherche veraltet)
- Formale Konsensusprozesse beschrieben, externes Begutachtungsverfahren nicht dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig, die Verbindung der Evidenzbewertung zu der zugrundeliegenden Literatur ist über Hintergrundtext nur teilweise möglich,
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

A systematic literature search […] was conducted using the following databases: MEDLINE via PubMed and the Cochrane Library. Searches for phase I were updated from January 2012 to July 2016. […] Searches for phase II modified the phase I search to retrieve the additional interventions.

Phase I was an update of the prior review that was conducted by AHRQ, and phase II was a review of the new pharmacologic and nonpharmacologic interventions.

LoE/GoR

CHEST Grading System (⇨ Anhang Tabelle 2)

Empfehlungen (⇨ Anhang Abbildung 4)

PAH-specific pharmacotherapies

10. For treatment naive PAH patients with WHO FC II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6MWD (weak recommendation, moderate quality evidence).

Hintergrund

In the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial, Galiè et al[23] studied combination therapy with ambrisentan (10 mg daily) plus tadalafil (40 mg daily) vs either ambrisentan or tadalafil alone in PAH. A total of 610 patients were randomized 2:1:1 to receive ambrisentan (10 mg daily) plus tadalafil

(40 mg daily vs ambrisentan plus placebo vs tadalafil plus placebo, respectively. The primary outcome was the time to first event of clinical failure defined as the composite end point for death, hospitalization for worsening PAH (including transplant, atrial septostomy, and initiation of parenteral prostanoid therapy), disease progression (defined as a 15% decrease in the 6MWD combined with a FC III or IV at two consecutive visits separated by 14 days), or unsatisfactory long-term clinical response in patients completing at least 6 months of the trial (assessed as a decrease in 6MWD from baseline and FC III symptoms at two visits separated by at least 6 months).

The median change from baseline for 6MWD improved more in the combination treatment group than the pooled monotherapy groups (49 vs 24 m, respectively; P < .001). There was no effect on the WHO FC. The improvement in 6MWD in the treatment group suggests that initial combination treatment may be more efficacious than monotherapy in improving exercise capacity. Because there was only one study, and the clinical outcome measured demonstrated a borderline clinically significant effect on 6MWD, the panel supported a weak suggestion instead of a strong recommendation. It is important that each physician and patient work together to decide best treatment options based on each individual situation and what is in the best interest for the particular patient.

Referenzen

23. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-844.

Patients with WHO FC II symptoms

For treatment-naive patients with PAH with WHO FC II symptoms who are not candidate for, or who have failed, CCB therapy, we advise that therapy be initiated with a combination of ambrisentan and tadalafil as stated in Recommendation #10. For patients who are unwilling or unable to tolerate combination therapy, we advise monotherapy with a currently approved ERA, PDE5I inhibitor, or the soluble guanylate cyclase stimulator riociguat […].

More specifically in these patients:

11. We recommend ambrisentan to improve 6MWD (strong recommendation, low quality evidence).
12-13. We suggest bosentan to delay time to clinical worsening (ungraded consensus-based statement).
14. We suggest macitentan to delay the time to clinical worsening (ungraded consensus-based statement).
15. We recommend sildenafil to improve 6MWD (strong recommendation, low quality evidence).
16. We suggest tadalafil to improve 6MWD (ungraded consensus-based statement).
17-20. We suggest riociguat to improve 6MWD (ungraded consensus-based statement), improve WHO FC (ungraded consensus-based statement), delay the time to clinical worsening (ungraded consensus-based statement).
21. We suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naive PAH patients with WHO FC II symptoms or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals (ungraded consensus-based statement).

Patients with WHO FC III symptoms

For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for, or who have failed CCB therapy, we advise that therapy be initiated with a combination of ambrisentan and tadalafil as stated in Recommendation #10. For patients who are unwilling or unable to tolerate combination therapy, we advise monotherapy with a currently approved ERA, a PDE5I, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

22. We recommend the use of bosentan to improve 6MWD (strong recommendation, moderate quality evidence).

23-24. We suggest the use of bosentan to decrease hospitalizations related to PAH in the short-term (weak recommendation, low quality evidence).

25. We recommend the use of ambrisentan to improve 6MWD (strong recommendation, low quality evidence).

26-27. We suggest macitentan to improve WHO FC (ungraded consensus-based statement) and delay the time to clinical worsening (ungraded consensus-based statement).

28-30. We recommend the use sildenafil to improve 6MWD (strong recommendation, low quality evidence), to improve WHO FC (ungraded consensus-based statement).

31-34. We suggest the use of tadalafil to improve 6MWD (ungraded consensus-based statement), to improve WHO FC (ungraded consensus-based statement), to delay time to clinical worsening (ungraded consensus-based statement).

35-38. We suggest riociguat to improve 6MWD (ungraded consensus-based statement), improve WHO FC (ungraded consensus-based statement), delay the time to clinical worsening (ungraded consensus-based statement).

For treatment-naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, we advise consideration of initial treatment with a parenteral prostanoid. More specifically in these patients:

39-41. We suggest continuous IV epoprostenol to improve FC (ungraded consensus-based statement), improve 6MWD (ungraded consensus-based statement).

42. We suggest continuous IV treprostinil to improve 6MWD (ungraded consensus-based statement).

43-44. We suggest continuous subcutaneois treprostinil to improve 6MWD (ungraded consensus-based statement).

For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, we advise consideration of the addition of a parenteral or inhaled prostanoid. More specifically in these patients:

45-47. We suggest IV epoprostenol to improve WHO FC (ungraded consensus-based statement), improve 6MWD (ungraded consensus-based statement).

48-49. We suggest IV treprostinil to improve 6MWD (ungraded consensus-based statement).

50. In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5I, we suggest the addition of inhaled treprostinil to improve 6MWD (weak recommendation, low quality evidence).

51-52. In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5I, we suggest the addition of inhaled iloprost to improve WHO FC

(ungraded consensus-based statement) and delay the time to clinical worsening (ungraded consensus-based statement).

PAH patients on established PAH-specific therapy

60. In patients with PAH initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan (ungraded consensus-based statement).

For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of patients with PAH. More specifically:

61. In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5I, we suggest the addition of inhaled iloprost to improve 6MWD (ungraded consensus-based statement).
62. In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5I, we recommend the addition of inhaled treprostinil to improve 6MWD (strong recommendation, low quality evidence).
63. In patients with PAH who remain symptomatic on stable doses of established IV epoprostenol, we suggest the addition of sildenafil or up titration of epoprostenol to improve 6MWD (ungraded consensus-based statement).
64-66. In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, we suggest the addition of the soluble guanylate cyclase stimulator riociguat to improve 6 MWD (ungraded consensus-based statement), WHO FC (ungraded consensus-based statement) and to delay the time to clinical worsening (ungraded consensus-based statement).
67-69. In patients with PAH who remain symptomatic on stable doses of a PDE5I or an inhaled prostanoid we suggest macitentan to improve 6MWD (ungraded consensus-based statement), WHO FC (ungraded consensus-based statement) and to delay the time to clinical worsening (ungraded consensus-based statement).
70. For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, we suggest addition of a third class of PAH therapy (ungraded consensus-based statement).
71. For stable or symptomatic PAH patients on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD (weak recommendation, low quality evidence).

Hintergrund

Zhuang et al[26] conducted a prospective, double-blinded, randomized controlled study to investigate the efficacy of the addition of oral tadalafil in patients receiving background ambrisentan therapy for PAH. One hundred and twenty-four patients with symptomatic idiopathic pulmonary arterial hypertension (IPAH), heritable PAH, or PAH associated with connective tissue disease; anorexigen use; or repaired congenital heart disease who were treated with ambrisentan (10 mg daily) for ≥ 4 months received either placebo or tadalafil (40 mg daily) for 16 weeks. At 16 weeks, there was a nonsignificant improvement in 6MWD from baseline in the placebo group (mean change, 18.3 m; 95% CI, 4.3-34.8; P = not significant) and a significant improvement in the tadalafil group (mean change, 54.4 m; 95% CI, 30.2-80.1; P < .05). Compared with the placebo group, the increase in the treatment group was found to be significant (P = .042), but the mean difference between the treatment group and control group, and CIs, were not reported. Change in WHO FC did not differ between groups at 16 weeks. Because there was only one study, and the

clinical outcomes measured demonstrated a borderline clinically significant effect on 6MWD, the panel supported a weak suggestion instead of a strong recommendation […].

Referenzen

Zhuang Y, Jiang B, Gao H, Zhao W. Randomized study of adding tadalafil to existing ambrisentan in pulmonary arterial hypertension. Hypertens Res 2014;37:507-512.

Supportive Therapies

73. We suggest that patients with PAH participate in supervised exercise activity as part of the integrated care of their disease (ungraded consensus-based statement).

Humbert M et al., 2022 [3].

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Zielsetzung/Fragestellung

These comprehensive clinical practice guidelines cover the whole spectrumof PH, with an emphasis on diagnosing and treating pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH).

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

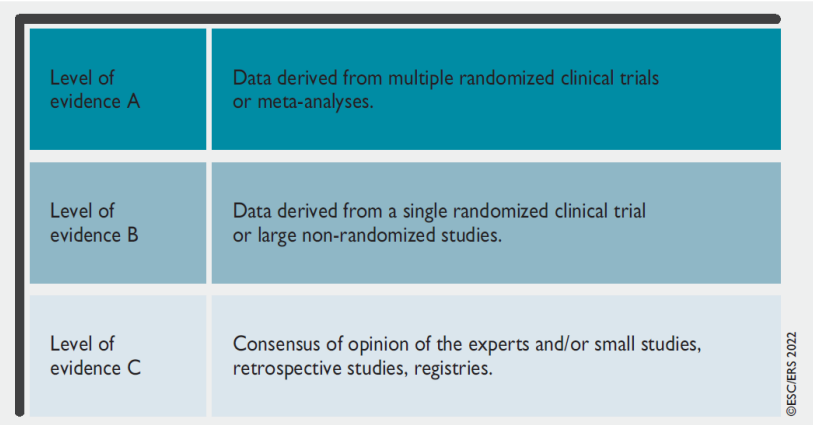
Grundlage der Leitlinie

- Repräsentatives Gremium; trifft zu
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft teilweise zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft zu
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Trifft nicht zu

LoE



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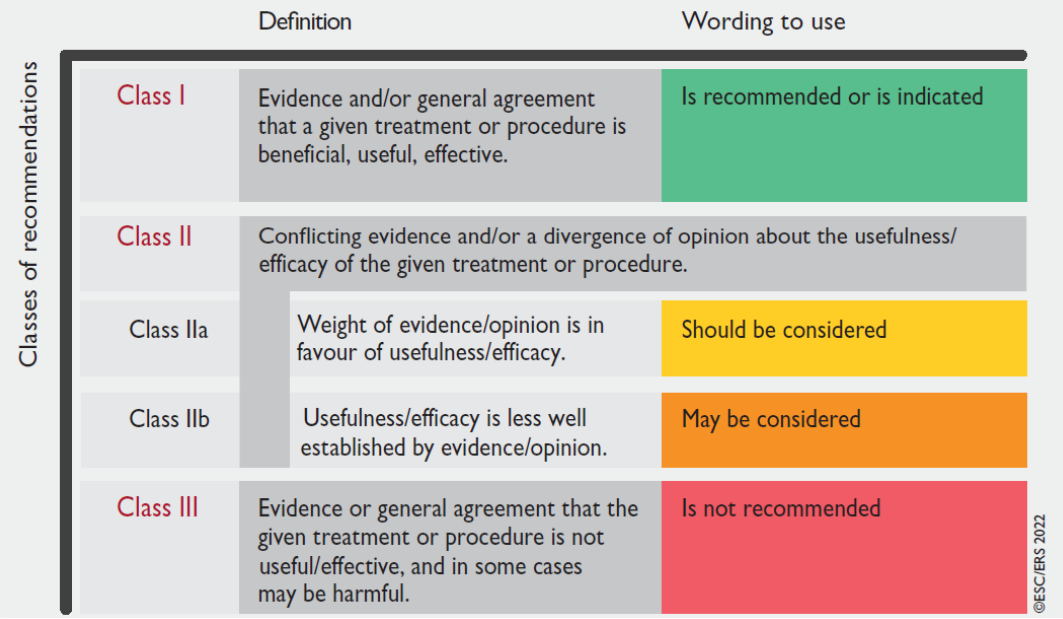

Sonstige methodische Hinweise

- Keine systematische Recherche der Evidenz

6.3.3. Pulmonary arterial hypertension therapies

Recommendation Table 7 — Recommendations for the treatment of vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension

Recommendations	Class[a]	Level[b]
High doses of CCBs are recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing	I	C
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH, or DPAH treated with high doses of CCBs	I	C
Continuing high doses of CCBs is recommended in patients with IPAH, HPAH, or DPAH in WHO-FC I or II with marked haemodynamic improvement (mPAP <30 mmHg and PVR <4 WU)	I	C
Initiating PAH therapy is recommended in patients who remain in WHO-FC III or IV or those without marked haemodynamic improvement after high doses of CCBs	I	C
In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered	IIa	C
CCBs are not recommended in patients without a vasoreactivity study or non-responders, unless prescribed for other indications (e.g. Raynaud's phenomenon)	III	C

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6.3.4. Treatment strategies for patients with idiopathic, heritable, drug-associated, or connective tissue disease-associated pulmonary arterial hypertension

Recommendation Table 8 — Recommendations for the treatment of non-vasoreactive patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension who present without cardiopulmonary comorbidities[a]

Recommendation Table 8A

Recommendations	Class[b]	Level[c]
Recommendations for initial therapy		
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 considered[d]	IIa	C
Recommendations for treatment decisions during follow-up		
In patients with IPAH/HPAH/DPAH who present at intermediate–low risk of death while receiving ERA/PDE5i therapy, the addition of selexipag should be considered[419]	IIa	B
In patients with IPAH/HPAH/DPAH who present at intermediate–high or high risk of death while receiving ERA/PDE5i therapy, the addition of i.v./s.c. prostacyclin analogues and referral for LTx evaluation should be considered	IIa	C
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[429]	IIb	B

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Recommendation Table 8B

	GRADE			
Recommendations	Quality of evidence	Strength of recommendation	Class[a]	Level[b]
Recommendations for initial therapy				
In patients with IPAH/HPAH/DPAH who present at low or intermediate risk of death, initial combination therapy with a PDE5i and an ERA is recommended[166]	Low	Conditional	I	B

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Recommendation Table 9 — Recommendations for initial oral drug combination therapy for patients with idiopathic, heritable, or drug-associated pulmonary arterial hypertension without cardiopulmonary comorbidities

Recommendations	Class[a]	Level[b]
Initial combination therapy with ambrisentan and tadalafil is recommended[166,420,423]	I	B
Initial combination therapy with macitentan and tadalafil is recommended[421,430]	I	B
Initial combination therapy with other ERAs and PDE5is should be considered[303]	IIa	B
Initial combination therapy with macitentan, tadalafil, and selexipag is not recommended[421]	III	B

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2023) am 02.01.2023

#	Suchfrage
1	MeSH descriptor: [Pulmonary Arterial Hypertension] explode all trees
2	MeSH descriptor: [Hypertension, Pulmonary] this term only
3	(pulmonary NEAR/6 hypertension):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Jan 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 02.01.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	"pulmonary arterial hypertension"[MeSH Terms]
2	"hypertension, pulmonary"[majr:noexp]
3	"pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT

#	Suchfrage
	(letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2018/01/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 02.01.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"pulmonary arterial hypertension"[MeSH Terms]
2	"hypertension, pulmonary"[majr:noexp]
3	"pulmonary hypertension"[Title/Abstract] OR "pulmonary arterial hypertension"[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2018/01/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 03.01.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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2. **Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T.** Prostacyclin for pulmonary arterial hypertension. Cochrane Database of Systematic Reviews [online]. 2019(5):Cd012785. URL: http://dx.doi.org/10.1002/14651858.CD012785.pub2.
3. **Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al.** 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43(38):3618-3731.
4. **Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al.** Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and expert panel report. Chest 2019;155(3):565-586.
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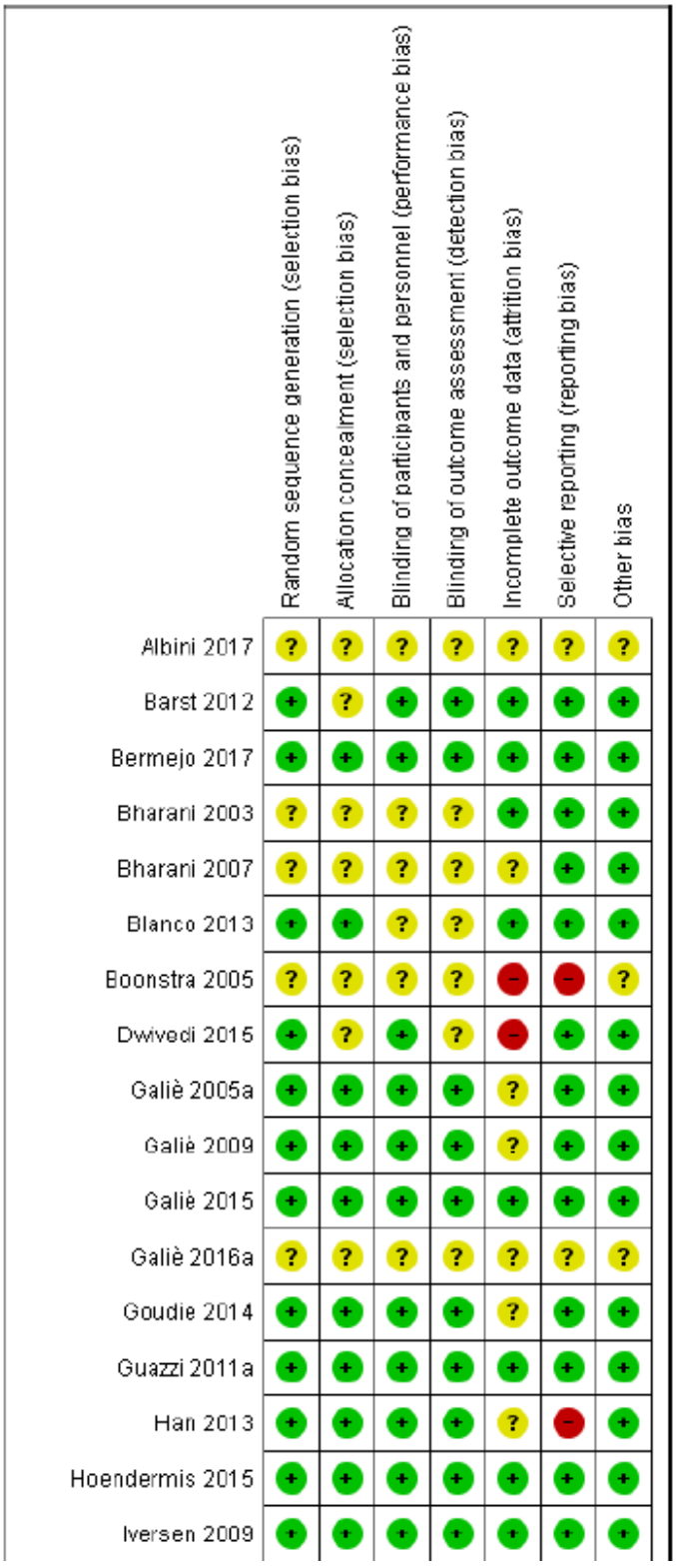
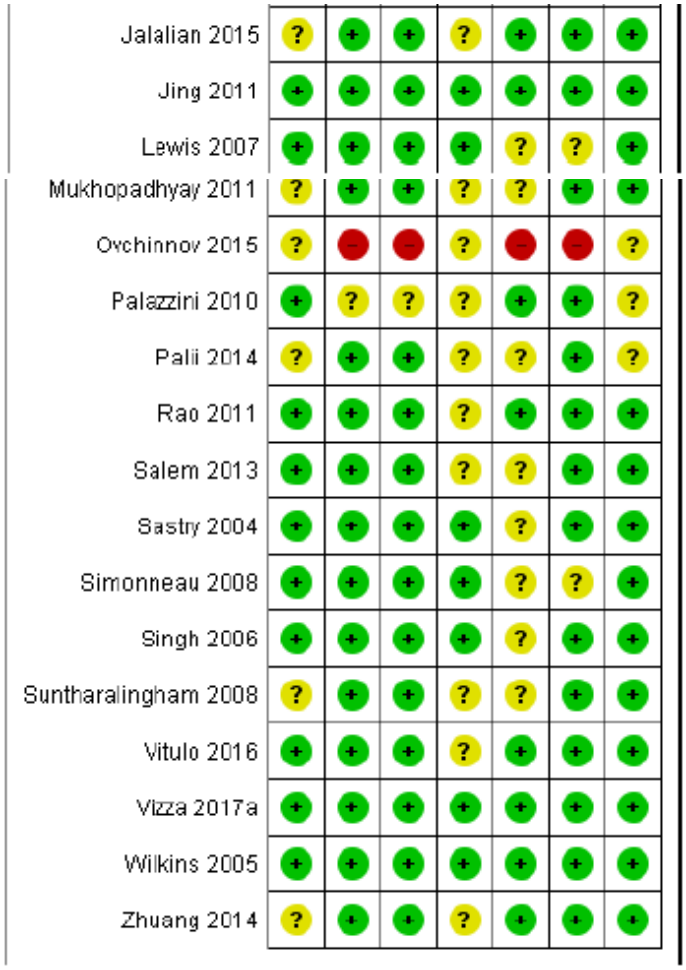
[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Anhang

Abbildung 1: Risk of bias summary: review authors' judgements about each risk of bias item for each included study (Barnes H et al., 2019 [1]).




Jalalian 2015
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Lewis 2007
Mukhopadhyay 2011
Ovchinnov 2015
Palazzini 2010
Palii 2014
Rao 2011
Salem 2013
Sastry 2004
Simonneau 2008
Singh 2006
Suntharalingham 2008
Vitulo 2016
Vizza 2017a
Wilkins 2005
Zhuang 2014

Abbildung 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study (Barnes H et al., 2019 [2]).

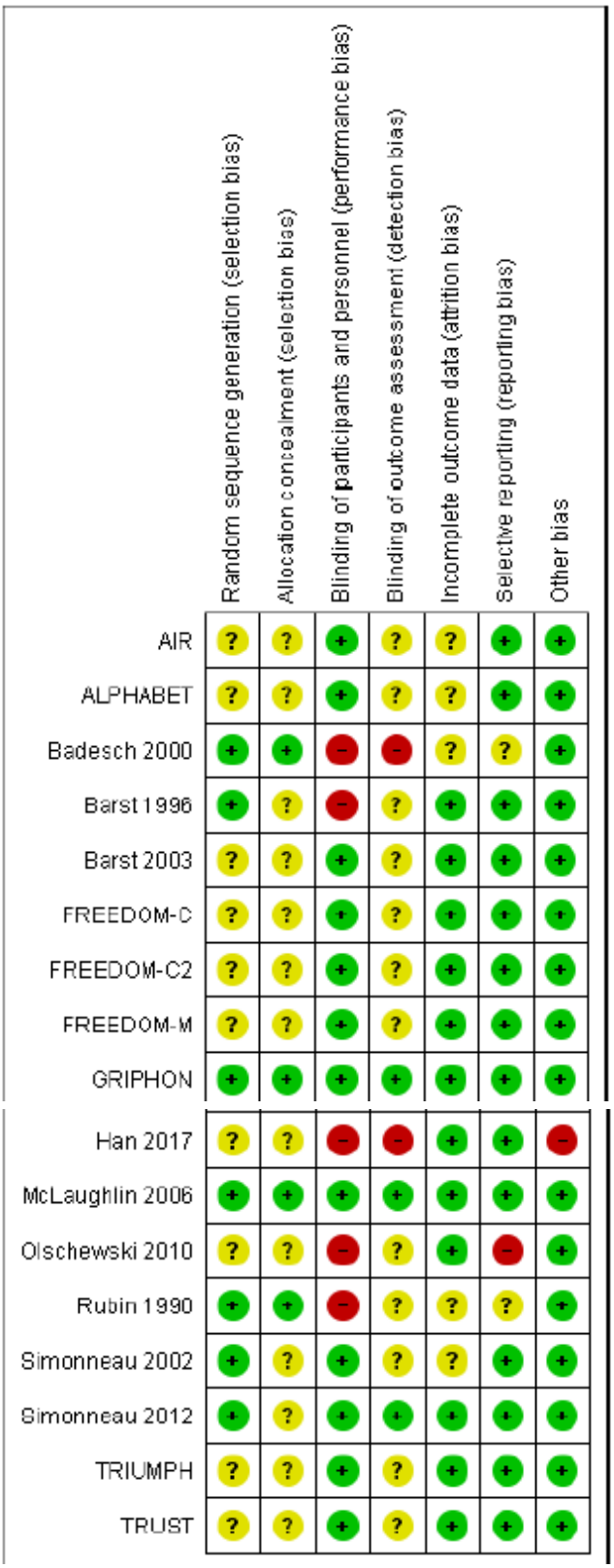


Abbildung 3 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study. (Liu et al., 2021 [5])

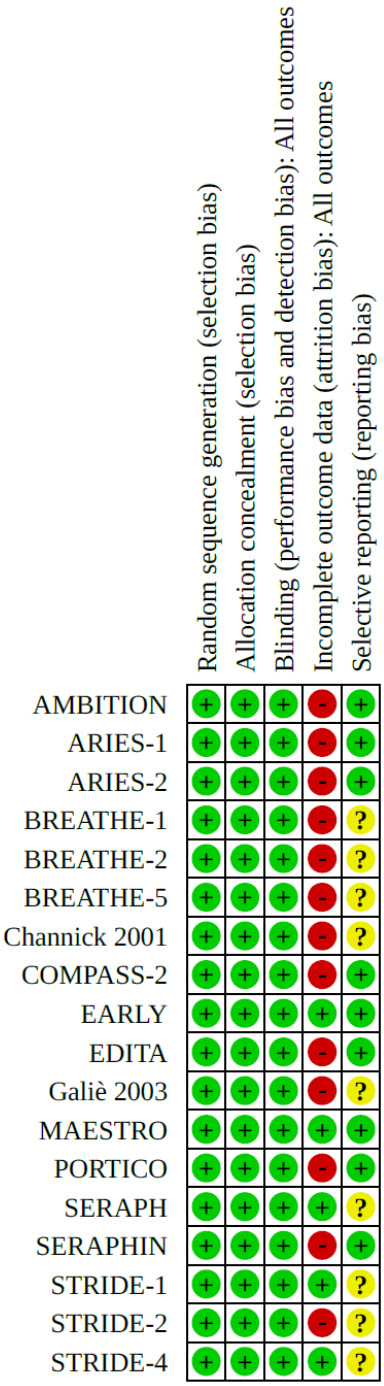
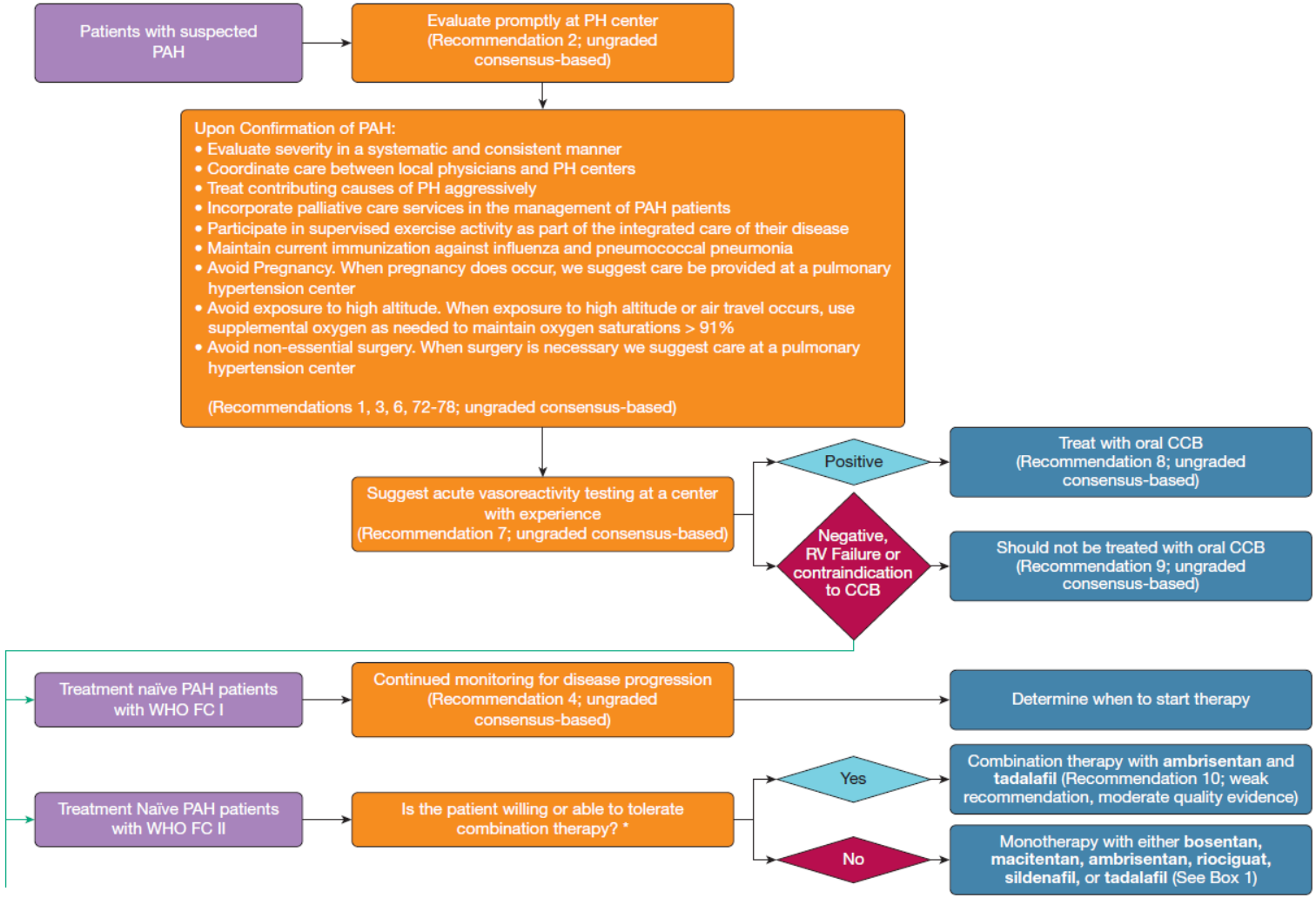


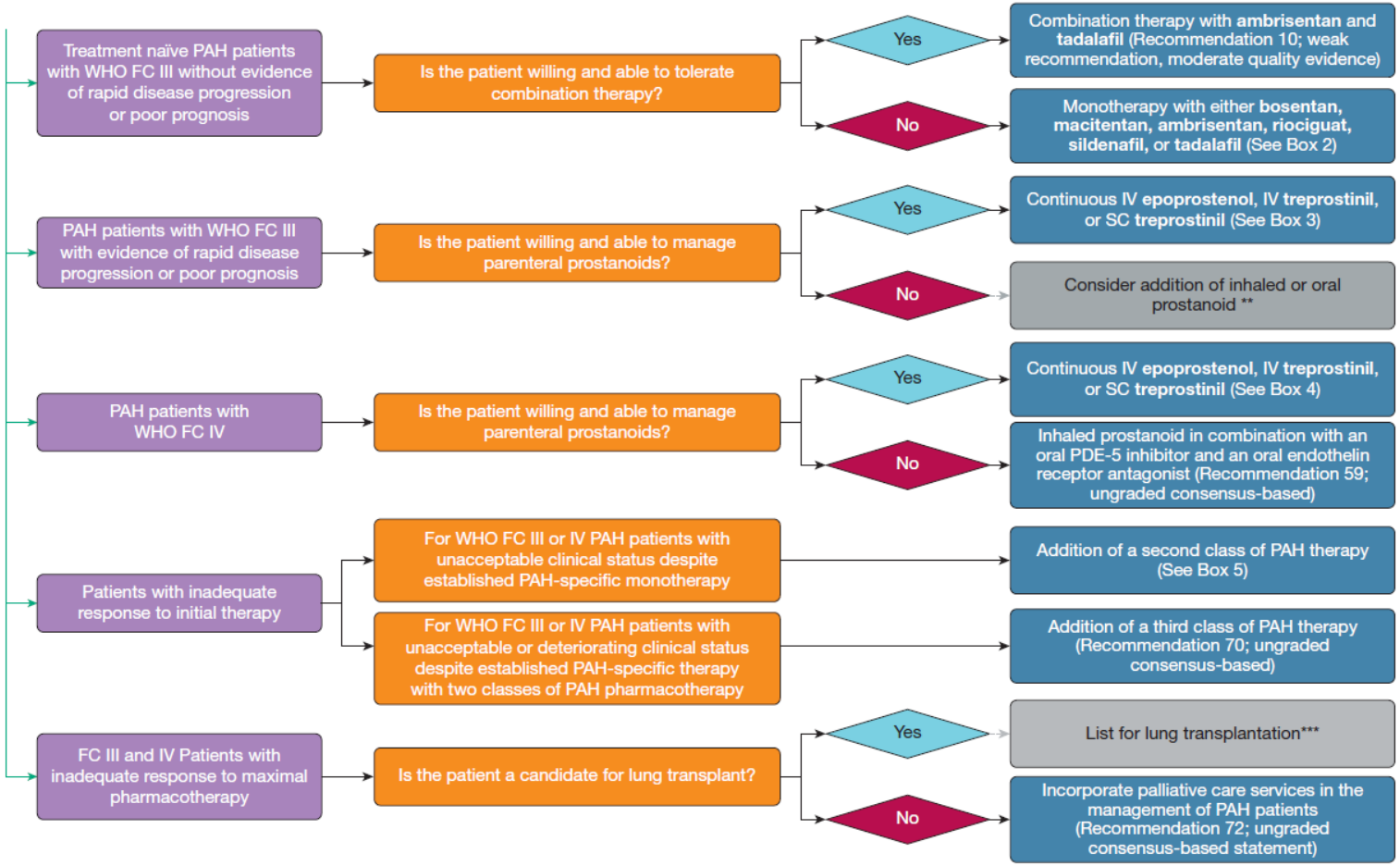
Tabelle 2 CHEST Grading System (Klinger JR et al., 2019 [4]).

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are very confident that the true effect lies close to that of the estimate of the effect.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are moderatly 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.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Strong recommendation, very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, high-quality evidence	Benefits closely balanced with risks and burden.	We are very confident that the true effect lies close to that of the estimate of the effect.	The best action may differ depending on circumstances or patients‘ or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak (conditional) recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden.	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.	Best action may differ depending on circumstances or patients‘ or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

Weak (conditional) recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Ungraded consensus-based suggestions			
Ungraded consensus-based statement	Uncertainty because of lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa.	Insufficient evidence for a graded recommendation.	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

Abbildung 4 Guideline algorithm for pharmacologic therapy for PAH in adults (Klinger JR et al., 2019 [4]).





** Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.*

*** No data available for the use of oral or inhaled prostanoids in patients in whom parental prostanoids are indicated, but patient is unable to comply. Thus, we do not have a specific recommendation for this population.*

**** Lung transplantation is outside the scope of this guideline, which focuses on pharmacotherapy for patients with PAH. Thus, the evidence-based for lung transplants in patients with PAH has not been evaluated by this panel.*

Box 1: Treatment Naïve PAH patients with WHO FC II			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Ambrisentan	Improve 6MWD	strong recommendation, low quality evidence	11
Bosentan	Delay time to clinical worsening	ungraded consensus-based statement	12-13
Macitentan	Delay time to clinical worsening	ungraded consensus-based statement	14
Sildenafil	Improve 6MWD	strong recommendation, low quality evidence	15
Tadalafil	Improve 6MWD	ungraded consensus-based statement	16
Riociguat	Improve 6MWD	ungraded consensus-based statement	17-20
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
Parenteral or inhaled prostanoids should not be chosen as initial therapy or as second line agent		ungraded consensus-based	21

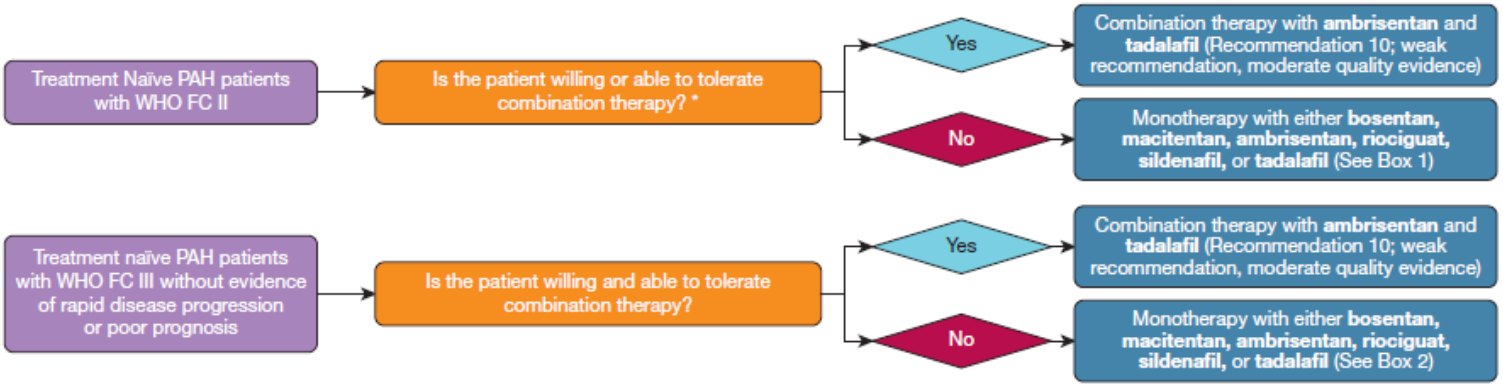
Box 2: Treatment Naïve PAH patients with WHO FC III			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Bosentan	Improve 6MWD	strong recommendation, moderate quality evidence	22
	Decrease hospitalizations related to PAH in the short-term	weak recommendation, low quality evidence	23-24
Ambrisentan	Improve 6MWD	strong recommendation, low quality evidence	25
Macitentan	Improve WHO FC	ungraded consensus-based statement	26-27
	Delay time to clinical worsening	ungraded consensus-based statement	
Sildenafil	Improve 6MWD	strong recommendation, low quality evidence	28-30
	Improve WHO FC	ungraded consensus-based statement	
Tadalafil	Improve 6MWD	ungraded consensus-based statement	31-34
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
Riociguat	Improve 6MWD	ungraded consensus-based statement	35-38
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	

Box 3: PAH patients with WHO FC III with evidence of rapid disease progression or poor prognosis			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Continuous IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	39-41
	Improve 6MWD	ungraded consensus-based statement	
Continuous IV treprostinil	Improve 6MWD	ungraded consensus-based statement	42
Continuous subcutaneous treprostinil	Improve 6MWD	ungraded consensus-based statement	43-44
For patients with continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, we advise consideration of the addition of a parenteral or inhaled prostanoid:			
IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	45-47
	Improve 6MWD	ungraded consensus-based statement	
IV treprostinil	Improve 6MWD	ungraded consensus-based statement	48-49
In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5 inhibitor, we suggest the addition of:			
Inhaled treprostinil	Improve 6MWD	weak recommendation, low quality evidence	50
Inhaled iloprost	Improve WHO FC	ungraded consensus-based statement	51-52
	Delay time to clinical worsening	ungraded consensus-based statement	

Box 4: PAH patients with WHO FC IV			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Continuous IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	53-55
	Improve 6MWD	ungraded consensus-based statement	
Continuous IV treprostinil	Improve 6MWD	ungraded consensus-based statement	56
Continuous subcutaneous treprostinil	Improve 6MWD	ungraded consensus-based statement	57-58

Box 5: Patients with inadequate response to initial therapy			
Drug	**Outcome**	**Grade**	**Recommendation Number**
In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5 inhibitor, we suggest the addition of:			
Inhaled iloprost	Improve 6MWD	ungraded consensus-based statement	61
Inhaled treprostinil	Improve 6MWD	strong recommendation, low quality evidence	62
In patients with PAH who remain symptomatic on stable doses of established IV epoprostenol, we suggest one of the following:			
Addition of sildenafil	Improve 6MWD	ungraded consensus-based statement	63
Up titration of epoprostenol	Improve 6MWD	ungraded consensus-based statement	
In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, we suggest the addition of			
Riociguat	Improve 6MWD	ungraded consensus-based statement	64-66
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid we suggest			
Macitentan	Improve 6MWD	ungraded consensus-based statement	67-69
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
For stable or symptomatic PAH patients on background therapy with ambrisentan			
Addition of tadalafil	Improve 6MWD	ungraded consensus-based statement	71

Abbildung 5: Combination therapy algorithm (Klinger JR et al., 2019 [4]).



** Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.*

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2022-B-349

Verfasser	
Name der Institution	DGf Kardiologie, DGf Innere Medizin, DGf Pneumologie, Dt. Hochdruckliga, DGf Prävention und Rehabilitation von Herz-Kreislauferkrankungen
Datum der Erstellung	24. Februar 2023

Indikation
„… zur Behandlung der Pulmonal Arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit WHO Funktionsklasse II und III“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*

Behandlungsstandard

Zur Beschreibung des Behandlungsstandards unter Berücksichtigung der vorliegenden Evidenz sind für Deutschland die aktuellen (zuletzt 2022 aktualisierten) Leitlinien der Europäischen Gesellschaft für Kardiologie (*European Society of Cardiology*, ESC) und der Europäischen Gesellschaft für Pneumologie (*European Respiratory Society*, ERS) zur Diagnostik und Therapie der pulmonalen Hypertonie maßgeblich [1, 2] Zudem wird auch die S3-Leitlinie der Deutschen Gesellschaft für Prävention und Rehabilitation von Herz-Kreislauferkrankungen (DGPR, (2020) berücksichtigt [3]. Unsere Stellungnahme fokussiert entsprechend der Fragestellung auf PAH-Patienten mit WHO-funktioneller Klasse (WHO-FC) II/III.

Die Therapie der PAH besteht aus supportiven Maßnahmen und gezielter medikamentöser Therapie. Zu den supportiven Maßnahmen gehören – je nach individuellem Bedarf – z.B. Diuretika oder Heimsauerstofftherapie. Auch Rehabilitationsmaßnahmen werden in regelmäßigen Abständen empfohlen (Klasse IA-Empfehlung) [1,2]. Letztere werden jedoch explizit unterstützend und zusätzlich zu optimierter medikamentöser Therapie bei stabil eingestellten Patienten empfohlen, da körperliche Anstrengung aufgrund der resultierenden Rechtsherzinsuffizienz andernfalls auch negative und sicherheitsrelevante Auswirkungen haben kann (z.B. Synkopen; kardiale Dekompensation). Zudem sind im Hinblick auf Rehabilitationsmaßnahmen folgende Punkte zu berücksichtigen: (i) Einige Patienten sind aufgrund ihrer körperlichen Einschränkungen oder aus anderen Gründen nicht zu solchen Maßnahmen in der Lage, (ii) die Kostenträger lehnen entsprechende Anträge in vielen Fällen ab (persönliche Erfahrung der Autoren dieser Stellungnahme, konkrete Zahlen liegen hierzu nicht vor), (iii) diese Maßnahmen sind während der Pandemie weitgehend zum Erliegen gekommen und laufen jetzt mit sehr viel Rückstau erst langsam wieder an, (iv) insgesamt besteht derzeit für eine flächendeckende Umsetzung ein Mangel an kardiologischen

Rehakliniken mit entsprechender Expertise, die ein spezialisiertes Programm für PAH-Patienten anbieten, so dass PAH-Patienten bezüglich dieser nicht medikamentösen Intervention unterversorgt sind.

Recommendation Table 5 — Recommendations for general measures and special circumstances

Recommendations	Class[a]	Level[b]
General measures		
Supervised exercise training is recommended in patients with PAH under medical therapy[314,315,317]	I	A

Zur gezielten medikamentösen Behandlung der PAH sind mit Stand 02/2023 Wirkstoffe aus vier Substanzklassen zugelassen, die als Mono- oder Kombinationstherapie eingesetzt werden können. Zu ihnen gehören (i) Endothelin-Rezeptor-Antagonisten (ERA), (ii) Phosphodiesterase-5-Inhibitoren (PDE-5-I), (iii) lösliche Guanylatzyklase (sGC)-Stimulatoren, und (iv) Prostazyklin-Analoga bzw. Prostazyklin-Rezeptor-Agonisten. Gemäß den aktuellen ESC/ERS-Leitlinien richtet sich der Behandlungsstandard bei Patienten mit pulmonal arterieller Hypertonie (PAH) nach der individuellen Risikoeinschätzung [1,2]. Hierbei werden Patienten nach der zu erwartenden 1-Jahres-Mortalität zum Zeitpunkt der Erstdiagnose in solche mit niedrigem (<5%),

intermediärem (5-20%) oder hohem (>20%) Risiko untergliedert. Im weiteren Krankheitsverlauf werden die Patienten in vier Risikokategorien eingeteilt (niedrig, intermediär-niedrig, intermediär-hoch, und hoch). Patienten in der WHO-FC II oder III gehören in der Regel den niedrig-Risiko oder intermediär-Risikogruppen an.

Die 2022 ESC/ERS-Leitlinien definieren eine ERA/PDE5-I-Kombinationstherapie als Standard-therapie für Patienten mit niedrigem oder intermediärem Sterblichkeitsrisiko (überwiegend WHO-FC II und III). Monotherapien werden nur noch empfohlen für Patienten mit seltenen Formen der PAH (PAH bei portaler Hypertension, HIV-Infektion, angeborenen Herzfehlern) sowie bei Patienten mit relevanten kardiopulmonalen Begleiterkrankungen [1,2].

Der Therapiealgorithmus der ESC/ERS-Leitlinien unterscheidet therapienaive Patienten mit neu diagnostizierter Erkrankung (initiale Therapieentscheidung) sowie Patienten mit präexistenter Erkrankung, welche bereits vorbehandelt sind (Therapieoptimierung im Verlauf).

Patienten mit neu diagnostizierter PAH und niedrigem bzw. intermediärem Risiko:

Für Patienten mit negativem Vasoreagibilitätstest und niedrigem oder intermediärem Risiko (überwiegend WHO-FC II und III) wird eine initiale duale orale Kombinationstherapie aus ERA und PDE-5-I empfohlen. Die Empfehlung dieser Behandlungsstrategie basiert im Wesentlichen auf den Ergebnissen der AMBITION-Studie (*first-line combination therapy with AMBbrIsentan and Tadalafil in patients with pulmonary arterial hypertensION*), in der gezeigt wurde, dass bei neu diagnostizierter PAH und demnach therapienaiven Patienten eine „upfront combination therapy“ mit dem PDE5i Tadalafil und dem ERA Ambrisentan im

Hinblick auf die Verhinderung von Morbiditäts-/Mortalitäts-Ereignissen einer Behandlung mit jeder Substanz alleine deutlich überlegen war [4]. In dieser randomisierten, doppelblinden Multicenter-Studie wurden 500 therapienaive Patienten mit PAH im Verhältnis 2:1:1 randomisiert und erhielten entweder eine „First-line"-Therapie mit Ambrisentan und Tadalafil, oder eine Monotherapie mit Ambrisentan oder Tadalafil. Die mittlere Beobachtungszeit betrug ca. 1,5 Jahre. Die initiale Kombinationstherapie reduzierte den primären Endpunkt („Clinical Failure", definiert als Zeit von der Randomisierung bis zum ersten Auftreten von Tod, Hospitalisierung wegen Verschlechterung der PAH, Krankheitsprogression oder unbefriedigendes klinisches Langzeitansprechen) um 50 % verglichen mit der gepoolten Ambrisentan oder Tadalafil Monotherapie-Gruppe (HR = 0,502; 95%-CI 0,348–0,724; p = 0,0002). Innerhalb der einzelnen Monotherapiearme ergaben sich keine signifikanten Unterschiede. Die Ergebnisse bezüglich des primären Endpunkts waren konsistent mit den Ergebnissen sekundärer Studienendpunkte. Die Verbesserung der 6 MWD betrug in der Kombinationstherapie-Gruppe +49,0 m, in der gepoolten Monotherapie-Gruppe +23,8 m.

Eine weitere Studie (TRITON), die untersucht hat, ob die zusätzliche Gabe des oralen Prostacyclin-Rezeptor-Antagonisten Selexipag zusätzlich zu einer initialen ERA/PDE5-I-Kombinationstherapie (hier Macitentan/Tadalafil) einen Zusatznutzen bringt, konnte einen solchen Zusatznutzen nicht zeigen, bestätigte aber die Wirksamkeit der ERA/PDE5-I-Kombinationstherapie mit deutlichen Verbesserungen von 6 min Gehstrecke (Zunahme von 56 m nach 26 Wochen) und Hämodynamik (Abfall des pulmonal-vaskulären Widerstands um 52% nach 26 Wochen) [5]. Die in dieser Studie beobachteten Verbesserungen von Hämodynamik und 6 min Gehstrecke lagen deutlich über dem, was bisher unter Monotherapie beobachtet wurde [6-8].

Die initiale Kombinationstherapie mit Ambrisentan bzw. Macitentan und Tadalafil hat in den europäischen Leitlinien den höchsten Empfehlungsgrad erhalten [1,2]. Eine initiale Kombinationstherapie mit anderen ERA bzw. PDE5-Hemmern kann ebenfalls erwogen werden, allerdings gab es dazu bisher lediglich unkontrollierte Daten aus Fallserien.

Eine initiale Monotherapie (üblicherweise mit einem PDE-5-I oder einem ERA) wird empfohlen bei älteren Patienten mit Komorbiditäten sowie bei Patienten mit assoziierter PAH, z.B. bei angeborenen Herzfehlern, HIV-Infektion oder Lebererkrankungen (siehe auch unten).

Vorbehandelte Patienten mit niedrigem oder intermediärem Risiko unter Therapie:

Eine Fortsetzung der gewählten Therapiestrategie wird bei Patienten mit niedrigem Risiko unter Therapie empfohlen.

Für Patienten, die unter bestehender PAH-Therapie ein intermediär-niedriges oder intermediär-hohes Risiko aufweisen, wird eine Therapieeskalation empfohlen. Bei Patienten mit intermediär-niedrigem Risiko (überwiegend, aber nicht ausschließlich WHO FC II und III) ist dies zunächst die Hinzunahme von Selexipag [9] oder alternativ der Wechsel von PDE-5-I auf den sGCs-Stimulator Riociguat [10].Bei Patienten mit intermediär-hohem oder hohem Risiko (überwiegend, aber nicht ausschließlich WHO-FC III und IV) gilt die Hinzunahme eines intravenös oder subkutan verabreichten Prostazyklinderivates als Therapie der Wahl, alternativ können aber auch die oben genannten Optionen (Hinzunahme von Selexipag, Wechsel auf Riociguat) in Frage kommen.

Versorgungspraxis in Deutschland

Zur Beantwortung der Frage nach der aktuellen Versorgungspraxis in Deutschland wurde eine ad-hoc-Analyse des COMPERA-Registers durchgeführt, in dessen Rahmen alle Patienten mit neu diagnostizierter PAH in dem Zeitraum 01.01.2018 bis 31.12.2022 ausgewertet wurden. COMPERA ist ein prospektives, multizentrisches, multinationales Register, welches Patienten mit allen Formen der pulmonalen Hypertonie einschließt. Die hier gezeigte Analyse beschränkt sich auf in Deutschland eingeschlossene PAH-Patienten der WHO funktionellen Klasse (WHO-FC) II oder III. Insgesamt waren zum Stichtag 11.712 Patienten in COMPERA registriert. Von diesen Patienten waren folgende Gruppen aus den jeweils genannten Gründen nicht für die Auswertung relevant (mehr als einer der folgenden Gründe konnte zutreffen):

- n=236 Patienten nicht ≥ 18 Jahre alt,
- n=5.315 Patienten nicht PAH nach Nizza-Klassifikation (PH-Gruppe 1),
- n=2.010 Patienten nicht aus deutschen Zentren,
- n=8.614 Patienten diagnostiziert vor 2018,
- n=2.305 Patienten mit WHO-FC nicht der Klasse II oder III zugehörig.

Somit waren n=1.096 Patienten mit PAH in der WHO-FC II oder III, mit Diagnosestellung zwischen 01.01.2018 und 31.12.2022 für die Analyse verwertbar. Die entsprechenden Daten dieser Patienten sind den Tabellen 1 und 2 zu entnehmen. **Tabelle 1** fasst die Basis-Charakteristika der Patienten bei Diagnosestellung zusammen. **Tabelle 2** zeigt das Therapieregime der gezielten PAH-Therapie nach 3 Monaten sowie nach 1, 2 bzw. 3 Jahren. Wie den Zahlen zu entnehmen ist, sind die am häufigsten eingesetzten PAH Therapien in Deutschland somit eine orale Mono- oder 2-fach-Kombinationstherapie, ganz überwiegend bestehend aus ERA und PDE-5-I. Das zahlenmäßige Überwiegen der Monotherapie erklärt sich aus dem hohen Anteil älterer Patienten (im Median, 70 Jahre) mit kardiopulmonalen Begleiterkrankungen in COMPERA [11, 12]. Vorangegangene Analysen haben gezeigt, dass die Mehrzahl der in Deutschland behandelten PAH-Patienten ohne relevante kardiopulmonale Begleiterkrankungen mit einer ERA/PDE5-I-Kombinationstherapie behandelt wird [13].

Tabelle 1 Baseline-Charakteristika der selektierten, erwachsenen PAH-Patienten im WHO-Stadium II oder III in Deutschland, bei denen während des Zeitraums 01.01.2018 und 31.12.2022 eine gezielte PAH-Therapie eingeleitet wurde. Daten repräsentieren mean (SD), median (min, max), Q1-Q3 oder Anzahl (%).

	n=1096
Age [years]	67.1 (14.5), 70.0 [18.0, 95.0], 59.0 - 78.0
Sex	
Male	389 (35.5%)
Female	707 (64.5%)
Dana Point classification	
1.1 Idiopathic PAH	772 (70.4%)
1.2 Heritable PAH	20 (1.8%)
1.3 Drug- and toxin-induced PAH	11 (1.0%)
1.4 Associated PAH	293 (26.7%)
NYHA FC	
II	222 (20.3%)
III	874 (79.7%)
Year of diagnosis	
2018	223 (20.3%)
2019	249 (22.7%)
2020	243 (22.2%)
2021	215 (19.6%)
2022	166 (15.1%)

Tabelle 2 Therapie-Regime 3 Monate sowie 1, 2 bzw. 3 Jahre nach Diagnosestellung bzw. Therapie-Einleitung. n(%).

Table 2: Therapy at 3 months, 1, 2 and 3 years after diagnosis: No. (%)

	3 months n=1016	1 year n=602	2 years n=375	3 years n=220
PDE5i	864 (85.0%)	494 (82.1%)	297 (79.2%)	169 (76.8%)
ERA	341 (33.6%)	272 (45.2%)	184 (49.1%)	105 (47.7%)
sGC	47 (4.6%)	39 (6.5%)	40 (10.7%)	26 (11.8%)
PCA	30 (3.0%)	64 (10.6%)	52 (13.9%)	32 (14.5%)
IV/SC	3 (0.3%)	9 (1.5%)	9 (2.4%)	11 (5.0%)
other	27 (2.7%)	55 (9.1%)	43 (11.5%)	21 (9.5%)
No therapy	32 (3.1%)	31 (5.1%)	24 (6.4%)	13 (5.9%)
Mono therapy	706 (69.5%)	322 (53.5%)	171 (45.6%)	108 (49.1%)
Dual therapy	258 (25.4%)	200 (33.2%)	138 (36.8%)	73 (33.2%)
Triple therapy	20 (2.0%)	49 (8.1%)	42 (11.2%)	26 (11.8%)

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Die Behandlungsentscheidungen richten sich nach den o.g. Kriterien, also (i) Form der PAH, (ii) Schwere der Erkrankungen (festgelegt anhand einer strukturierten Risikoabschätzung sowie an hämodynamischen Kriterien), und (iii) dem Vorliegen relevanter kardiopulmonaler Begleiterkrankungen.

Die üblichen Therapieentscheidungen lassen sich wie folgt zusammenfassen:

- Patienten mit idiopathischer, hereditärer, oder Medikamenten-assoziierter PAH sowie PAH bei Bindegewebserkrankungen ohne relevante kardiopulmonale Begleiterkrankungen in FC II/III: Primäre ERA/PDE5-I Kombinationstherapie (bei hohem Sterblichkeitsrisiko + IV/SC Prostazyklin).
- Patienten mit PAH bei portaler Hypertension, HIV-Infektion, oder angeborenen Herzfehlern unabhängig von der Funktionsklasse: Primäre Monotherapie mit ERA oder PDE5-I; bei unzureichendem Ansprechen im Verlauf ERA/PDE5-I-Kombinationstherapie.
- Patienten mit allen Formen der PAH und relevanten kardiopulmonalen Begleiterkrankungen: Primäre Monotherapie, üblicherweise mit PDE5-I; im Verlauf individuelle Entscheidung bezüglich des Einsatzes von Kombinationstherapie.

Bei dem Thema Begleiterkrankungen ist es wichtig hervorzuheben, dass es nicht einzelne Begleiterkrankungen wie z.B. Hypertonus, Adipositas oder Diabetes mellitus sind, die *per se* als relevant gelten, sondern ob ein klinischer Phänotyp vorliegt, der trotz des Vorliegens der diagnostischen Kriterien für eine PAH davon ausgehen lässt, dass Linksherzerkrankungen (v.a. eine diastolische Dysfunktion des linken Ventrikels) oder Lungenerkrankungen an der Pathogenese der PAH beteiligt sind. Daten aus dem COMPERA-Register zeigen, dass in

Deutschland bei diesen Patientengruppen sowohl in der Initialtherapie als auch im Verlauf vorzugsweise orale Monotherapien, zumeist mit PDE5-I eingesetzt werden [11].

Eine Erhebung aus drei großen deutschen PH-Zentren (Gießen, Heidelberg, Köln) zu den Patienten-Profilen von 182 PAH-Patienten, die aktuell mit einer Monotherapie behandelt werden, ergab folgende Gründe für eine Monotherapie (Summe übersteigt 100%, da mehrere Gründe bei einem Patienten vorliegen konnten) [14]:

(i) Erfolgloser Versuch der Therapie-Eskalation aufgrund von Unverträglichkeiten (26.9%);
(ii) Niedrig-Risiko-Profil unter Monotherapie, gutes Therapieansprechen, kein Grund für Eskalation (24.2%);
(iii) Hämodynamisch milde PAH (mPAP ≤ 30 mmHg, PVR ≤ 4 WU) (36.3%);
(iv) "PAH mit Komorbiditäten" bei älteren Patienten (38.5%);
(v) Spezifische PAH-Subgruppen / assoziierte Formen der Gruppe 1 PH, bei denen die Evidenz für die Überlegenheit von Kombinationstherapien niedrig ist, oder bei denen einzelne Substanzklassen kontraindiziert sind (16.5%).

Zusammenfassend ist eine ERA/PDE5-I-Kombinationstherapie mittlerweile Standard der PAH-Therapie, ggf. ergänzt um Prostazyklinderivate. Initiale Monotherapien mit ERA oder PDE5-I werden nur noch empfohlen für Patienten mit seltenen Formen der PAH (PAH bei portaler Hypertension, HIV-Infektion, angeborenen Herzfehlern) sowie bei Patienten mit PAH und relevanten kardiopulmonalen Begleiterkrankungen.

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