Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-123 Riociguat

Stand: August 2018

I. Zweckmäßige Vergleichstherapie: Kriterien der VerfO	
Riociguat zur Behandlung der pulmonal arteriellen Hypertonie (PAH)	
Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO/AM-NutzenV	
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.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	<u>Verfahren der frühen Nutzenbewertung nach § 35a SGB V</u> • Beschluss zu Macitentan vom 6. April 2017 • Beschluss zu Selexipag vom 15. Dezember 2016 • Beschluss zu Riociguat vom 16. Oktober 2014
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:	
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 idiopathischen oder hereditären PAH oder einer mit einer Bindegewebserkrankung assoziierten PAH nachgewiesen. (FI Adempas® März 2018)
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. (FI Opsumit® Januar 2017)
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. (FI Bosentan Heumann® Januar 2018)
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. (FI Volibris® April 2017)
Phosphodiesterase-Typ-5 (PDE5)-Inhibitoren:	

Sildenafil C02KX04 Revatio®	Behandlung von erwachsenen Patienten mit pulmonaler arterieller Hypertonie (PAH) der WHO-Funktionsklassen II und III zur Verbesserung der körperlichen Leistungsfähigkeit. Die Wirksamkeit konnte nachgewiesen werden bei primärer PAH und bei pulmonaler Hypertonie in Verbindung mit einer Bindegewebskrankheit. (FI Revatio® Oktober 2017)
Tadalafil C02KX05 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. (FI Adcirca® März 2017)
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. (FI Ventavis® Juni 2017)
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. (FI Remodulin® Mai 2017)
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). (FI Epoprostenol-Rotexmedica® März 2018)
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). (FI Uptravi® Juli 2017)

Quelle: Fachinformation; Lauer Fischer-Taxe

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-123 (Riociguat)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	19. Juni 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

6MWD	6-minute walk distance
AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BDIs	Borg dyspnea index scores
CCB	calcium channel blockers
CCW	Combined clinical worsening
CHD	congenital heart disease
CHFQ	Chronic Heart Failure Questionnaire
CI	cardiac index
CI	Confidence interval
CT	Combination therapy
CTEPH	chronic thromboembolic pulmonary hypertension
CW	Clinical worsening
DAHTA	DAHTA Datenbank
ERA	Endothelin-Rezeptor-Antagonisten
ES	Eisenmenger syndrome
FC	functional class
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
HR	heart rate Borg
HRQoL	health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
mPAP	mean pulmonary arterial pressure
MT	monotherapy

NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	Odds Ratio
PAE	prostacyclin analogs (PGI) combined with ERA
PAH	pulmonal arteriellen Hypertonie
PCWP	pulmonary capillary wedge pressure
PDE-5I	Phosphodiesterase-5-Inhibitor
PGI	prostacyclin analogs
PO/INH	oral/inhaled
PRA	prostacyclin receptor agonist
PVR	pulmonary vascular resistance
PVRi	pulmonary vascular resistance index
RCT	Randomized controlled trial
RR	Relatives Risiko
SC	IV/subcutaneous
sGCS	soluble guanylate cyclase stimulators
SIGN	Scottish Intercollegiate Guidelines Network
SpO2	resting oxygen saturation
SVO2	venous oxygen saturation
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung der pulmonalen arteriellen Hypertonie (PAH) der WHO-Funktionsklasse (FK) II und III zur Verbesserung der körperlichen Leistungsfähigkeit.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *pulmonale arterielle Hypertonie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 11.05.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 613 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 26 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 IQWiG-Berichte/G-BA-Beschlüsse

G-BA, 2014 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Riociguat. vom 16. Oktober 2014

Anwendungsgebiet

(…) Pulmonal arterielle Hypertonie (PAH)

Riociguat (Adempas®) als Monotherapie oder in Kombination mit Endothelin-Rezeptorantagonisten, ist indiziert für die Behandlung erwachsener Patienten mit pul-monal arterieller Hypertonie (PAH) der WHO-Funktionsklassen (FK) II bis III zur Ver-besserung der körperlichen Leistungsfähigkeit.

Die Wirksamkeit wurde in einer PAH-Population einschließlich Ätiologien einer idiopathischen oder hereditären PAH oder einer mit einer Bindegewebserkrankung assoziierten PAH nachgewiesen.

Zweckmäßige Vergleichstherapie

Nicht zutreffend, da Orphan Drug Indikation

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Erwachsene Patienten mit PAH: gering

G-BA, 2017 [9].

Siehe auch IQWiG, 2017 [13].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Macitentan (Neubewertung eines Orphan – Drugs nach Überschreitung der 50 Mio. Euro Grenze). Vom 06. April 2017.

Anwendungsgebiet

Opsumit, als Monotherapie oder in Kombination, ist indiziert für die Langzeitbehandlung der pulmonal arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit WHO Funktionsklasse (WHO-FC) 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 an geborenen Herzfehlern.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Macitentan zur Langzeitbehandlung der pulmonal arteriellen Hypertonie (PAH) bei erwachsenen Patienten mit funktioneller WHO-/NYHA-Klasse II bis III ist eine patientenindividuell optimierte medikamentöse Therapie nach Maßgabe des Arztes unter Berücksichtigung des jeweiligen Zulassungsstatus.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [10].

Siehe auch IQWiG, 2016 [14].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Selexipag Vom 15. Dezember 2016

Anwendungsgebiet

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.

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Selexipag zur 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, ist eine patientenindividuell optimierte medikamentöse Therapie nach Maßgabe des Arztes unter Berücksichtigung des jeweiligen Zulassungsstatus.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Zheng YG et al., 2014 [26].

Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials

Fragestellung

Wirksamkeit und Sicherheit oraler PAH-zielgerichteter Therapien

Methodik

Population:

- erwachsene Patienten mit PAH

Intervention:

- any study on oral targeted therapies including oral prostanoids, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin receptor agonists, and soluble guanylate cyclase stimulators (sGCS)

Komparator:

- Placebo

Endpunkt:

- Mortalität, klinische Verschlechterung (death, lung transplantation, interatrial fistulization, hospitalization due to decompensated PAH, the initiation of a new therapy, or worsening WHO functional class)

Recherche/Suchzeitraum:

- bis 2013

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 Studien (RCTs), 4363 Patienten were included. Among them, eight RCTs assessed the effects of endothelin receptor antagonists (bosentan, ambrisentan and Macitentan), four RCTs assessed the effects of phosphodiesterase type 5 inhibitors (sildenafil, tadalafil and vardenafil), five RCTs assessed the effects of prostacyclin analogs (beraprost and treprostinil), and one RCT assessed the effects of soluble guanylate cyclase stimulators (riociguat).

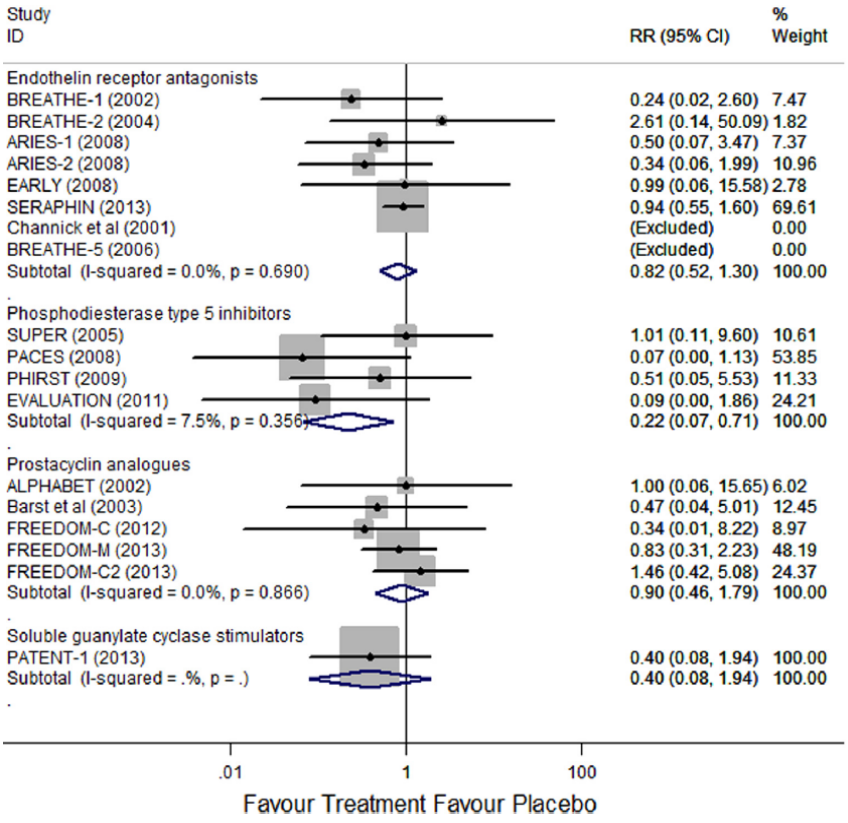
Qualität der Studien:

- Jadad Score aller Studien zwischen 3 und 4, eine Studie (Bosentan vs. Placebo) erreichte 5

Studienergebnisse:

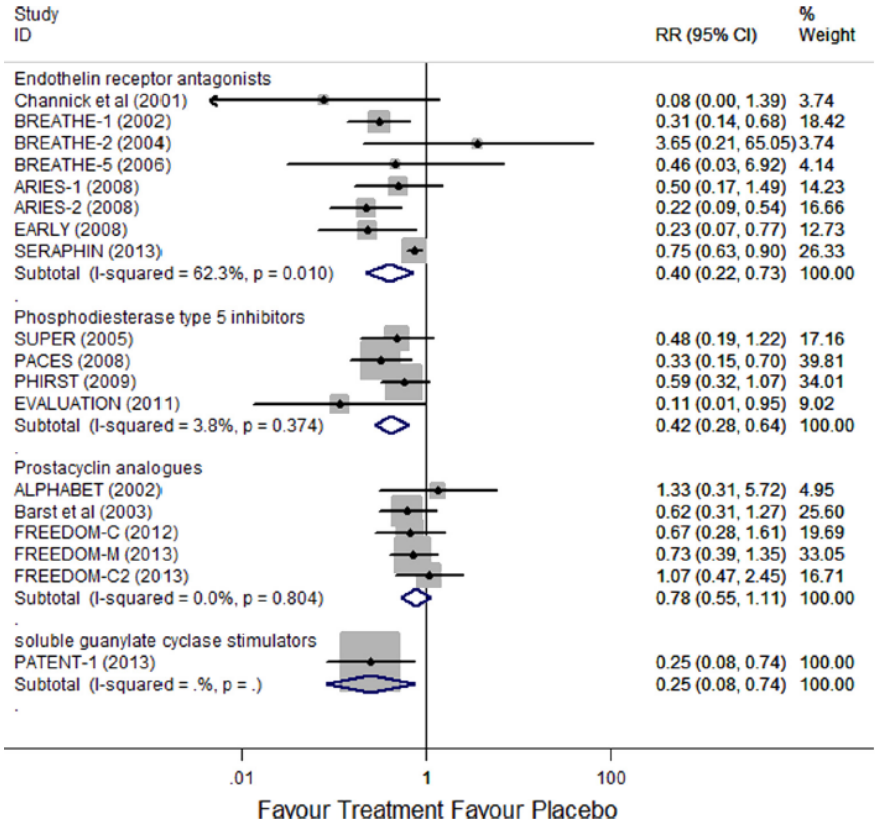
Mortalität

- Statistisch signifikanter Unterschied zugunsten von PDE-5 Hemmern im Vergleich zu Placebo
- Kein statistisch signifikanter Unterschied von ERA oder Prostanoiden
- Keine der 18 Einzelstudien zeigte signifikanten Unterschied



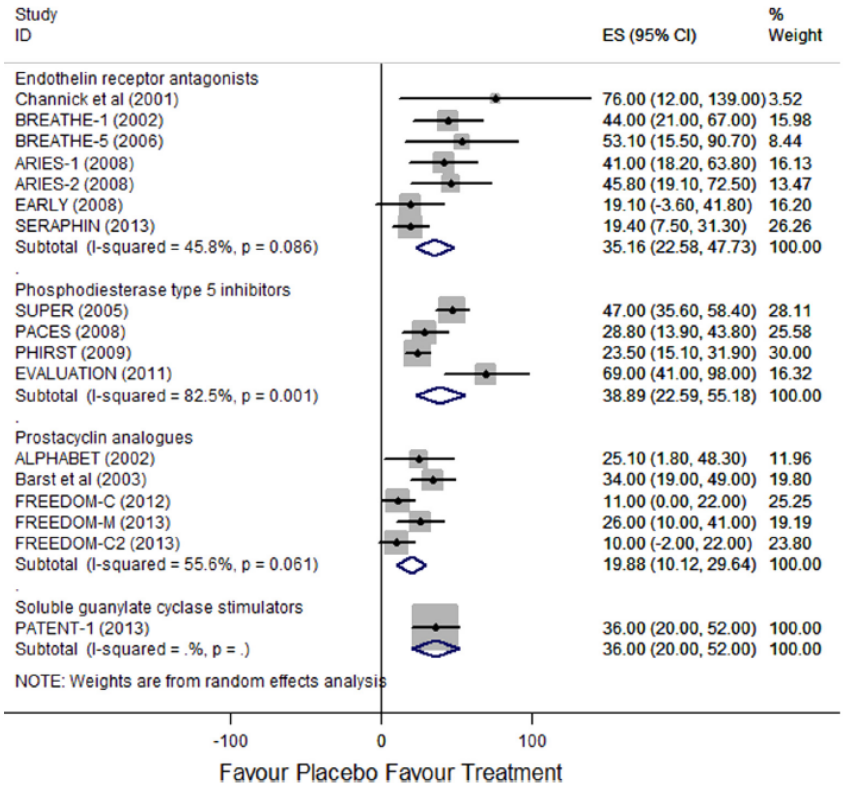
Klinische Verschlechterung

- Statistisch signifikanter Unterschied zugunsten von ERA und PDE-5 Hemmern im Vergleich zu Placebo
- Kein statistisch signifikanter Unterschied von Prostanoiden



6MWD

- Statistisch signifikanter Unterschied zugunsten von PDE-5 Hemmern, ERA und Prostanoiden im Vergleich zu Placebo



Anmerkung/Fazit der Autoren

In this meta-analysis, we included three new oral agents available for PAH treatment in recent years. Our study suggested that phosphodiesterase type 5 inhibitors significantly improved mortality in patients with PAH. Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased the 6-min walk distance. However, oral prostanoids only showed a mild effect on 6-min walk distance, and significantly increased the incidence of withdrawal due to adverse effects.

In this study, we found that PDE-5Is were associated with a statically significant reduction in mortality. However, in a previous meta-analysis, Ryerson et al. did not find any favorable effects of PDE-5Is on survival. This difference may be explained by a larger sample size in our study. We included a new RCT and had a larger number of studies and patients. However, in Coeytaux et al.'s meta-analysis, they analyzed the same data, but got different results. This discrepancy was caused by different model which was adopted in the meta-analysis. In Coeytaux et al.'s study, they used random-effects model to calculate summary estimates. However, we chose the fixed-effect model according to the heterogeneity test (I^2=3.8%; p=0.374). Random-effect model was more inclined to give less significant p values than fixed-effect model and draw a conservative conclusion. Therefore, we got a statistically significant result, while they got a non-significant result. The discrepancy also reflected that the mortality reduction of PDE-5I in this metaanalysis was unstable. This could be explained by small sample size, short duration and few end-point events in the four trials of PDE-5I. We also found that ERAs and oral prostanoids were not associated with a change in mortality. The results are in accordance with previous studies.

Notably, this study suggested that oral prostanoids only showed a mild effect on 6 MWD, and did not have any effect on mortality, clinical worsening, and WHO functional class amelioration. Moreover, they obviously increased the incidence of withdrawal. These results suggested that among the three classes of oral drugs, oral prostanoids might have the weakest therapeutic effects and most adverse effects. Therefore, although FDA has approved beraprost and treprostinil for the treatment of PAH, we think they should be less recommended in clinical practice.

In conclusion, our meta-analysis suggests that all oral agents confer a therapeutic benefit. Of these, only PDE-5Is has a proven survival benefit. ERAs and riociguat are efficient in reducing clinical worsening, and ameliorating exercise capacity. These observations support the use of oral targeted therapies in the treatment of PAH. However, among the four classes of drugs, oral prostanoids should be less recommended as the adverse effects and weak therapeutic effects.

Kommentare zum Review

- Kuwana et al. (2013) untersuchten nur Auswirkungen auf 6MWD und fanden vergleichbare Ergebnisse. Für alle Substanzklassen wurde ein statistisch signifikanter Vorteil gegenüber Placebo aufgezeigt und auch für alle Wirkstoffe innerhalb dieser Substanzklassen, bis auf inhaliertes Iloprost.
- Zusätzlich wurde in dieser Studie die Subgruppe der Patienten mit PAH, die mit Bindegewebserkrankungen assoziiert ist, untersucht. Hier zeigte sich für Sildenafil, Tadalafil, Ambrisentan, Epoprostenol und Beraprost ein statistisch signifikanter Vorteil gegenüber Placebo aber nicht für Bosentan und Treprostinil.

He CJ et al., 2015 [12].

Efficacy and safety of phosphodiesterase type-5 inhibitors for pulmonary arterial hypertension: A meta-analysis focusing on 6MWD

Fragestellung

Wirksamkeit und Sicherheit von PDE-5 Hemmern bei PAH mit Fokus auf 6MWD

Methodik

Population:

- Patienten mit PAH

Intervention:

- PDE-5 Hemmer

Komparator:

- k.A.

Endpunkt:

- 6MWD, NYHA Funktionsklasse, klinische Verschlechterung, Mortalität

Recherche/Suchzeitraum:

- Bis 08/2014

Qualitätsbewertung der Studien:

- We used the Jadad scale modified by Gummesson for assessment of the study quality. The quality scale ranges from 0 to 5 points with a report of score <3 as low quality and report of score ≥4 as high quality.
- Erfassung der Heterogenität: A fixed-effect model was used for consistent studies, whereas a random-effect model was used for heterogeneous studies. Statistic value I^2 was used to quantify the degree of inconsistency with a score of 25, 50, and 75% representing low, moderate, and high levels of inconsistency. $P < 0.05$ was regarded as statistically significant.

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs, 1056 Patienten

Charakteristika der Population:

- 729 patients in the PDE-5 inhibitors treatment group and 327 patients in the placebo group. The mean follow-up duration ranged from 6 weeks to 16 weeks. The majority etiology was idiopathic PAH or associated PAH. Iversen's study only enrolled Eisenmenger syndrome (ES) patients, and half participants in Singh's studies were ES patients, others were idiopathic PAH. All six studies predominantly included NYHA class II or III patients.

Table 1
The baseline characteristics and Jadad score of six studies included in meta-analysis.

Study/publish year	Sample size (n)	Etiology (%)	Mean age (y)	Female (%)	NYHA II/III/IV (%)	Treatment group	Control group	Follow-up duration (weeks)	Jadad score
Singh 2006	20	IPAH(50) PAH-ES(50)	25	75	40/55/5	Sildinafil 100 mg tid	placebo	6	4
Iversen 2010	21	PAH-ES(100)	42	67	43/48/5	Sildinafil 50 mg tid	placebo + bosentan	12	4
Galiè 2005	278	IPAH(63), APAH(37)	49	75	27/58/3	Sildinafil20 mg, 40 mg,80 mg tid	placebo	12	5
Simonneau 2008	267	IPAH(79), APAH(21)	48	80	25/66/6	Sildinafil 80 mg tid	placebo + epoprostenol	16	5
Galiè2009	405	IPAH(61), APAH(39)	54	78	32/65/3	Tadalafil2.5 mg,10 mg, 20 mg, 40 mg qd	Placebo + bosentan	16	5
Jing 2011	66	IPAH(59), APAH(29)	31	80	45/54/0	Vardenafil 5 mg bid	placebo	12	4

Qualität der Studien:

- all six articles were of high quality according to four criteria: randomization, concealment of allocation, double blinding, withdrawal and dropouts

Studienergebnisse:

- 6MWD (6 RCTs): Statistisch signifikante Verbesserung gegenüber Placebo in 5 von 6 Studien. Mittlere Verbesserung von 40,17 Metern (95% KI: 22,56 bis 57,78; p<0,0001, I^2=74%)

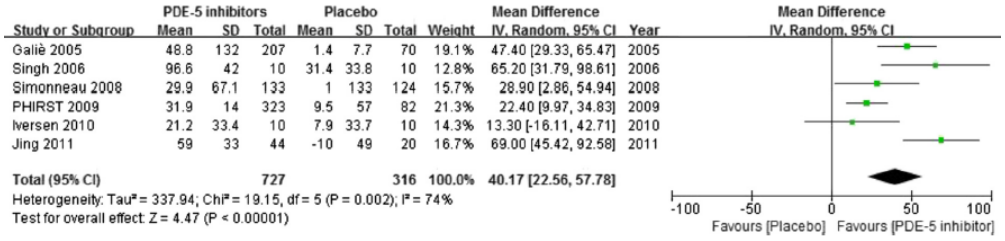


Fig. 2. Mean change from baseline in 6MWD for PDE-5 inhibitors versus placebo.

Subgruppenanalyse bezüglich Monotherapie und Kombinationstherapie zeigte bessere Ergebnisse für Patienten mit Monotherapie (Verbesserung um 49 Meter) im Vergleich zu Patienten, die zusätzlich Bosentan oder Epoprostenol erhielten (Verbesserung um 22 Meter).

- Gesamtmortalität (4 RCTs, 1016 Patienten): kein stat. signifikanter Unterschied.
- Klinische Verschlechterung (4 RCTs, 853 Patienten): stat. signifikanter Unterschied zugunsten PDE-5 Hemmern (OR=0,34, 95% KI: 0,21 bis 0,56; p<0,0001; I^2=0%)

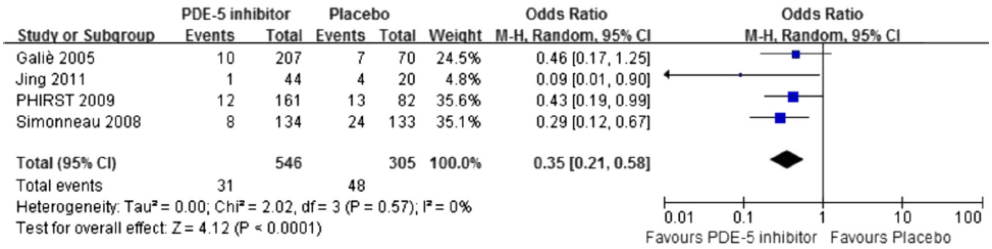


Fig. 6. Incidence of clinical worsening for PDE-5 inhibitor versus placebo.

Anmerkung/Fazit der Autoren

In conclusion, PDE-5 inhibitors improve 6MWD, clinical symptoms, hemodynamic parameters and have a tendency of survival benefits of patients with PAH. As for monotherapy, it can substantially increase 6MWD compared with combination therapy. Further large, well-designed randomized controlled trials focusing on long-term efficacy is necessary.

Rival G et al., 2014 [21].

Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review.

Fragestellung

Auswirkungen verschiedener PAH-spezifischer Therapien auf die gesundheitsbezogene Lebensqualität

Methodik

Population:

- erwachsene Patienten mit PAH

Intervention:

- PAH-spezifische Therapie

Komparator:

- Placebo

Endpunkt:

- gesundheitsbezogene Lebensqualität (HRQoL)

Recherche/Suchzeitraum:

- 1990-2013

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 Studien (RCTs)
- The generic Medical Outcomes Study 36-item Short Form (SF-36) questionnaire was most commonly used either alone (n=7) or in combination with the EuroQol 5D (EQ-5D) (n=2). Other instruments included the Medical Outcomes Study 12-item Short Form (SF-12) (n=1), the Nottingham Health Profile 35 (NHP) (n=1), the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (n=4), the Living with Pulmonary Hypertension Questionnaire (LPHQ) (n=1), and the Chronic Heart Failure Questionnaire (CHFQ) (n=2).

Qualität der Studien:

- Alle Studien hatten ein geringes Bias Risiko

Studienergebnisse:

- ERAs: HRQoL assessed using the SF-36 questionnaire was a secondary endpoint in five RCTs evaluating endothelin receptor antagonists. Significant improvements in the physical functioning scale were observed at 12 weeks for combined ambrisentan doses (2.5 and 5 mg) in the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, double-Blind, Placebo-Controlled, Multicenter, Efficacy Study (ARIES)-2. In ARIES-1, similar trends were reported without statistical significance. Conversely, none of the eight domains of SF-36 was

significantly improved in patients with World Health Organization functional class II PAH treated with bosentan in the Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY). Nonetheless, 57% of patients treated with bosentan improved their SF-36 health transition index at 24 weeks compared with 38% of patients on placebo (P=.02). In the Study With and Endothelin Receptor Antagonist in Pulmonary Hypertension to Improve Clinical Outcome (SERAPHIN), both doses of macitentan (3 mg and 10 mg) improved the physical and mental component scores at 6 months, as well as seven out of eight domains of the SF-36 questionnaires. 28 Macitentan also significantly delayed time to first occurrence of a five point or more decrease in the physical score component (hazard ratio [HR], 0.70; 95% CI, 0.54-0.92; P 5 .008; and HR, 0.65; 95% CI, 0.50-0.85; P 5 .001 for the 3-mg and 10-mg doses, respectively), whereas it tended to delay the occurrence of a ≥ 5-point decrease in the mental score (HR, 0.81; 95% CI, 0.63-1.03; P 5 .085; and HR, 0.79; 95% CI, 0.61-1.01; P 5 .053 for the 3-mg and 10-mg doses, respectively). Thus, except for macitentan, the effect of endothelin receptor antagonists on HRQoL remains largely unknown.

- PDE-5 Hemmer: In their crossover trial, Sastry et al documented significant improvement in dyspnea and fatigue as well as a trend for an improved emotional function assessed by the CHFQ during the 6-week treatment with sildenafil. The effect of sildenafil on HRQoL was further evaluated in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-1 study, in which improvements in physical functioning, general health, and vitality domains of the SF-36 were observed at 12 weeks when the 20-, 40-, and 80-mg doses were pooled. Statistically significant improvements were also seen in the EQ-5D utility index score. In the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) trial, tadalafil 40 mg was associated with statistically significant improvements in six of the eight domains of the SF-36 questionnaire and all sections of EQ-5D. Improvements in the US and UK population based EQ-5D utility index scores were significant in all tadalafil treatment groups, with the largest improvement seen with tadalafil 40 mg. However, a significant improvement on the EQ-5D current health state score was found only for tadalafil 40 mg (P<.05; effect size, 0.35). More recently, the EQ-5D score did not differ significantly between riociguat and the placebo group, whereas exploratory analyses suggested improvements in HRQoL assessed using the LPHQ. Hence, phosphodiesterase type 5 inhibitors consistently showed improvements in HRQoL measures.
- Prostanoide: Barst et al first showed that the four domains of the CHFQ and two of the six dimensions of the NHP were improved by IV epoprostenol. Inhaled iloprost was also associated with significant improvement on the EQ-5D visual-analog scale, whereas no changes were observed for the mean EQ-5D health state or the SF-12. Subcutaneous treprostinil was associated with significant improvement in the physical dimension score of the MLHFQ, and subgroup analysis suggested this improvement was of similar magnitude in PAH associated with connective tissue disease (P=.075). Consequently, IV epoprostenol, subcutaneous treprostinil, and inhaled iloprost have been associated with statistically significant changes in HRQoL.
- Kombinationstherapie: In the Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES)-1, positive changes were observed in patients randomized to sildenafil in addition to epoprostenol in six of eight domains of SF-36 compared with Epoprostenol alone. Similarly, in the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study, the addition of inhaled treprostinil over concomitant bosentan or sildenafil resulted in improved global and physical scores of the MLHFQ.

Anmerkung/Fazit der Autoren

Most recent RCTs evaluating the efficacy of PAH specific therapies used HRQoL as a secondary endpoint and demonstrated statistically significant improvements, especially in the physical domains of generic instruments. These improvements were generally smaller than the MID previously reported in PAH. Moreover, many pivotal trials did not assess HRQoL. More commonly, HRQoL results were only minimally detailed. Therefore, it remains difficult to draw any firm conclusion about the effects of current PAH-specific therapies on HRQoL. Further work is thus mandatory to validate PAH-specific questionnaires that are responsive to clinical changes as well as to determine their interpretability.

Wang RC et al., 2014 [23].

Efficacy and safety of sildenafil treatment in pulmonary arterial hypertension: a systematic review

Fragestellung

Wirksamkeit und Sicherheit von Sildenafil

Methodik

Population:

- erwachsene Patienten mit PAH

Intervention:

- Sildenafil

Komparator:

- Placebo oder Vasodilatatoren

Endpunkt:

- klinische Verschlechterung (death, hospitalization, symptomatic deterioration, lack of improvement and the need for treatment escalation, for example, additional drugs, or lung transplantation), 6MWD, Mortalität, WHO Funktionsklasse, HRQoL, Borg Skala, Sicherheit

Recherche/Suchzeitraum:

- bis 2013

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 Studien (RCTs), 545 Patienten

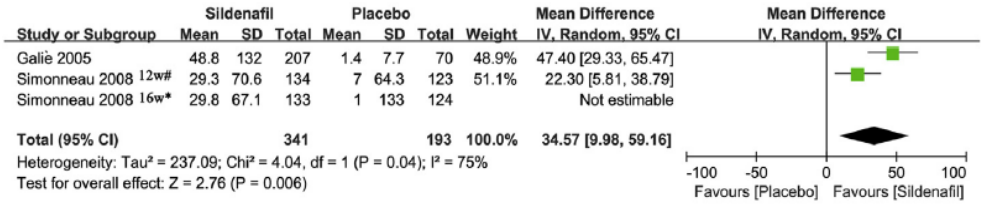
Qualität der Studien:

- Die Studien wiesen ein geringes Bias Risiko auf

Studienergebnisse:

- Klinische Verschlechterung: statistisch signifikanter Unterschied zugunsten von Sildenafil gegenüber Placebo (siehe Abbildung).

- Mortalität: kein statistisch signifikanter Unterschied.
- 6MWD: statistisch signifikanter Unterschied zugunsten von Sildenafil gegenüber Placebo (siehe Abbildung).



- WHO-Funktionsklasse (1 Studie): statistisch signifikanter Unterschied zugunsten von Sildenafil gegenüber Placebo. *Placebo-corrected difference of 21% (95% CI 9%-33%, P=0.003).*
- HRQoL basierend auf SF-36 (2Studien): Subgroup analysis indicated that the sildenafil group showed greater adjusted improvement from baseline than did the placebo group in the domains of physical functioning (MD 8.76, 95% CI 4.81 to 12.80; I^2=0%; P=0.78), general health (MD 7.84, 95% CI 4.55 to 11.12; I^2 =0%; P=0.93), vitality (MD 8.76, 95% CI 3.80 to 11.53; I^2=0%; P=0.42), social heath (MD 7.15, 95% CI 2.15 to 11.56; I^2=0%; P=0.83), and mental health (MD 5.38, 95% CI 2.05 to 8.72; I^2=0%; P= 0.43). The sildenafil and placebo groups did not differ significantly in bodily pain (MD 3.54, 95% CI 1.13 to 8.22; I^2=0%; P Z 0.52).
- Sicherheit: Two studies reported information on serious adverse events and total adverse events. In one trial, 68 serious adverse events occurred among 267 patients, but among them, only 2 in the placebo group and 3 in the sildenafil group were considered to be treatment-related. A total of 138 treatment-related adverse events were reported by 61 patients (47%) in the placebo group, significantly fewer than the 290 reported by 92 patients (69%) in the sildenafil group (difference of 22%, 95% CI 11%e34%). Most adverse events were mild or moderate in nature. In another trial, 42 of 278 patients (15%) reported 68 serious adverse events, of which only 2 were considered to be related to sildenafil. Most adverse events in either treatment group were of mild or moderate severity. Many of the adverse events were attributed to the vasodilatory effect of sildenafil; these events included headache, flushing, body pain (back, extremity pain or myalgia) and blurred vision.

Anmerkung/Fazit der Autoren

The present study suggests that sildenafil therapy for 12-16 weeks significantly reduces the likelihood of clinical worsening and improves 6MWD, WHO FC, HRQoL, mPAP, PVR, and cardiac index. However, the drug was associated with similar mortality, incidence of serious adverse events, and Borg dyspnea scores as placebo. Although sildenafil was associated with a larger number of total adverse events than was placebo, most of these additional events were mild or moderate in intensity. Our study suggests that sildenafil therapy over 12-16 weeks is effective in improving the symptoms of PAH and delaying disease progression in adults. These

findings should be verified in large, well-designed RCTs, which should also aim to determine optimal therapeutic doses.

Zhang HD et al., 2015 [24].

Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: A systematic review and meta-analysis

Fragestellung

Wirksamkeit oraler Arzneimitteltherapie bei Patienten mit PAH

Methodik

Population:

- erwachsene Patienten mit PAH

Intervention:

- orale Arzneimittel

Komparator:

- Placebo

Endpunkt:

- klinische Verschlechterung (included all-cause mortality, lung or heart-lung transplantation, hospitalization for PAH, and escalation of treatment), Gesamtmortalität, 6MWD, hämodynamische Werte

Recherche/Suchzeitraum:

- bis 04/2014

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool
- Heterogenität: The meta-analysis was performed using a fixed-effects model when there was no significant heterogeneity. In other situations, the DerSimonian-Laird random-effects model was used. For dichotomous outcomes, the Mantel and Haenszel or Peto method was used in the fixed-effects model.

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 RCTs, 5.105 Patienten

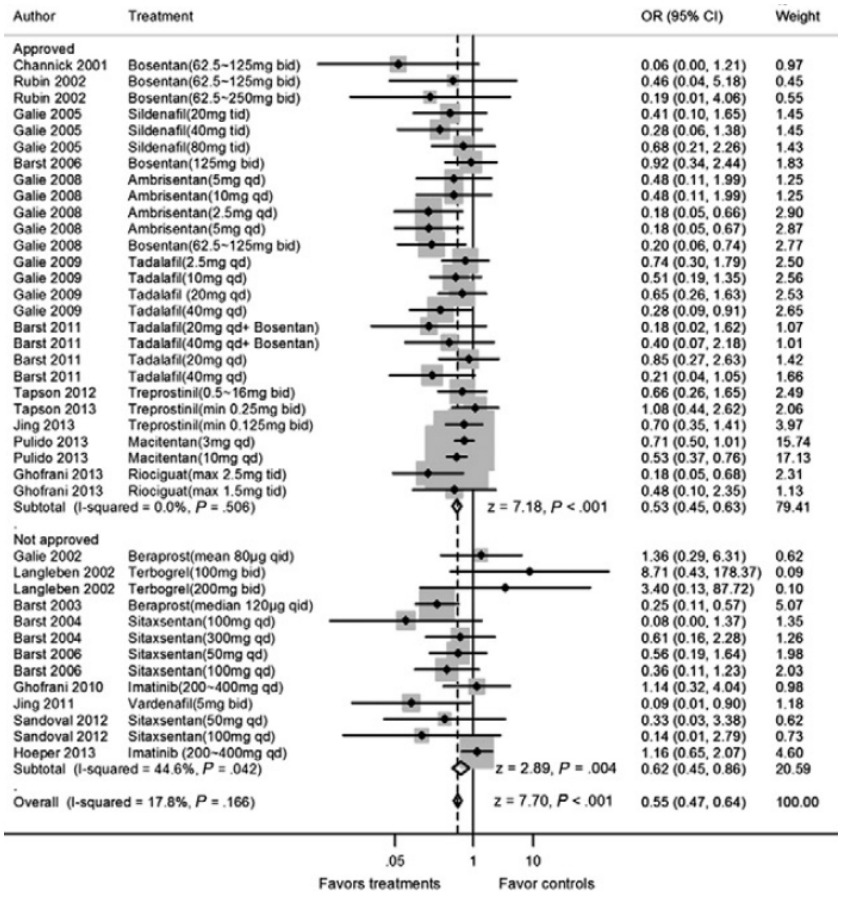
Qualität der Studien:

Author, year (reference)	Bias types: Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel and outcome assessors (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other potential bias
Channick et al, 2001[3]	Low	Unclear	Low	Low	Low	Unclear
Galiè et al, 2002[4]	Unclear	Unclear	Low	Low	Low	Unclear
Rubin et al, 2002[5]	Unclear	Unclear	Low	Low	Low	Unclear
Langleben et al, 2002[6]	Unclear	Unclear	Low	High	High	High
Barst et al, 2003[7]	Unclear	Unclear	Low	Low	Low	High
Barst et al, 2004[8]	Low	Low	Low	Low	Low	Low
Galiè et al, 2005[9]	Unclear	Low	Low	Low	Low	Unclear
Barst et al, 2006[10]	Low	High	Low	Low	Low	High
Galiè et al, 2008[11]	Unclear	Low	Low	Low	Low	Unclear
Galiè et al, 2008[12]	Low	Low	Low	Low	Low	Low
Galiè et al, 2009[13]	Unclear	Unclear	Low	Low	Low	Unclear
Ghofrani et al, 2010[14]	Unclear	Unclear	Low	High	Low	High
Jing et al, 2011[15]	Low	Unclear	Low	Low	Low	Unclear
Barst et al, 2011[16]	Unclear	Unclear	Low	Low	Low	Unclear
Tapson et al, 2012[17]	Unclear	Unclear	Low	Unclear	Low	Unclear
Sandoval et al, 2012[18]	Unclear	Unclear	Low	Low	Low	Unclear
Tapson et al, 2013[19]	Unclear	Unclear	Low	Low	Low	Unclear
Hoeper et al, 2013[20]	Low	Low	Low	High	Low	High
Jing et al, 2013[21]	Unclear	Unclear	Low	Low	Low	Unclear
Pulido et al, 2013[22]	Unclear	Unclear	Low	Low	Low	Unclear
Ghofrani et al, 2013[23]	Low	Low	Low	Low	Low	Low

Studienergebnisse:

- Klinische Verschlechterung (21 RCTs): Stat. signifikanter Vorteil zugunsten der oralen Therapie im Vergleich zu Placebo (OR 0.55, 95% CI 0.47-0.64, P<.001, heterogeneity P=.166).

  Der Effekt in der Sensitivitätsanalyse zur klinischen Verschlechterung (nur von der FDA zur Therapie der PAH zugelassene Arzneimittel) war vergleichbar mit der Gesamtauswertung aller AM.



- Mortalität: kein stat. signifikanter Unterschied, weder in Einzelstudien noch gepoolt, noch in der Subgruppenanalyse mit ausschließlich zugelassenen AM.

Anmerkung/Fazit der Autoren

The use of oral drugswas associated with a 45% reduction in OR of CCW events in the entire population, which was not statistically dependent on trial characteristics. Our analysis showed no sufficient efficacy on reduce mortality with oral active treatments (P = .192).

Although in a meta-analysis of 23 RCTs by Galiè et al, active treatments were associated with a 43% reduction in mortality (P = .023). This former analysis of active treatment strategies included 4 trials of epoprostenol, 2 of inhaled iloprost, and 1 of subcutaneous treprostenil.

It can be postulated that oral treatments benefited patients in WHO-FC I, II, or III with mild-to-moderate symptoms, whereas for patients in WHO-FC III with severe symptoms or in WHO-FC IV, a change in therapy or combined therapy with inhaled, subcutaneous, or intravenous prostanoids may be required.

In the cumulative analysis, our results showed that new drugs including oral treprostinil, macitentan, and riociguat may exhibit favorable effects by stabilizing the reduction in CCW events and by lowering all-cause mortality.

Chen X et al., 2018 [3].

Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: A systemic review and meta-analysis

Fragestellung

to evaluate the efficacy and safety of bosentan for both PAH and CTEPH.

Methodik

Population:

- patients with unspecified type of pulmonary hypertension or other type of pulmonary hypertension; or (2) they were performed in infants.

Intervention/ Komparator:

- Bosentan (alone or as add on) with placebo in patients with either PAH or CTEPH

Endpunkte:

- Efficacy: 6-minute walk distance (6MWD); (2) hemodynamic parameters; (3) cardiac FC; and (4) clinical worsening
- Safety: (1) liver function abnormality, (2) all-cause mortality, and 3 adverse events and serious adverse events

Recherche/Suchzeitraum:

- A systemic search of relevant RCTs was performed through major biomedical databases, including PubMed, EMBASE, Cochrane Library, and Chinese BioMedical Literature Database (from their inception to June 30, 2017).

Qualitätsbewertung der Studien:

- The methodological quality was evaluated for the risk of bias independently by 2 authors (Wan and Xie) according to Cochrane Handbook for Systematic Reviews of Interventions

Ergebnisse

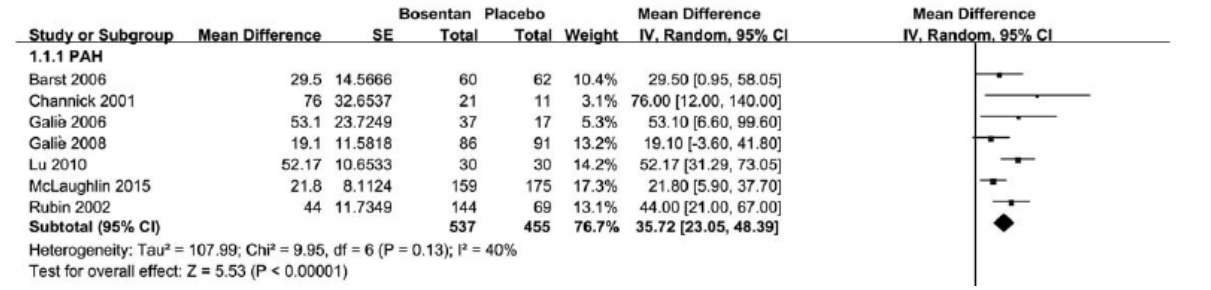
Anzahl eingeschlossener Studien:

Eight studies were conducted in PAH patients (n=1003) of which 536 were on bosentan-treated group and 467 on placebo-controlled group

Studienergebnisse:

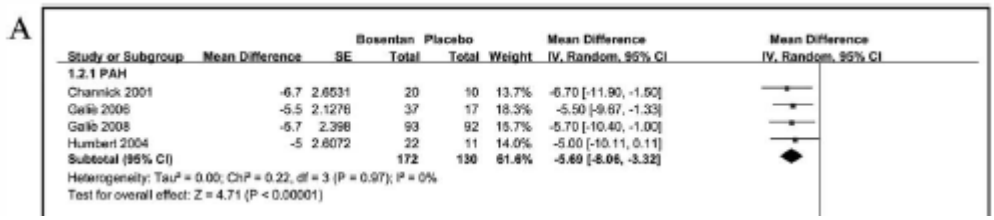
- For PAH patients, bosentan prolonged 6-minute walk distance with a weighted mean difference of 35.7 m, reduced mean pulmonary arterial pressure by 5.7 mm Hg, increased cardiac index by 0.4 L/min/m2, reduced pulmonary vascular resistance by 305.1 dyn us/cm5, prevented functional class from deterioration and reduced clinical worsening as compared with placebo.

Meta-analysis results of bosentan on 6-minute walk distance as compared with placebo

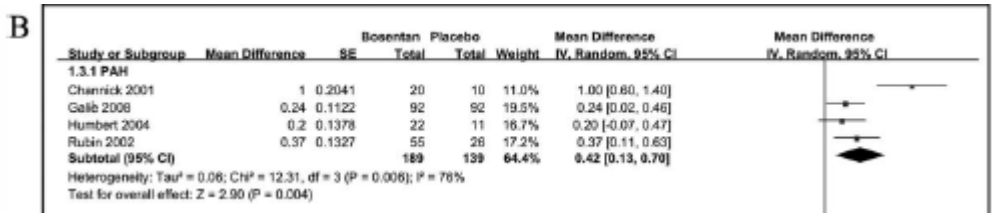


Meta-analysis results of bosentan on hemodynamics as compared with placebo.

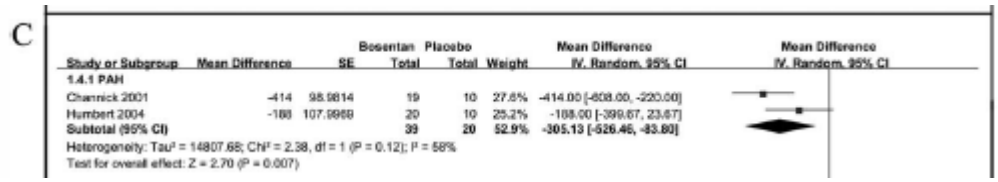
A: Mean pulmonary mPAP



B: CI



C: PVR



Anmerkung/Fazit der Autoren

Our study shows that bosentan effectively improves exercise capacity and hemodynamics of PAH patients, and prevents exacerbation. While for CTEPH, apart from certain hemodynamic parameters amelioration, bosentan does not improve symptoms or prevent deterioration. Oral bosentan is relatively safe and well tolerated, but could raise the risk of abnormal liver function.

Fox BD et al., 2016 [5].

Combination Therapy for Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis

Fragestellung

to perform an updated metaanalysis.

Methodik

Population:

- PAH (class I)

Intervention/Komparator:

- CT or MT with pulmonary vasodilators in a parallel group design or to an MT vs placebo trial in which some participants were enrolled having received previous MT

Endpunkt:

clinical events, 6MW, and cardiac index

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Cochrane Database, and clinicaltrials.gov; we also manually searched review articles and conference abstracts from 1980-December 2015.

Qualitätsbewertung der Studien:

- Cochrane method

Ergebnisse

Anzahl eingeschlossener Studien:

- We extracted data from 18 randomized controlled trials (RCTs) (N = 4162).

Qualität der Studien:

Table 1. Study characteristics

Study	Year	Follow-up	Baseline therapy	Active therapy arm	Risk of bias*
BREATHE-2[21]	2004	16 wk	Epoprostenol IV	Bosentan 125 mg bid	Unclear
COMBI[22]	2006	12 wk	Bosentan po	Inhalational iloprost 5 µg q6d	Low
STEP[23]	2006	12 wk	Bosentan po	Inhalational iloprost 5 µg q6d-q9d	Low
PACES[7]	2008	16 wk	Epoprostenol IV	Sildenafil 20-80 mg tid	Low
TRIUMPH-1[24]	2010	12 wk	Bosentan (70%) or sildenafil (30%)	Inhalational treprostinil 18-54 µg qid	Medium
PHIRST-1b[18]	2011	16 wk	Bosentan	Tadalafil 40 mg qd	Low
FREEDOM-C[25]	2012	16 wk	PDE5I (25%); ERA (30%); both (44%)	Oral treprostinil 0.5-16 mg bid	Medium
SELEXIPAG-II[26]	2012	17 wk	PDE5I (28%); ERA (37%); both (35%)	Selexipag 200-800 µg bid	Low
FREEDOM-C2[27]	2013	16 wk	PDE5I (42%); ERA (37%); both (40%)	Oral treprostinil 0.25+ mg bid	Unclear
PATENT-1[28,†]	2013	12 wk	ERA (44%); prostacyclin (6%)	Riociguat 2.5 mg tid	Low
SERAPHIN[29,†]	2013	85-104 wk	PDE5I (61%); prostacyclin (4%)	Macitentan 10 mg qd	Low
ZHUANG[30]	2014	16 wk	Ambrisentan	Tadalafil 10 mg qid	Low
COMPASS-2[31]	2015	16 wk	Sildenadil	Bosentan 125 mg bid	Low
AMBITION[32]	2015	517 d	Ambrisentan 10 mg qid (25%); tadalafil 40 mg qid (25%)	Combined ambrisentan/tadalafil	Low
GRIPHON[33,†]	2015	63-71 wk	PDE5I (32%); ERA (15%); PDE5I and ERA (32%)	Selexipag 200-1600 µg bid	Low
SR-PAAS[34]	Unpub	12 wk	Sitaxsentan	Sildenafil 20 mg tid	Unclear
VISION[35]	Unpub	16 wk	Sildenafil ± bosentan	Inhalational iloprost 5 µg q4-6d	Unclear
PFIZER[36]	Unpub	12 wk	Bosentan	Sildenafil	Unclear

Studienergebnisse:

- CT was associated with a significant 38% reduction of risk of CCW (15 RCTs: n = 3906; risk ratio [RR], 0.62; 95% confidence interval [CI], 0.50-0.77). This reduction in risk was driven by a reduction in nonfatal endpoints (12 RCTs: n= 2611; RR, 0.56; 95% CI, 0.40-0.78) and not by a reduction of mortality (12 RCTs: n = 2717; RR, 0.79; 95% CI, 0.53-1.17).
- CT was also associated with improvement in 6-minute walking distance (10 RCTs: n = 1553; weighted mean difference [WMD], þ23.0 m; 95% CI, 15.9-30.1), improved functional class (9 RCTs: n = 1737; RR, 1.26; 95% CI, 1.05-1.51), and beneficial effects on pulmonary hemodynamics such as cardiac index (WMD: 0.35 L/min/m; 95% CI, 0.14-0.56).

Anmerkung/Fazit der Autoren

We performed a comprehensive meta-analysis on the sum total of PAH CT trials over more than a decade of clinical trials. CT definitively reduces CCW endpoints, driven by a significant reduction in nonfatal end points. Mortality was not significantly reduced. CT also improved pulmonary hemodynamics, exercise capacity, and functional class. CT should be tailored to individual patients according to the guidelines and the judgement of an expert PAH physician.

Jain S et al., 2017 [15].

Comparative Effectiveness of Pharmacologic Interventions for Pulmonary Arterial Hypertension A Systematic Review and Network Meta-Analysis

Fragestellung

to examine comparative efficacy and tolerability of pharmacologic interventions for pulmonary arterial hypertension (PAH)

Methodik

Population:

- Patients were primarily adults with symptomatic PAH (group 1 pulmonary hypertension).

Intervention:

- all FDA-approved drugs specifically for PAH, including ERA (bosentan, ambrisentan, macitentan), PDE5i (sildenafil, tadalafil), oral/inhaled (PO/INH) prostanoids (treprostinil, iloprost), IV/subcutaneous (SC) prostanoids (epoprostenol, treprostinil), the soluble guanylate cyclase simulator riociguat, and the selective prostacyclin-receptor agonist selexipag, alone or in combination, administered for 8 weeks or longer

Komparator:

- another active agent, placebo, or conventional therapy

Endpunkt:

- clinical worsening, hospitalization, mortality, and improvement in functional class or 6-min walk distance [6MWD])

Recherche/Suchzeitraum:

- MEDLINE, the Cochrane Register, EMBASE, CINAHL, and clinicaltrials.gov were searched (January 1, 1990 to March 3, 2016).

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias assessment tool / GRADE framework,

Ergebnisse

Anzahl eingeschlossener Studien:

- Thirty-one RCTs with 6,565 patients were selected.

Charakteristika der Population:

- Across studies, a majority of patients were in NYHA/WHO functional classes III (median, 70%; range, 33%-100%) and II (median, 24%; range, 0%-67%).

Qualität der Studien:

- Risk of Bias: Most studies reported adequate randomization and allocation concealment. Six RCTs reported inadequate blinding of participants and personnel or outcome assessment. Overall, most studies had a low to moderate risk of bias.
- GRADE: Placebo comparisons were rated down for indirectness due to differences in study population (background therapy and PAH subtypes) as well as the definition of outcomes (for clinical worsening). Head-to-head comparisons were further downgraded for indirectness and imprecision due to limited head-to-head trials and wide CIs, respectively. Moderate-quality evidence supported the use of ERA, PDE5i, their combination, riociguat, and selexipag for reducing clinical worsening in PAH. The combination of ERA þ PDE5i was supported by high quality and moderate-quality evidence in the comparison against monotherapy with ERA and PDE5i, respectively. Other head-to-head comparisons were supported by lowto very low-quality evidence. For the functional class outcome, moderate-quality evidence supported ERA, ERA þ PDE5i, IV/SC prostanoids, and selexipag in improving functional class over placebo, whereas low quality evidence supported the use of PDE5i and riociguat. In head-to-head comparisons, most agents were supported by only low-quality evidence.

Studienergebnisse:

Network meta-analysis

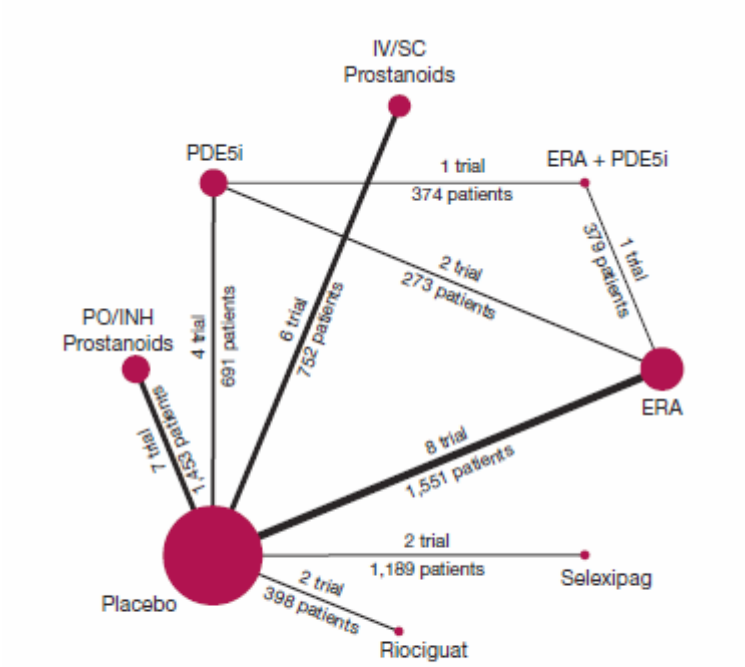


Figure 2 – *Network diagram of all available direct comparisons. e-Figures 1, A-F include network diagrams for each individual outcome. ERA = endothelin receptor antagonist; INH = inhaled; PDE5i = phosphodiesterase-5 inhibitor; PO = orally.*

- When compared with a median placebo rate of 14.5%, clinical worsening was estimated at 2.8% with riociguat (risk ratio [RR], 0.19; 95% CI, 0.05-0.76); at 3.9% with ERA + PDE5i (RR, 0.27; 95% CI, 0.14-0.52), and at 5.7% with PDE5i (RR, 0.39; 95% CI, 0.24-0.62).
- For improvement in functional status, when compared with 16.2% in the placebo group, improvement in at least one New York Heart Association/World Health Organization (NYHA/WHO) functional class was estimated at 81.8% with IV/SC prostanoids (RR, 5.06; 95% CI, 2.3211.04), at 28.3% with ERA þ PDE5i (RR, 1.75; 95% CI, 1.05-2.92), and at 25.2% with ERA (RR, 1.56; 95% CI, 1.22-2.00).
- Differences in mortality were not significant.
- Adverse events leading to discontinuation of therapy were highest with the PO/INH prostanoids (RR, 2.92; 95% CI, 1.68-5.06) and selexipag (RR, 2.06; 95% CI, 1.04-3.88) compared with placebo.

Anmerkung/Fazit der Autoren

Among oral agents, ERA, PDE5i, and their combination are associated with improvement in patient morbidity (both clinical worsening and hospitalization) and functional status. Other approved agents are associated with improvement in different measures of efficacy, and selection of an agent may be guided by the most desired outcome for each particular patient. Our findings are limited by few head-to-head trials and differences in reporting across trials. We therefore emphasize the need for future studies focusing on head-to-head comparisons with uniform enrollment and outcome assessment to improve comparability and produce higher-quality evidence that informs clinical decision-making.

Kuang HY et al., 2018 [16].

The efficiency of endothelin receptor antagonist bosentan for pulmonary arterial hypertension associated with congenital heart disease. A systematic review and meta-analysis

Siehe auch Guo L et al., 2014 [11]

Fragestellung

systemic review and meta-analysis was conducted for a therapeutic evaluation of oral bosentan in both adult and pediatric patients with PAH-CHD

Methodik

Population:

- patients were diagnosed with PAH-CHD and monitored not mixed with other causes (including age of <18 years or adults or both)

Intervention:

- a monotherapy of bosentan

Komparator:

- k.A.

Endpunkt:

- Primär: mortality, exercise capacity (6MWD), World Health Organization (WHO) modification of FC, heart rate (HR), Borg dyspnea index scores (BDIs), and the resting oxygen saturation (SpO2)
- Sekundär: cardiopulmonary hemodynamic parameters, mostly like mPAP, PVRi, and PCWP, etc., the morbidity of adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, Medline, the Cochrane Library, and EMBASE were searched for records. The last search was conducted on September 29, 2017.

Qualitätsbewertung der Studien:

- RCTs were assessed using the Cochrane Risk-of-Bias tool / Newcastle-Ottawa Scale for assessing the quality of Case–Control studies and Cohort studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 17 trails were enrolled in the meta-analysis. N= 418/456 participants were treated with oral bosentan for a diagnosis of PAH secondary to CHD.

  Hinweis: 3 studies enrolled the pediatric patients!

Qualität der Studien:

- Almost all articles were evaluated as a high quality, except for 1 study of 5 stars

Studienergebnisse:

Short-term outcomes:

- With a term less than 6 months of bosentan therapy, there existed a significant improvement in 6-minute walk distance (6MWD) (I^2= 53.3%, SMD=1.201; 95%CI=0.696–1.705; P<.01) and the World Health Organization functional class (WHOFC) ((I2=39.1%, SMD=1.332; 95% CI=0.931–1.734; P<.01), but no such differences in Borg dyspnea index scores (BDIs) and the resting oxygen saturation (SpO2).
- Although with a prolonged treatment, not only 6MWD and FC, but also the resting SpO2 and heart rate were changed for a better exercise capability ((I2=44.7%, SMD=-0.139; 95%CI=-0.418–0.140; P=.328).
- Additionally, compared with the basic cardiopulmonary hemodynamics, it showed a statistically significant difference in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance index (PVRi). → Great heterogeneity: After a discussion, meta-analysis could not be employed in these parameters.

Long-term outcomes:

- Stat. significant difference in 6MWD assessment during a long-term (I2=21.5%, SMD=0.697; 95%CI= 0.552–0.872; P<.001).
- Stat. significant improvement in FC (SMD=-1.394, 95%CI=-1.652 to -1.137; P<.001), revealing a statistically significant difference in a decrease of FC evaluation which suggested a great improvement in exercise tolerance.
- Resting SpO2 and HR were also as the symbols of exercise capacity, which was evaluated a lasting efficiency respectively in 8 studies and 4 studies of statistical significance (I^2=15.9%, SMD =0.268, 95%CI=0.065–0.472, P=.01; HR: I2=44.2%, SMD =-0.323, 95%CI=-0.599 to -0.047, P=.022).
- The BDIs were monitored comparing with baseline data in 5 pooled studies, indicating an unobvious decline to baseline condition (I^2=45.1%, SMD=-0.257, 95%CI=-.528–0.014, P=.063).
- For a further hemodynamic changes rather than an acute response, bosentan could significantly lower the parameter in mPAP (I^2=0%, SMD=-0.236, 95%CI= -.458 to -0.014, P=.037), in PVRi (I^2=0%, SMD=-0.423, 95%CI=-0.663 to -0.184, P=.001), but with little change in PCWP (n.s).

Sicherheit:

- In bosentan treatment group, a total of 14 patients was reported with a death endpoint. Although AEs occurred in 43 subjects mentioned in 13 articles, with a greater proportion of edema (25.6%), liver dysfunction (18.6%), headache (14.0%), palpitations (11.6%), chest pain (6.9%), flushing (6.9%), and other AEs (11.6%), which included a throat pain and hypoglycemia each episode.

Comparative outcomes

- A comparative analysis was conducted between short-term and long-term treatment for a quantitative review. Between a short-term and a long-term period, 6MWD was compared in 6 pooled trails with a great heterogeneity (I^2=89.1%).

- After a sensitivity analysis, the study by Apostolopoulou et al was excluded, and it indicated an increase 6MWD not significantly compared with short-term outcomes.
- Although it was identified with a significant decrease in WHO-FC (I^2=0%, SMD=-0.401, 95%CI=-0.677 to 0.125, P=.004).
- The resting SpO2 in a long-term period was showed a higher level than that in a short-term period without statistical difference.
- Meanwhile, after a prolonged treatment of oral bosentan in 3 studies, the scores of BDIs were decreased, but the difference was not significant.

Anmerkung/Fazit der Autoren

Current evidence indicates that bosentan is a safe and effective specific-PAH therapy for PAH-CHD patients. Although this review was conducted without a differentiated analysis in CHD classification. We can conclude that this dual ERA is an effective treatment both in a short-term and a long-term, which suggesting an irreplaceable strategy in PAH with systemic-to-pulmonary shunts.

Kuntz M et al., 2016 [17].

Systematic Review of Randomized Controlled Trials of Endothelin Receptor Antagonists for Pulmonary Arterial Hypertension

Fragestellung

To compare the available evidence from randomized clinical trials for specific outcomes of different endothelin antagonists for the treatment of PAH

Methodik

Population:

- Patients with PAH.

Intervention:

- ERA monotherapy

Komparator:

- Placebo

Endpunkt:

- 6-min walking distance, pulmonary vascular resistance, pulmonary arterial pressure, or WHO functional status

Recherche/Suchzeitraum:

- PubMed and clinicaltrials.gov literature search was conducted for randomized controlled trials of ERAs up to March, 2016

Qualitätsbewertung der Studien:

- points-based system using the Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 15 double-blind, randomized, placebo-controlled published trials and 2 subgroup analyses were obtained

Qualität der Studien:

Table 3 Jadad scale for quality of randomized controlled trials

Study	Randomization (1–2)	Blinding (1–2)	Account of all patients (1–2)	Total Score (0–6)	Jadad Scoring methodology [34]
Channick [4]	2	2	1	5	*Randomization*
BREATHE-1	2	2	1	5	1 point if randomization is mentioned
STRIDE-1	2	2	1	5	1 point if randomization is appropriate (computer-generated random number list, coin toss, or well-shuffled envelopes)
STRIDE-2	2	2	1	5	
BREATHE-5	1	2	1	4	Deduct one point if method of randomization is inappropriate (minimum 0)
EARLY	2	2	1	5	
ARIES-1	2	2	1	5	*Blinding*
ARIES-2	2	2	1	5	1 point if blinding is mentioned
BREATHE-5 ASD subanalysis	1	2	1	4	1 point if the method of blinding is appropriate (identical tablets or injectables, identical vials)
BREATHE-5 Subanalysis: VSD/ ASD + VSD	1	2	1	4	Deduct 1 point if the method of blinding is inappropriate (minimum 0)
					Account of all patients
ASSET-1	2	2	1	5	1 point if the fate of all patients is known
Mohamed [15]: PPHN	2	2	1	5	*Total score*
Sandoval [16]	1	2	1	4	*1–2 poor*
SERAPHIN	2	2	1	5	*3–4 fair*
Surie et al. [38]	1	1	1	3	*5–6 good*

Studienergebnisse:

- A constant decrease in pulmonary vascular resistance and pulmonary arterial pressure was globally reported among the different studies, resulting in increased 6-min walking distance and functional status compared to placebo (siehe Abbildungen; keine gepoolten Ergebnisse!)

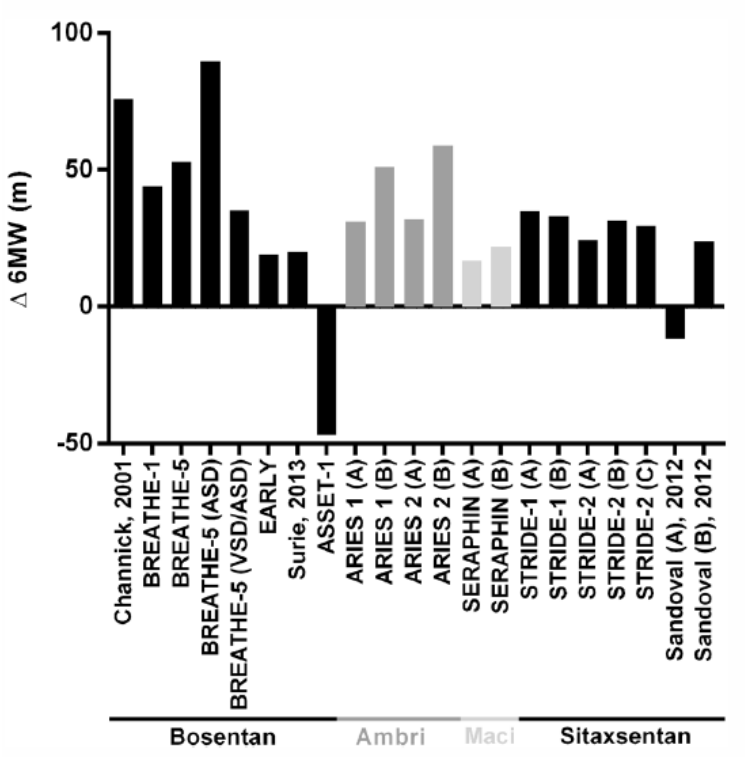


Fig. 2 Treatment effects for 6 MWD. Treatment effects are plotted as absolute differences in improvements in 6 MWD (meters) between ERA and placebo

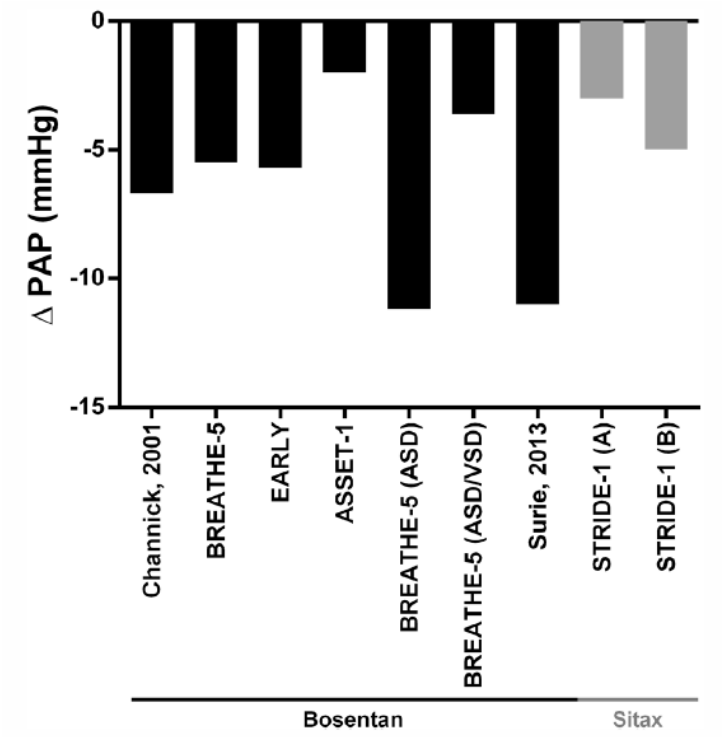


Fig. 3 Treatment effect for pulmonary vascular resistance (PVR). Treatment effects are plotted as absolute differences (dyn s/cm^5) between improvements for ERA and placebo

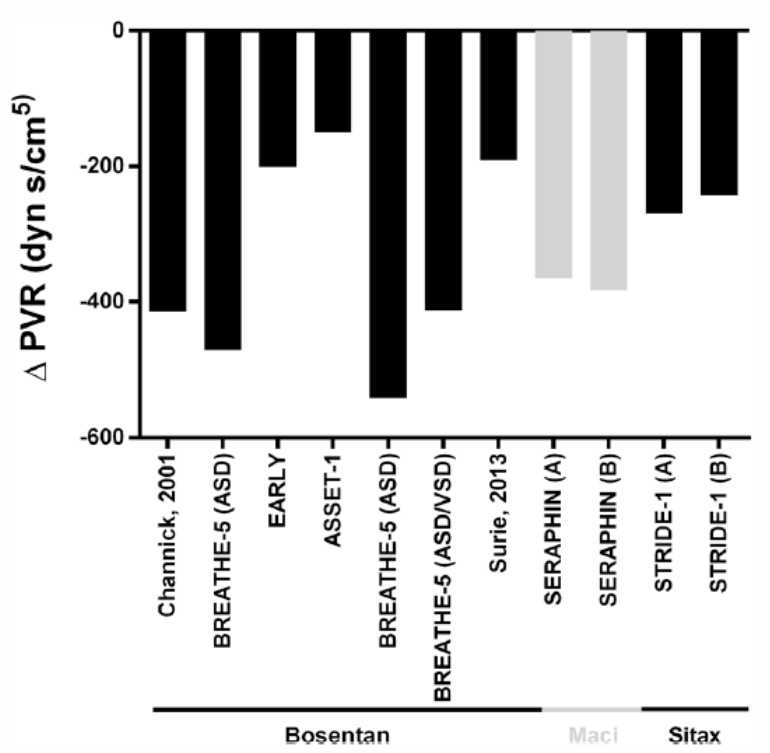


Fig. 4 Treatment effect for pulmonary artery pressure (PAP). Treatment effects are plotted as absolute differences (mm Hg) between improvements for ERA and placebo

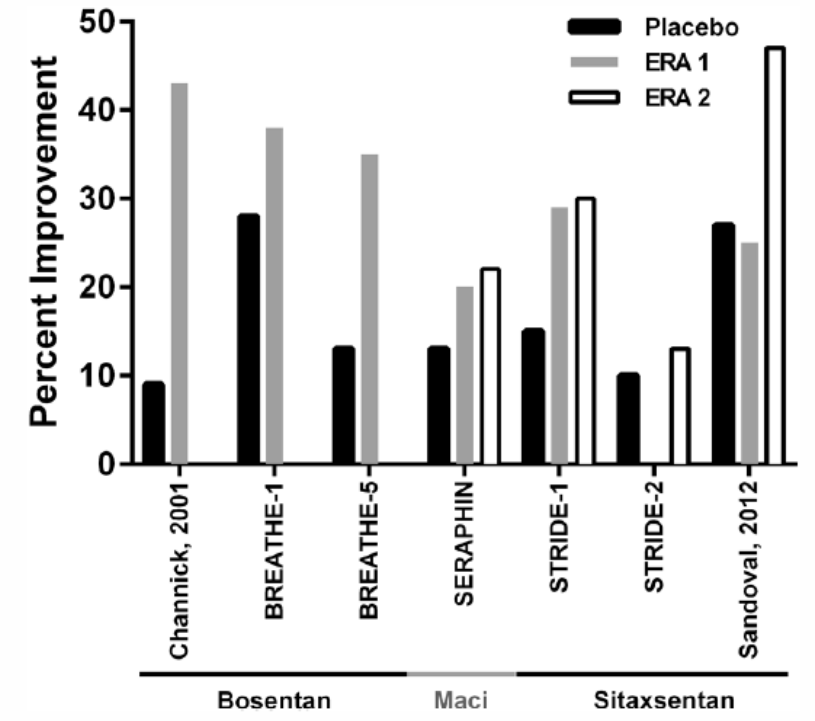


Fig. 5 Percent of patients showing improvement in functional class over the course of a study

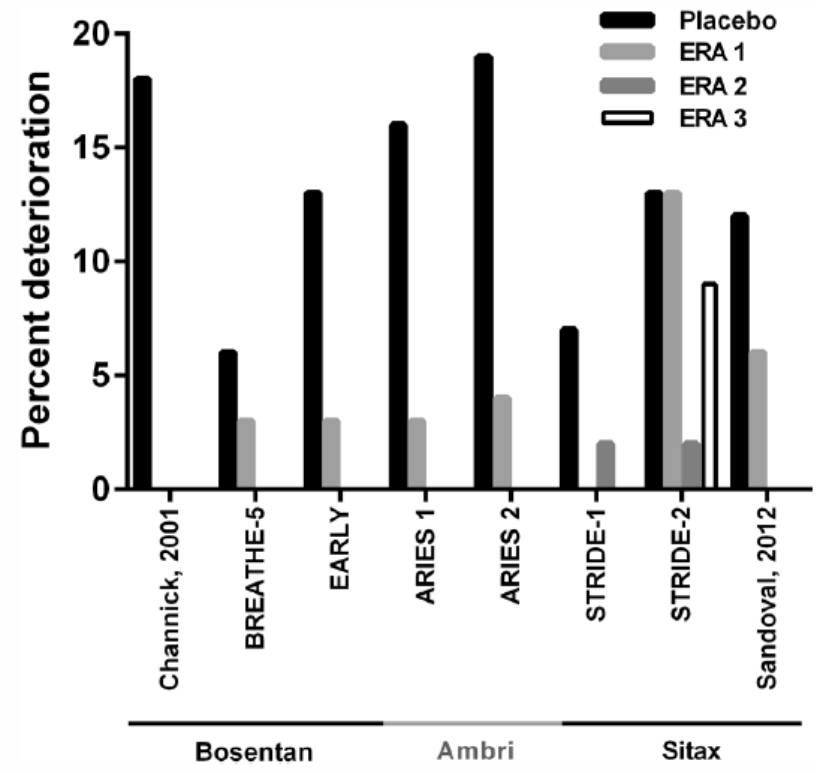


Fig. 6 Percent of patients showing deterioration in functional class over the course of a study

Mortality Data

- Most of the reported trials have looked at the softer endpoints of clinical and hemodynamic improvement rather than the harder end points of survival and mortality. SERAPHIN reported a trend towards reduction of all-cause death and death from PAH in the 10-mg macitentan group. However, the differences were not significant and the trial was not powered to detect these differences.

Anmerkung/Fazit der Autoren

ERAs have favorable hemodynamic and clinical effects in PAH. They reduce disease progression, hospitalization rates, and improve long-term morbidity and mortality of PAH of various etiologies. These effects are consistent in standalone therapies. Based on these findings, ERAs appear to be an appropriate treatment option for patients with progressive PAH. Newer agents have a better toxicity profile while maintaining the favorable hemodynamic and clinical effects. Larger trials with longer follow-up are, however, needed for comparison as standalone agents and in combination therapies.

Zheng Y et al., 2014 [25].

Prostanoid therapy for pulmonary arterial hypertension: a meta-analysis of survival outcomes

Fragestellung

to evaluate the efficacy and safety of prostanoids in PAH, focusing on the improvement in overall survival

Methodik

Population:

- patients definitely diagnosed as having PAH according to the clinical classification of PAH

Intervention:

- prostanoids

Komparator:

- k.A.

Endpunkt:

- Primär: all-cause mortality
- Sekundär: clinical worsening, 6MWD, and hemodynamic parameters, including mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), cardiac index (CI), and mixed venous oxygen saturation (SVO2)
- Sicherheit: Withdrawal due to adverse effects

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library databases, previous reviews, and reference lists from identified articles through to April 2013.

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 2,244 patients were enrolled in the 14 RCTs, with 1,189 patients in the prostacylcin treatment group and 1,055 patients in the placebo group

Charakteristika der Population:

- In 13 studies, the exclusive or predominant etiology was idiopathic PAH and/or familial PAH. One study included a minority of patients (28 %) with inoperable chronic thromboembolic pulmonary hypertension, and one study included exclusively patients with scleroderma-associated PAH. Most of the participants were in New York Heart Association/World Health Organization (NYHA/WHO) functional class III. The primary endpoint was 6MWD in 13 studies and maximal oxygen consumption in one study.

Qualität der Studien:

- Studies had a Jadad Scale between 3-4.

Studienergebnisse:

- All-cause mortality rate in the control group was 4.17 %. In a 13.4-week follow-up, prostanoid treatment was associated with a 44 % reduction in mortality (RR 0.56; 95 % CI 0.35–0.88; P = 0.01).

  Subgroup analysis suggested that only treatment with intravenous prostanoids provided a survival benefit.

- Compared with placebo, prostanoids significantly reduced clinical worsening (RR 0.60; 95 % CI 0.46–0.80; P =0.0003), increased the 6-min walk distance by 27.95 m, reduced mean pulmonary arterial pressure and pulmonary vascular resistance, and increased the cardiac index and mixed venous oxygen saturation.
- However, patients receiving prostanoid treatment showed a much higher incidence (RR 3.25; 95 % CI 2.07–5.10; P <0.00001) of withdrawal due to its adverse effects.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis suggests that prostanoids are efficient in improving survival, reducing clinical worsening, and improving exercise capacity, functional capacity, and hemodynamics. These observations support the use of prostanoids in the treatment of PAH. However, a high incidence of withdrawal due to adverse effects of prostanoids was also observed. Therefore, additional efforts are also required to explore new prostacyclin analogues with few adverse effects.

Kommentare zum Review

- The time between the publication of the first and the last trial was prolonged (about 23 years)
- Some trials were not blinded
- Some trials adopted combination therapy, among which prostanoids were added to background treatment with bosentan or sildenafil
- The majority of the included RCTs had a small sample size and relatively short duration, making it difficult to assess the long-term effect of prostanoids
- Only some of the RCTs reported some secondary outcome parameters, which may have led to reporting bias

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Liu HL et al., 2016 [20].

Efficacy and Safety of Pulmonary Arterial Hypertension-specific Therapy in Pulmonary Arterial Hypertension A Meta-analysis of Randomized Controlled Trials

Fragestellung

to evaluate the efficacy and safety of PAH-specific therapy in patients with PAH, especially to separately address PAH-specific monotherapy and combination therapy.

Methodik

Population:

- patients with PAH

Intervention/Komparator:

- treatment had to involve prostanoids (epoprostenol, treprostinil, iloprost, beraprost, and selexipag), endothelin antagonists (bosentan, ambrisentan, and macitentan), phosphodiesterase inhibitors (sildenafil, tadalafil, and vardenafil), soluble guanylate cyclase stimulators (riociguat), or a rho-kinase inhibitor (fasudil); treatment had to involve comparison of one pharmacotherapy vs placebo or conventional therapy or monotherapy vs combination therapy.

Endpunkt:

- primary outcomes: mortality, exercise capacity (as measured by a 6MWD), World Health Organization (WHO) functional class or New York Heart Association functional class
- secondary outcomes: cardiopulmonary hemodynamics (including mean pulmonary artery pressure [mPAP], pulmonary vascular resistance [PVR], and cardiac index) and withdrawal due to adverse effects.

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library were searched (last search in October 2015)

Qualitätsbewertung der Studien:

- Risk of bias based on Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- In total, 35 randomized controlled trials involving 6,702 patients were included

Qualität der Studien:

- k.A.

Studienergebnisse:

- Monotherapy vs placebo/conventional therapy: Significance was obtained in mortality reduction (OR, 0.50 [95% CI, 0.33 to 0.76]; P = .001), 6-min walk test (mean difference, 31.10 m [95% CI, 25.40 to 36.80]; P < .00001), New York Heart Association/World Health Organization functional class (OR, 2.48 [95% CI, 1.51 to 4.07]; P = .0003), and hemodynamic status based on mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, and incidence of withdrawal due to adverse effects.
- In combination therapy vs monotherapy: Significance was reached for the 6-min walk test (mean difference, 19.96 m [95% CI, 15.35 to 24.57]; P < .00001), functional class (OR, 1.65 [95% CI, 1.20 to 2.28]; P = .002), hemodynamic status, and incidence of withdrawal due to adverse effects (OR, 2.01 [95% CI, 1.54 to 2.61]; P < .00001) but not for mortality reduction (OR, 0.98 [95% CI, 0.57 to 1.68]; P = .94).

TABLE 2] Meta-analysis of PAH-specific Therapy for PAH

Study Group	No.	Heterogeneity		Pooled Results	
		P_h	I^2 (%)	Effect Estimate (95% CI)	*P* Value
Mortality					
Overall PAH-specific therapy	30	.86	0	OR, 0.71 (0.56 to 0.90)	.004
Monotherapy vs placebo/conventional therapy	16	.86	0	OR, 0.50 (0.33 to 0.76)	.001
Combination therapy vs monotherapy	8	.37	8	OR, 0.98 (0.57 to 1.68)	.94
Exercise capacity (6MWD)					
Overall PAH-specific therapy	34	.03	32	MD, 24.44 (21.18 to 27.71)	<.00001
Monotherapy vs placebo/conventional therapy	18	.30	12	MD, 31.10 (25.40 to 36.80)	<.00001
Combination therapy vs monotherapy	15	.56	0	MD, 19.96 (15.35 to 24.57)	<.00001
WHO or NYHA FC					
Overall PAH-specific therapy	26	.004	48	OR, 1.76 (1.37 to 2.25)	<.00001
Monotherapy vs placebo/conventional therapy	14	.001	62	OR, 2.48 (1.51 to 4.07)	.0003
Combination therapy vs monotherapy	9	.11	39	OR, 1.65 (1.20 to 2.28)	.002
Mean pulmonary artery pressure					
Overall PAH-specific therapy	21	.27	14	MD, −4.13 (−4.90 to −3.37)	<.00001
Monotherapy vs placebo/conventional therapy	13	.18	24	MD, −3.85 (−4.67 to −3.03)	<.00001
Combination therapy vs monotherapy	4	.22	31	MD, -4.81 (−6.36 to −3.26)	<.00001
Pulmonary vascular resistance					
Overall PAH-specific therapy	21	.0005	55	MD, −233 (−276 to −191)	<.00001
Monotherapy vs placebo/conventional therapy	13	.0001	68	MD, −241 (−300 to −182)	<.00001
Combination therapy vs monotherapy	4	.54	0	MD, −187 (−262 to −111)	<.00001
Cardiac index					
Overall PAH-specific therapy	21	.00001	75	MD, 0.40 (0.34 to 0.46)	<.00001
Monotherapy vs placebo/conventional therapy	13	.00001	73	MD, 0.38 (0.23 to 0.52)	<.00001
Combination therapy vs monotherapy	4	.07	58	MD, 0.34 (−0.03 to 0.71)	.07
Withdrawal due to adverse effects					
Overall PAH-specific therapy	29	.007	44	OR, 1.53 (1.27 to 1.85)	<.00001
Monotherapy vs placebo/conventional therapy	14	.07	38	OR, 1.70 (1.15 to 2.50)	.007
Combination therapy vs monotherapy	12	.69	0	OR, 2.01 (1.54 to 2.61)	<.00001

N = No. of included studies; MD = mean difference; PAH = pulmonary arterial hypertension; P_h = *P* values for heterogeneity of Q test; P_i = *P* values for interaction of χ^2 test; WHO or NYHA FC = World Health Organization or New York Heart Association functional class. See Table 1 legend for expansion of other abbreviation.

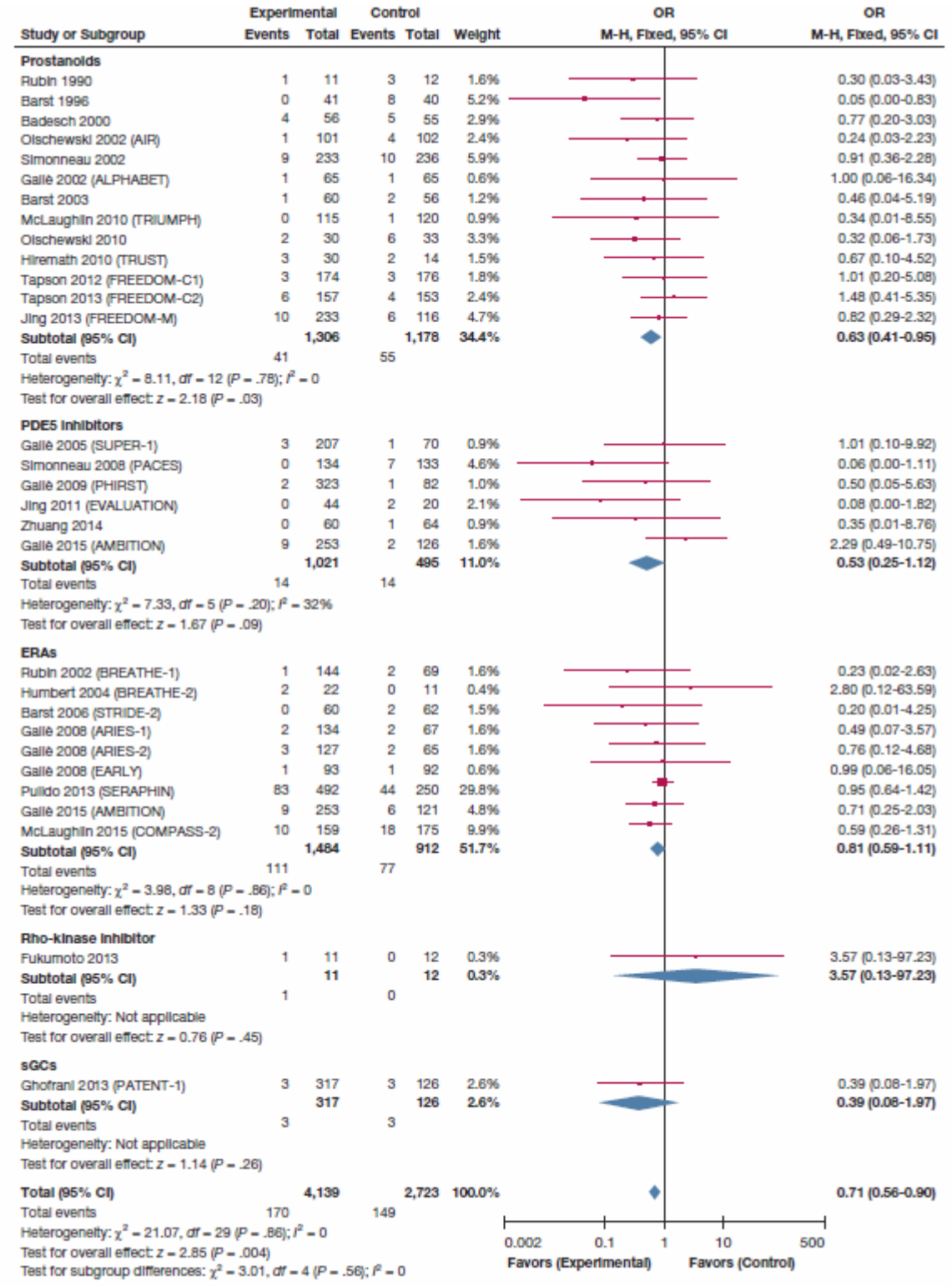

Figure 2 – Effect of all pulmonary arterial hypertension–specific therapy on mortality in patients with pulmonary arterial hypertension. ERAs = endothelin receptor antagonists; PDE5 = phosphodiesterase type 5; sGCs = soluble guanylate cyclase stimulators.

Anmerkung/Fazit der Autoren

To our knowledge, this meta-analysis is the first to assess the efficacy and safety of PAH-specific therapy by analyzing monotherapy and combination therapy separately. The meta-analysis revealed that PAH-specific monotherapy could improve mortality, exercise capacity,

functional class, and hemodynamic status compared with placebo or conventional therapy. However, combination therapy could further improve exercise capacity, functional class, and hemodynamic status compared with monotherapy but had no proven effect on mortality. Combination therapy had a much higher incidence of withdrawal due to adverse effects than monotherapy.

CADTH, 2015 [2].
Siehe auch **Lajoie AC et al., 2016 [18].**

Canadian Agency for Drugs and Technologies in Health (CADTH)

Drugs for Pulmonary Arterial Hypertension: Comparative Efficacy, Safety, and Cost-Effectiveness

Fragestellung

1. What is the comparative efficacy, safety, and cost-effectiveness of monotherapy with macitentan or riociguat compared with each other or with a PDE-5 inhibitor, another ERA, or a prostanoid?

2. What is the comparative efficacy, safety, and cost-effectiveness of dual (add-on) combination therapy versus monotherapy with PAH drugs?

3. What is the comparative efficacy, safety, and cost-effectiveness among different dual (add-on) combination therapies of PAH drugs?

4. What is the comparative efficacy, safety, and cost-effectiveness of triple (add-on) combination therapy versus dual (add-on) combination therapy with PAH drugs?

Methodik

Population:

- Adult patients (≥ 18 years) diagnosed with PAH

Intervention/Komparator

- Macitentan — oral
- Riociguat — oral

Komparator:

- Drug therapies
  - Epoprostenol — injectable
  - Treprostinil — injectable
  - Bosentan — oral
  - Ambrisentan — oral
  - Sildenafil — oral and injectable
  - Tadalafil — oral
- Placebo or conventional medical treatment

Endpunkt:

Ranking based on hierarchy of importance:

- Death (all-cause, PAH-related)

- Hospitalization
- Clinical worsening
- Improvement, unchanged or worsening in NYHA or WHO FC
- 6MWD
- Hemodynamic variables, including but not restricted to PVR, mPAP, and cardiac index
- Quality of life
- BDI
- SAEs
- AEs
- Laboratory abnormalities
- Withdrawals due to AEs

Recherche/Suchzeitraum:

- MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; Cochrane Central Register of Controlled Trials via Ovid; and PubMed (Zeitraum: 2013 to present)

Qualitätsbewertung der Studien:

- Quality assessment of RCTs was performed independently by two reviewers using a standardized table based on major items from the SIGN 50 instrument for internal validity. Further critical appraisal was performed based on input from clinical experts.

Ergebnisse

Anzahl eingeschlossener Studien:

- The systematic review included 20 unique studies, of which 1518-31 studies had treatment-naive populations and five32-36 had mixed populations (naive and pre-treated with a PAH drug). Of those five studies with mixed populations, three33-35 provided data for certain clinical outcomes in naive and pre-treated subpopulations. One study32 with a mixed population did not provide data on subpopulations based on treatment history. Thus, 1818-31,33-35 provided comparisons of PAH treatments in treatment-naive populations (i.e., monotherapy) and four33-36 provided comparisons between dual combination (add-on) therapy and background therapy. All included studies were RCTs (14 double-blinded and 18 placebo-controlled); no published comparative observational studies that met the inclusion criteria for the systematic review were identified in the literature search.
- Evidence was available for the following drug therapies: macitentan (one RCT), riociguat (one RCT), ambrisentan (three RCTs), bosentan (four RCTs), sildenafil (one RCT), tadalafil (one RCT), epoprostenol (three RCTs), and treprostinil (four RCTs). NMAs were conducted for four outcomes including clinical worsening, WHO FC improvement, WHO FC worsening, and 6MWD. For the remaining outcomes, only direct pairwise meta-analysis results are presented.

Studienergebnisse:

Hinweis: Due to the lack of head-to-head comparisons, a NMA to compare treatments that may not have been compared directly was conducted (Bayesian NMAs)

Monotherapy (Treatment-Naive Population)

- For clinical worsening: Data from eight treatment options (macitentan 10 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, and placebo) were subjected to meta-analyses. Despite the slight difference in definition among studies, clinical worsening (a mortality and morbidity composite outcome) was generally defined as time to first occurrence of all-cause death, worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, heart or lung transplantation, or atrial septostomy.
  - Direct pairwise meta-analysis showed that all treatments were numerically favoured in reducing the risk of clinical worsening compared with placebo. Treatment effects (relative risk [RR]) ranged from 0.25 (tadalafil) to 0.59 (macitentan). A statistically significant difference versus placebo was reached for macitentan, ambrisentan 5 mg, and bosentan, but not for riociguat, ambrisentan 10 mg, sildenafil, and tadalafil in a treatment-naive population.
  - The treatment effects estimated from NMA were similar in both magnitude and direction to the results of direct pairwise estimates, with relative risks ranging from 0.21 for tadalafil to 0.46 for macitentan. There were no statistically significant differences between drugs with respect to clinical worsening outcomes.

    Excluding the study examining the efficacy of macitentan (a long-term study with median follow-up of 115 weeks) from the analysis did not affect the effect sizes of other treatments. Likewise, sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect.
- For FC improvement: Data from nine treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were available for analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients with FC improvement were available from published sources for macitentan.
  - Direct pairwise meta-analysis showed that, for naive populations, epoprostenol, sildenafil, and tadalafil showed statistically significant improvement in FC compared with placebo, while riociguat, ambrisentan, bosentan, and treprostinil did not.
  - The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Epoprostenol, which had the highest treatment effect, was statistically significantly superior compared with all other treatments in the naive populations.
  - Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect. The minimal clinically important difference (MCID) of WHO FC improvement is unknown.
- For FC worsening: Data from eight treatment options (riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, and placebo) were available for analyses. Data for macitentan were not available for the treatment-naive population; only results for the total study population (i.e., treatment-naive plus treatment-experienced) regarding the proportion of patients experiencing FC worsening were available from published sources.
  - Direct pairwise meta-analysis showed that all treatments were numerically favoured in the reduction of FC worsening compared with placebo. Statistically significant differences

were reached only for ambrisentan (5 and 10 mg) and riociguat (max 2.5 mg) in naive populations.

- The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. There were no statistically significant differences between riociguat and other drugs or between other drugs themselves.
- Sensitivity analyses adjusted for baseline FC and baseline PAH etiology revealed no marked change in the relative treatment effect. The MCID of WHO FC worsening is unknown.

- For 6MWD: Data for all 11 treatment options (macitentan 10 mg, riociguat max 1.5 mg, riociguat max 2.5 mg, ambrisentan 5 mg, ambrisentan 10 mg, bosentan 125 mg, sildenafil 20 mg, tadalafil 40 mg, epoprostenol, treprostinil, and placebo) were available for analysis.
  - Direct pairwise meta-analysis showed that all drugs, except macitentan, statistically significantly increased 6MWD compared with placebo in the naive populations.
  - The results of the NMA and direct pairwise comparisons were similar in both magnitude and direction. Increase in 6MWD with riociguat (both doses) was not statistically significantly different compared with all other drugs. Numerically, epoprostenol showed the highest increase in 6MWD compared with all remaining drugs. The mean differences in 6MWD relative to other drugs ranged from 18.3 m (compared with ambrisentan 5 mg) to 56.9 m (compared with macitentan 10 mg). The MCID for the change in 6MWD from baseline has been estimated to be 33.0 m (range: 25.1 m to 38.6 m).
  - Sensitivity analysis was not performed for this outcome.

→ In summary, of the four outcomes analyzed using NMA, there were no statistically significant differences between drugs with respect to clinical worsening and FC worsening. For FC improvement and 6MWD, epoprostenol had highest activity in treatment-naive populations, while there were no apparent differences among the remaining treatments. Acknowledging the limitations in the available evidence, these findings suggest that there may not be statistically or clinically meaningful differences between drugs currently available in Canada for the treatment of PAH. There is, however, an exception with epoprostenol, which appears to be the most effective in improving clinical status, as measured by FC improvement and 6MWD.

Combination Therapy (Add-on)

- Evidence of clinical worsening, FC improvement, FC worsening, and 6MWD was available for riociguat max 2.5 mg or tadalafil 40 mg added to ERA background therapy of ambrisentan or bosentan that had been stable for at least three months. Furthermore, evidence for clinical worsening and 6MWD was also available for addition of macitentan to PDE-5 inhibitor or prostanoid background therapy. However, the macitentan data could not be combined with those of riociguat or tadalafil in the NMA because of different background therapies and the much longer study duration of the macitentan RCT. The following findings address the comparison of dual therapy versus monotherapy:
  - Addition of macitentan 10 mg to PDE-5 inhibitor or prostanoid background therapy statistically significantly reduced clinical worsening compared with background therapy alone.
  - Addition of riociguat max 2.5 mg to ERA background therapy reduced clinical worsening versus ERA monotherapy, but this effect was not statistically significant. However, addition of tadalafil 40 mg to ERA background therapy statistically significantly reduced clinical worsening versus ERA monotherapy.

- For FC improvement, there were no statistically significant differences between combination therapy of riociguat max 2.5 mg and ERA or of tadalafil 40 mg and ERA versus ERA alone.
- Addition of riociguat max 2.5 mg or tadalafil 40 mg to ERA background therapy reduced FC worsening versus ERA alone; however, neither combination resulted in a statistically significant difference versus monotherapy.
- Addition of macitentan 10 mg, riociguat max 2.5 mg, or tadalafil 40 mg to corresponding background therapy numerically improved 6MWD compared with background therapy alone. Statistically significant differences were reached for macitentan and tadalafil, but not for riociguat.
- There were no statistically significant differences between combination therapy of riociguat plus ERA and tadalafil plus ERA for clinical worsening, FC improvement, FC worsening, and 6MWD.

Other Efficacy Outcomes

- Direct pairwise meta-analyses were performed for hospitalization, mortality, BDI, hemodynamics (PVR, mPAP, cardiac index), and health-related quality of life (HRQoL). These outcomes were mostly available for total populations; i.e., including both treatment-naive and treatment-experienced patients.
  - The number of deaths in all studies was relatively low, except in one study of epoprostenol and one study of treprostinil, where the percentage of patients who died in the placebo groups reached 25% (9% in the epoprostenol group) and 36% (10% in the treprostinil group), respectively, albeit among patients with more severe disease (predominantly NYHA or WHO FC III or IV). Epoprostenol showed a statistically significant lower risk of mortality compared with placebo, while there were no statistically significant differences between other drugs and placebo.
  - Of all drugs, except epoprostenol, macitentan 10 mg was the only drug that showed a statistically significant reduction in hospitalization compared with placebo.
  - Compared with placebo, all drugs improved breathlessness (measured by BDI), PVR, mPAP, and cardiac index. However, statistically significant improvements were less consistent across drugs for improved BDI scores as compared with hemodynamic parameters and cardiac index.
  - HRQoL was poorly reported in most studies, using different instruments such as the Short-Form (36-Item) health survey (SF-36), the EuroQol 5-Dimensions Questionnaire (EQ-5D), Living with Pulmonary Hypertension questionnaire, Minnesota Living with Heart Failure Questionnaire, Chronic Heart Failure Questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating. Overall, all drugs showed improvement in HRQoL compared with placebo. Statistically significant differences were not reached for bosentan.

Safety

- Safety data from the published studies included in this review were available only for total populations; i.e., including both treatment-naive and treatment-experienced patients.
  - Serious adverse events (SAEs) were less frequent with macitentan (45% versus 55%), riociguat (11% versus 18%), ambrisentan (9% versus 16%), and tadalafil (9% versus 15%) compared with placebo. In contrast, treprostinil (62% versus 20%) had frequent SAEs related to injection site reactions. Bosentan, sildenafil, and epoprostenol showed no numerically notable differences in SAEs compared with placebo.

- Discontinuation of treatment was more frequent with treprostinil than placebo (7.7% versus 0.4%). This was mainly due to abdominal subcutaneous injection site pain. There was no apparent difference between other drugs and placebo with respect to discontinuation of treatment due to AEs.
- Common AEs compared with placebo:
  - Risk of liver toxicity: bosentan (12% versus 2%)
  - Risk of peripheral edema: riociguat (18% versus 11%), ambrisentan (22% versus 11%), bosentan (13% versus 8%), and treprostinil (9% versus 3%)
  - Risk of anemia: macitentan (13% versus 3%), riociguat (8% versus 2%), and ambrisentan (68% versus 17%)
  - Risk of hypotension: riociguat (10% versus 2%), epoprostenol (13% versus 0%), and treprostinil (5% versus 2%)
  - Epoprostenol and treprostinil were frequently associated with nausea, diarrhea, jaw pain, headache, and injection site reactions.

Anmerkung/Fazit der Autoren

Results from the systematic review and NMA suggest that there were no significant differences in clinical worsening and FC worsening between drugs used to treat PAH as monotherapy. For FC improvement and 6MWD, epoprostenol appeared to be the most effective treatment option in improving clinical status, while there were no apparent differences among other treatments.

Addition of macitentan on PDE-5 inhibitor or prostanoids background therapy and addition of riociguat or tadalafil on ERA background therapy produce improvement in clinical worsening, FC improvement, FC worsening, and/or 6MWD compared with monotherapy. There were no differences between combination therapy of riociguat plus ERA and tadalafil plus ERA for all four clinical outcomes.

All drugs showed improvement in pulmonary hemodynamics and HRQoL compared with placebo. AEs were treatment specific and may be an important consideration in treatment selection.

Kommentare zum Review

- No head-to-head RCTs comparing the efficacy and safety of any of the drugs were identified for inclusion in the review.

Duo-Ji MM et al., 2017 [4].

Comparative efficacy and acceptability of endothelin receptor antagonists for pulmonary arterial hypertension: A network meta-analysis

Fragestellung

(…) no head-to-head comparison among the four ERA therapeutic drugs to indicate their differences in efficacy, tolerability and other clinical outcomes. Compared with traditional metaanalysis, network meta-analysis (NMA) provided us with a more comprehensive viewpoint which synthesizes both direct and indirect evidence. Therefore, a NMA was carried out in our study to compare the four drugs mentioned above so that the most appropriate and efficacious therapy for PAH patients can be identified.

Methodik

Population:

- patients had documented (WHO FC II, III, IV) symptomatic PAH, idiopathic PAH or PAH associated with other diseases

Intervention/Komparator

- any of bosentan, sitaxsentan macitentan, ambrisentan and placebo

Endpunkt:

- 6MWD, clinical worsening, serious adverse effects (SAE), death and all-cause discontinuation

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library (Suchzeitraum nicht angegeben)

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 studies with a total number of 2172 patients

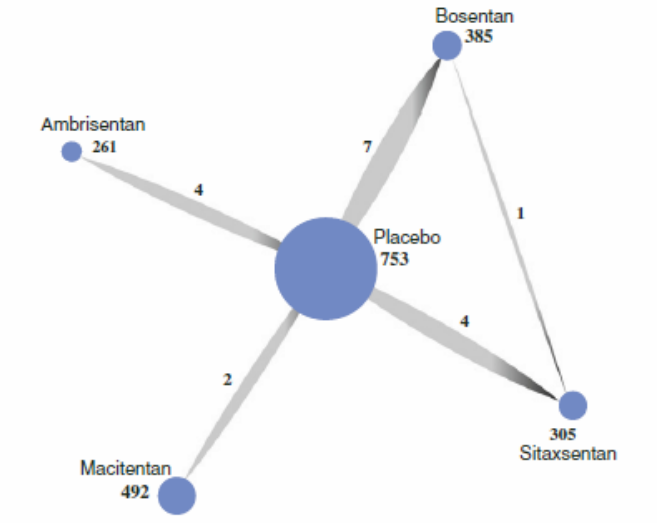

Fig. 2. Network diagram: each node represents a PAH therapy and the number between two nodes represents the number of study involved in the head-to-head comparison. The nodes correspond to each endothelin receptor antagonists to be compared in our network meta-analysis. The size of the node corresponds to the total number of patients for each endothelin receptor antagonist. Direct evidence is obtained from direct comparisons that are connected by solid lines. The width of the solid lines corresponds to the number of comparisons. Indirect evidence can be obtained from closed network. For instance, if both bosentan and ambrisentan are directly compared to placebo, Then, indirect comparisons can be made between bosentan and ambrisentan.

Qualität der Studien:

- All included studies achieved a Jadad score 3, thus the quality of included studies is plausible.

Studienergebnisse:

- All of the four PAH therapies significantly increased the average 6MWD in comparison to the placebo (P-value < 0.05).
- Moreover, bosentan and ambrisentan both showed significant association with a decrease in the risk of clinical worsening compared to placebo.
- Regarding of all-cause discontinuation, ambrisentan is the only therapy which was significantly associated with a risk decrease compared to placebo. However, there was no sufficient evidence suggesting significant difference in any efficacy or acceptability outcomes between any two of the PAH therapies (P-value > 0.05).

Anmerkung/Fazit der Autoren

Conclusively, ambrisentan could be considered as the most recommended ERAs for its remarkable performance in 6MWD, SAE and clinical worsening. Future studies adjusting for dosage and different PAH subtypes should be designed to confirm our conclusion.

Gao XF et al., 2017 [7].

Siehe auch Badiani B et al., 2016 [1].

Targeted drugs for pulmonary arterial hypertension: a network meta-analysis of 32 randomized clinical trials

Fragestellung

This network meta-analysis was conducted to comprehensively compare the efficacy of these targeted drugs for PAH.

Methodik

Population:

- PAH patients

Intervention/Komparator:

- at least one of the prostanoids (epoprostenol, iloprost, beroprost, and treprostinil), ERAs (bosentan, ambrisentan, and macitentan), PDE-5Is (sildenafil, tadalafil, and vardenafil), sGCS (riociguat), and combination therapy were used, regardless of drug dosage forms

Endpunkt:

- primär: 6-minute walk distance (6MWD)
- sekundär: mean pulmonary arterial pressure (mPAP), PVR, all-cause mortality, and clinical worsening events

Recherche/Suchzeitraum:

- Medline, the Cochrane Library, and other Internet sources were searched from January 1990 to December 2015.

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- Thirty-two eligible trials including 6,758 patients were identified

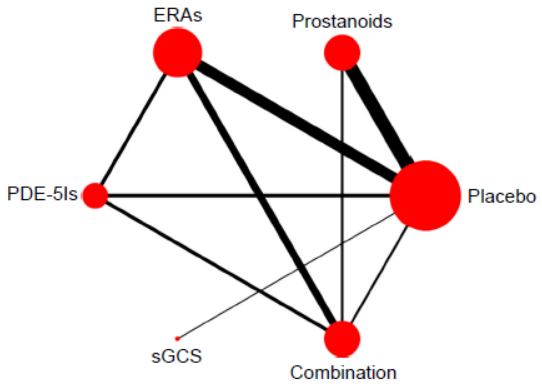

Figure 1 Network of available drugs for PAH.
Note: The size of nodes is proportional to the number of individuals randomized to each treatment, and the thickness of lines to the number of direct comparisons in trials.
Abbreviations: ERAs, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE-5Is, phosphodiesterase 5 inhibitors; sGCS, soluble guanylate cyclase stimulator.

Qualität der Studien:

- The quality of each study was good according to the Jadad score

Studienergebnisse:

- There was a statistically significant improvement in 6MWD, mean pulmonary arterial pressure, pulmonary vascular resistance, and clinical worsening events associated with each of the four targeted drugs compared with placebo.
- Combination therapy improved 6MWD by 20.94 m (95% confidence interval [CI]: 6.94, 34.94; P=0.003) vs prostanoids, and 16.94 m (95% CI: 4.41, 29.47; P=0.008) vs ERAs.
- PDE-5Is improved 6MWD by 17.28 m (95% CI: 1.91, 32.65; P=0.028) vs prostanoids, with a similar result with combination therapy.
- In addition, combination therapy reduced mean pulmonary artery pressure by 3.97 mmHg (95% CI: -6.06, -1.88; P,0.001) vs prostanoids, 8.24 mmHg (95% CI: -10.71, -5.76; P,0.001) vs ERAs, 3.38 mmHg (95% CI: -6.30, -0.47; P=0.023) vs PDE-5Is, and 3.94 mmHg (95% CI: -6.99, -0.88; P=0.012) vs sGCS.
- There were no significant differences in all-cause mortality and severe adverse events between prostanoids, ERAs, PDE-5Is, sGCS, combination therapy, and placebo.

Anmerkung/Fazit der Autoren

In conclusion, this network meta-analysis suggests that all targeted drugs for PAH are associated with improved clinical outcomes, especially combination therapy. However, all these drugs seem to show less favorable effects on survival in the short-term follow-up, suggesting further clinical trials are required.

Kommentare zum Review

- *different clinical worsening events definition used in the studies*

- *no publication bias evaluation in the present study*
- *not enough data about PAH-related SAEs and treatment-related SAEs in most of the enrolled studies*
- *follow-up period in all enrolled studies was relatively different for comparison of targeted drugs*

Lin H et al., 2018 [19].

Efficacy and tolerability of pharmacological interventions for pulmonary arterial hypertension: A network meta-analysis

Fragestellung

network meta-analysis (NMA) to compare the efficacy and tolerability of various therapies and combinations for pulmonary arterial hypertension (PAH).

Methodik

Population:

- PAH patients

Intervention/Komparator:

- any of the 5 medications in separate (ERA, GCS, PDE-5Is, PGI, and PRA) or in combination

Endpunkt:

- 6 min walking distance (6MWD), functional class amelioration (FCA), death, clinical worsening (CW), serious adverse effects (SAEs), withdrawal, pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), cardiac index (CI), and mean right atrial pressure (mRAP)

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library. The search was finalized in April 2017.

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- 43 RCTs with 9200 patients

Charakteristika der Population:

-

Qualität der Studien:

- All studies were of good quality

Studienergebnisse:

- In current study, 6MWD, FCA, CW, death, PVR, mPAP, CI, and mRAP were considered as efficacy outcomes:

- EAP (MD = 53.26, 95% CrIs = 36.31–70.81), ERA (MD = 30.67, 95% CrIs = 21.45–41.06), PDE-5Is (MD = 29.02, 95% CrIs = 14.41–43.87), and GCS (MD = 25.13, 95% CrIs = 7.75–43.51) performed better than placebo in 6MWD. Performance of EAP is significantly better than ERA (MD = 22.60, 95% CrIs = 6.42–38.40), GCS (MD = 28.16, 95% CrIs = 3.17–52.65), PAP (MD = 61.02, 95% CrIs = 29.66–91.77), PGI (MD = 33.09, 95% CrIs = 12.05–53.48), and PDE-5Is (MD = 24.19, 95% CrIs = 7.82–40.98).
- As for CW and FCA, indicated a desirable performance of EAP (OR = 0.11, 95% CrIs = 0.02–0.57; OR = 0.21, 95% CrIs = 0.06–0.78), ERA (OR = 0.36, 95% CrIs = 0.19–0.60; OR = 0.36, 95% CrIs = 0.17–0.76), and PAE (OR = 0.19, 95% CrIs = 0.05–0.76; OR = 0.08, 95% CrIs = 0.01–0.48) when compared with placebo. PAP (OR = 0.17, 95% CrIs = 0.03–0.79) and PDE-5Is (OR = 0.40, 95% CrIs = 0.15–0.98) also had a lower risk in CW compared with placebo.
- PAP performed better than EAP (OR = 0.07, 95% CrIs = 0.01–0.73), ERA (OR = 0.09, 95% CrIs = 0.01–0.81), placebo (OR=0.06, 95% CrIs=0.01–0.47), PDE-5Is (OR=0.06, 95% CrIs = 0.01–0.60), PGI (OR = 0.11, 95% CrIs = 0.01–0.80), and PRA (OR = 0.04, 95% CrIs = 0.01–0.16) with respect to death.

Supplementary efficacy endpoints:

- The treatment comparisons revealed that only ERA (MD = -0.43, 95% CrIs = -0.79 to -0.10) turned out to be more effective than placebo in CI.
- As for PVR, placebo also showed a lower resistance drop compared with EAP (MD = -496.4, 95% CrIs = -887.71 to -102.98), ERA (MD = -390.91, 95% CrIs = -575.13 to -210.77), PAE (MD = - 496.74, 95% CrIs = -767.76 to -236.19), and PGI (MD = -375.12, 95% CrIs = -529.30 to -221.60). In addition, PDE-5Is (MD = -345.15, 95% CrIs = -660.4–28.97) was inferior to PAE in PVR.
- When it came to mRAP, the right atrial pressure decrease of placebo (MD = 3.31, 95% CrIs = 0.98–5.83) and PRA (MD = 6.52, 95% CrIs = 1.05–12.16) was lower than ERA. EAP (MD = -8.9, 95% CrIs = -14.62 to -2.98), ERA (MD = -4.92, 95% CrIs = -7.35 to -2.08), GCS (MD = -3.74, 95% CrIs = -7.43 to -0.20), PDE-5Is (MD = -3.41, 95% CrIs = -5.77 to -0.70), and PAE (MD = -10.78, 95% CrIs = -14.94 to -6.70) were more efficient than placebo due to their lower pulmonary artery pressure in mPAP. Similarly, PAE was superior to ERA (MD = -4.92, 95% CrIs = -7.35 to -2.08), GCS (MD = -3.74, 95% CrIs = -7.43 to -0.20), PDE-5Is (MD = -7.38, 95% CrIs = -12.45 to -2.73), and PGI (MD = -8.88, 95% CrIs = -12.70 to -4.67) regarding mPAP reduction.

Tolerability

- The withdrawal risk of PGI was obviously higher than ERA (OR = 1.84, 95% CrIs = 1.11–3.10) and placebo (OR = 1.43, 95% CrIs = 1.01–1.97). Besides, no differences in other comparisons reached a significant level. Similarly, no statistical significance was found in SAEs.

Relative ranking analysis

- A series of ranking possibilities for different treatments were shown in SUCRA and cluster plots: EAP and PAE showed advantageous efficacy over other treatments with high probabilities regarding 6MWD (94%, 76%), FCA (63%, 87%), CW (88%, 75%), PVR (79%, 83%), and mPAP (85%, 95%). PAP seemingly performed well in CW (79%) and death (96%). Moreover, PDE-5Is could be considered as the safest intervention among the 9 therapies with respect to SAEs (82%).

- The cluster analysis was calculated to categorize the therapies into different groups in view of different combinations of certain outcomes. It can be concluded that PAE and PDE-5Is performed better than others when taking 6MWD and FCA into account at the same time. EAP, PAE, ERA, and PDE-5Is turned out to be more efficacious than the other treatments when it comes to 6MWD and CW. A similar pattern was observed when evaluating FCA and CW, among which EAP and PAE are the top 2 treatments. While considering 6MWD and death simultaneously, PAE and ERA ranked high.

Anmerkung/Fazit der Autoren

Overall, we recommend EAP as the optimal choice for patients with PAH in clinical practice and PAE as suboptimal in view of their desirable performance in efficacy. Most of the combination therapies performed better than monotherapies.

Kommentare zum Review

- *sample sizes of each RCT included ranging from 18 to 1156*
- *analysis of tolerability outcomes is of questionable validity as clinical and hemodynamic backgrounds vastly differ among numerous trials*

3.4 Leitlinien

Taichman DB et al., 2014 [22].

American College of Chest Physicians (CHEST)

Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report.

Leitlinienorganisation/Fragestellung

Key questions:

- "For patients with PAH, what are the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers (CCB), prostanoids, endothelin antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?"
- "For patients with PAH, what are the comparative effectiveness and safety for PAH using macitentan or riociguat on intermediate-term and long-term patient outcomes?"

Methodik

Grundlage der Leitlinie

Systematic Search:

- MEDLINE, EMBASE and Cochrane Library: 1990 to April 2013 for CCBs, prostanoids, endothelin antagonists, PDE-inhibitors *
- MEDLINE and Cochrane Library: 2003-October 2013 for macitentan and riociguat
- RCTs
- published in English language
- *based on AHRQ- Comparative Effectiveness Report (McCrory et al . Pulmonary Arterial Hypertension: Screening, Management, and Treatment. Rockville, MD: Agency for Healthcare Research and Quality; 2013.)

Cochrane Risk of Bias tool for critical appraisal of studies

Evaluating Body of Evidence using GRADE

LoE

CHEST grading system: A, B, C or Insufficient

- based on the evidence level of the body of literature supporting each intervention and outcome comparison.
- (C= 2 or more studies addressing a particular intervention and outcome; 'insufficient' only 1 study available)
- Downgrading from higher evidence levels into an "Insufficient" level of evidence if indicated by domains set forth by a GRADE methodologic approach.

GoR

- LoE A, B or C→ evidence-based recommendations
- LoE insufficient→ a consensus statement "CB"
- Grading of recommendation:
  - 1 ('we recommend') or

o 2 (‘we suggest’)

A) Patients With WHO FC II Symptoms:

For treatment naive PAH patients with WHO FC II symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

- We recommend ambrisentan to improve 6-min walk distance (6MWD) (Grade 1C).
- We suggest bosentan to delay time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.
- We suggest macitentan to delay the time to clinical worsening (Grade CB).
- We recommend sildenafil to improve 6MWD (Grade 1C).
- We suggest tadalafil to improve 6MWD (Grade CB).
- We suggest riociguat to improve 6MWD (Grade CB), improve WHO FC (Grade CB) , delay the time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.
- We suggest also 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 (Grade CB) .

Evidenzgrundlage:

- Direct comparisons of available oral therapies for PAH monotherapy for treatment-naive patients have not been performed no recommendations or suggestions of one agent, or class of agent, over another.
- RCTs mostly included patients with PAH WHO FC III; only about one-third of the patients were FC II at baseline; total number of FC II patients in all studies is small.

Endothelin Receptor Antagonists:

29. Channick RN , Simonneau G , Sitbon O , et al . Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet . 2001 ; 358 (9288): 1119 - 1123 .
30. Rubin LJ , Badesch DB , Barst RJ , et al . Bosentan therapy for pulmo nary arterial hypertension . N Engl J Med . 2002 ; 346 (12): 896 - 903 .
31. Galiè N , Beghetti M , Gatzoulis MA , et al ; Bosentan Randomized Trial of Endothelin Antagonist Th erapy-5 (BREATHE-5) Investigators . Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo controlled study . Circulation . 2006 ; 114 (1): 48 - 54 .
32. Galiè N , Rubin Lj , Hoeper M , et al . Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial . Lancet . 2008 ; 371 (9630): 2093 – 2100.
33. Galiè N , Olschewski H , Oudiz RJ , et al ; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Effi cacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2 . Circulation. 2008 ; 117 (23): 3010 – 3019.
34. Pulido T , Adzerikho I , Channick RN , et al ; SERAPHIN Investigators . Macitentan and morbidity and mortality in pulmonary arterial hypertension . N Engl J Med . 2013 ; 369 (9): 809 – 818.

- Bosentan: 4 double-blind placebo-controlled RCTs show improvements in exercise capacity, hemodynamics, and time to clinical worsening, with a signifi cantly decreased hazard for hospitalization compared with placebo; AEs associated with bosentan treatment in included abnormal liver function tests, peripheral edema, palpitations, and chest pain

  a) patients with WHO FC III or IV (n=29)

  b) patients with WHO FC III or IV (n=213)

  c) patients with WHO FC III Eisenmenger syndrome (n=54)

d) WHO FC II patients (n=185)

- Ambrisentan: 2 concurrent, double-blind, placebo-controlled RCTs show improvement in exercise capacity and time to clinical worsening, no significant differences in death and hospitalization rates compared with placebo

  a) ARIES-1 with 32% patients in WHO FC II, 58% III, 7% IV, and 2.5% I; (n=202)

  b) ARIES-2 with 45% patients in WHO FC II, 52% III, 2% IV, and 2% I; (n=192)

- Macitentan: 1 multicenter, double-blind, placebo-controlled, event-driven, phase 3 RCT (n=742);
  - Patients with WHO FC II, III, or IV; 60% of patients were on PDE5, oral or inhaled prostanoids, CCBs, or l -arginine.
  - composite primary end point: the time from the initiation of treatment to the first event related to PAH (worsening of PAH, initiation of treatment with IV or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment;

    results for primary endpoint 3-mg macitentan vs placebo:HR 0.70 (97.5% CI, 0.52-0.96; P =0.01) / 10-mg macitentan vs placebo HR 0.55 (97.5% CI, 0.39-0.76; P <0.001).

Phosphodiesterase Type-5 Inhibitors

35. Galiè N , Ghofrani HA , Torbicki A , et al ; Sildenafi l Use in Pulmonary Arterial Hypertension (SUPER) Study Group . Sildenafi lcitrate therapy for pulmonary arterial hypertension . N Engl J Med. 2005 ; 353 (20): 2148 - 2157 .
36. Galiè N , Brundage BH , Ghofrani HA , et al ; Pulmonary Arterial Hypertension and Response to Tadalafi l (PHIRST) Study Group. Tadalafi l therapy for pulmonary arterial hypertension [published correction appears in Circulation . 2011;124(10):e279]. Circulation . 2009 ; 119 (22): 2894 – 2903.

- Sildenafil: 1 placebo controlled RCT (n=278)
  - treatment naïve patients with WHO FC II or III
  - results:placebo-adjusted increase in the 6MWD: significant improvement
  - significant greater proportion of patients with an at least 1 WHO FC class improvement in sildenafil groups vs placebo
  - no difference in the number of clinical worsening events
- Tadalafil: 1 placebo-controlled RCT (n=405)
  - 50% treatment naive and 50% background therapy with an ETRA that was continued during the study
  - Primary endpoint: placebo-adjusted increase in 6MWD
  - Results for 40 mg tadafil :mean increases in 6MWD from baseline:
    - 24 m for patients in WHO FC I or II
    - 36 m for patients in WHO FC III or IV
  - Data are not available to compare the effect in treatment-naive patients in WHO FCs II and III.
  - no differences in the proportions of patients with improved or worsened WHO FC among the tadalafil or placebo groups

Prostanoids

37. Barst RJ , Rubin LJ , Long WA , et al ; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension . N Engl J Med. 1996; 334 (5): 296 – 301.

38. Badesch DB , Tapson VF , McGoon MD , et al . Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med . 2000 ; 132 (6): 425 – 434.
39. Hiremath J , Th anikachalam S , Parikh K , et al . Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial . J Heart Lung Transplant . 2010 ; 29 (2): 137 – 149.
40. Simonneau G , Barst RJ , Galie N , et al ; Treprostinil Study Group . Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial . Am J Respir Crit Care Med . 2002 ; 165 (6): 800 - 804 .
41. Olschewski H , Simonneau G , Galiè N , et al ; Aerosolized Iloprost Randomized Study Group . Inhaled iloprost for severe pulmonary hypertension . N Engl J Med . 2002 ; 347 (5): 322 - 329 .

- Epoprostenol: 2 open-label RCTs supporttreatment benefits of this therapy in patients with IPAH as well as in systemic sclerosis-associated PAH
  - 1 RCT (n=81) comparing continuous IV infusion of epoprostenol plus conventional therapy (including oral vasodilators [CCBs], anticoagulation, diuretic, digoxin, and oxygen) with conventional therapy alone) in patients with severe IPAH (WHO FC III or IV) shows improvements in indices of exercise, quality of life, hemodynamics, and survival
  - 1 RCT comparing long-term IV epoprostenol treatment in patients with PAH occurring in association with the systemic sclerosis spectrum of disease showed improvement in exercise capacity and hemodynamics.
- Treprostinil: placebo-controlled, double blind RCTs on IV treprostinil and subcutaneous treprostinil and a nonblinded, placebo-controlled randomized trial of inhaled iloprost supported treatment benefits with based on 6MWD and show improvements in hemodynamics vs placebo
  - RCT (n=44)with treatment-naive PAH FC III and IV patients
  - RCT (n=470) with patients with PAH FC II, III, or IV
- Iloprost: 1 double-blind, placebo-controlled, multicenter RCT (n=146)
  - composite primary end point:10% improvement in the 6MWD and WHO FC improvement in the absence of clinical deterioration or death
  - results: significant difference in primary endpoint (17% intervention vs 5% placebo)
  - AE more commonly reported with the use of IV epoprostenol or treprostinil than placebo (headache, jaw pain, diarrhea, abdominal pain, anorexia, vomiting, photosensitivity, cutaneous flushing, and arthralgias)

B) 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 monotherapy be initiated with a currently approved ETRA, a PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:
- We recommend the use of bosentan to improve 6MWD (Grade 1B).
- We suggest the use of bosentan to decrease hospitalizations related to PAH in the short-term (Grade 2C), and to improve cardiopulmonary hemodynamics.
- We recommend the use of ambrisentan to improve 6MWD (Grade 1C).
- We suggest macitentan to improve WHO FC (Grade CB) and delay the time to clinical worsening (Grade CB).
- We recommend the use of sildenafil to improve 6MWD (Grade 1C) and to improve WHO FC (Grade CB). We suggest the use of sildenafil to improve cardiopulmonary hemodynamics.

- We suggest the use of tadalafil to improve 6MWD (Grade CB), to improve WHO FC (Grade CB), to delay time to clinical worsening (Grade CB) and to improve cardiopulmonary hemodynamics.
- We suggest riociguat to improve 6MWD (Grade CB), improve WHO FC (Grade CB) , delay the time to clinical worsening (Grade CB) and improve cardiopulmonary hemodynamics.

Evidenz

- Direct comparisons of available oral therapies for PAH monotherapy for treatment-naive patients have not been performed no recommendations or suggestions of one agent, or class of agent, over another.
- Evidenz zu einzelnen Medikamenten siehe A) “Patients With WHO FC II Symptoms“

C) Patients with WHO FC IV Symptoms:

- For treatment naive PAH patients in WHO FC IV, we advise initiation of monotherapy with a parenteral prostanoid agent. More specifically in these patients:
- We suggest continuous IV epoprostenol to improve WHO FC (Grade CB), improve 6MWD (Grade CB), and improve cardiopulmonary hemodynamics.
- We suggest continuous IV treprostinil to improve 6MWD (Grade CB).
- We suggest continuous subcutaneous treprostinil to improve 6MWD (Grade CB) and improve cardiopulmonary hemodynamics.

Evidenz:

- Siehe Evidenz zu A) “Patients With WHO FC II Symptoms”
- Most experts consider IV epoprostenol the therapy of choice for WHO FC IV patients based on extensive clinical experience and the findings of improved survival in a single study [37]
- RCT data [39] are limited, but considerable clinical experience supports the exercise benefits of IV treprostinil.Data suggest that this therapy may have a greater risk of catheter-associated infection (with both gram-positive and gram-negative organisms) than IV epoprostenol, and it may require higher doses (ng/kg/min) to achieve comparable efficacy.

D) PAH Patients on Established PAH-Specific Therapy:

- In PAH patients initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan (Grade CB).

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 complex patients with PAH. More specifically:

- In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled iloprost to improve 6MWD (Grade CB).
- In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we recommend the addition of inhaled treprostinil to improve 6MWD (Grade 1C)
- In PAH patients who remain symptomatic on stable doses of established IV epoprostenol, we suggest the addition of sildenafil or up titration of epoprostenol to improve 6MWD (Grade CB).
- 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 6MWD (Grade CB), WHO FC (Grade CB) and cardiopulmonary hemodynamics and to delay the time to clinical worsening (Grade CB).

- In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid we suggest macitentan to improve 6MWD (Grade CB), WHO FC (Grade CB) and to delay the time to clinical worsening (Grade CB).

Evidenz

Combination Therapy for the Initial Treatment of Patients with PAH With FC III or IV Symptoms:

47. Humbert M , Barst RJ , Robbins IM , et al . Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2 . Eur Respir J . 2004 ; 24 (3): 353 - 359.

- 1 RCT (n=33) comparing initiation of IV epoprostenol combined with bosentan with epoprostenol + placebo
  - Patients with WHO FC III or IV
  - Improvement of 6MWD, WHO FC, and total pulmonary resistance in both groups, no significant difference in the primary outcome of change in total pulmonary resistance from baseline to 16 weeks in the epoprostenol/ bosentan group vs the poprostenol/placebo group; more SAEs in combination therapy group.

Addition of Inhaled Prostanoid to Stable Oral Monotherapy:

67. McLaughlin VV , Oudiz RJ , Frost A , et al . Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension . Am J Respir Crit Care Med . 2006 ; 174 (11): 1257 – 1263.
68. Benza RL , Seeger W , McLaughlin VV , et al . Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study open-label extension . J Heart Lung Transplant . 2011 ; 30 (12): 1327 – 1333.

- 2 RCTs compared addition of inhaled prostanoid against an inhaled placebo in patients with PAH on stable monotherapy with an ETRA or PDE5 inhibitor:

  a)RCT (n=235); patients with WHO FC III (98%) or IV treated for at least 3 months with bosentan (70%) or sildenafil (30%); Inhaled treprostinil improved exercise capacity and quality of life and was safe and well tolerated.

  b) RCT (n=67); patients with PAH who remained symptomatic (94% FC III) despite bosentan therapy ; inhaled iloprost showed a tendency for improved exercise capacity compared with placebo and significant improvement in WHO FC and in the occurrence of worsening events and was safe and well tolerated.

Addition of Sildenafil to Stable IV Epoprostenol:

48. Simonneau G , Rubin LJ , Galiè N , et al ; PACES Study Group. Addition of sildenafi l to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med . 2008; 149 (8): 521 – 530.

- 1 RCT (n=267); patients with PAH, most with WHO FC II (25%) or III (65%) symptoms and a 6MWD of 100 to 450 m while treated with stable doses of IV epoprostenol; shows improvements in 6MWD, hemodynamics and time to clinical worsening; higher risk of headaches and dyspepsia.

Addition of a Long-Acting PDE5 Inhibitor to Stable Background Therapy with an ETRA:

36. Galiè N , Brundage BH , Ghofrani HA , et al ; Pulmonary Arterial Hypertension and Response to Tadalafi l (PHIRST) Study Group. Tadalafi l therapy for pulmonary arterial hypertension [published correction appears in Circulation. 2011;124(10):e279]. Circulation . 2009 ; 119 (22): 2894 – 2903.

- Tadalafil: 1 placebo-controlled RCT (n=405)

- 50% treatment naive and 50% background therapy with an ETRA (bosentan) that was continued during the study
- Although tadalafil 40 mg daily provided clinical benefit in patients as monotherapy, data did not support additional benefit of the combination of tadalafil on background bosentan therapy.

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 (Grade CB).

Evidenz

- Data from RCTs not available to inform the addition of a third pharmacologic class of PAH medication;however, addition of a third class of PAH medication usually indicates poor functional status. In this setting, treatment with a parenteral prostanoid therapy must be considered.

Galie N et al., 2016 [6].

The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

Leitlinienorganisation/Fragestellung

Treatment recommendations for PH

Methodik

Grundlage der Leitlinie

Members of this Task Force were selected by the ESC and ERS to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the ERS. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in Tables 1 and 2. A systematic literature review was performed from MEDLINE to identify new studies published since 2009 concerning the topic of PH. The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest.

LoE

Table 2 Level of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

GoR

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

6.3 Therapy

The therapy for PAH patients has evolved progressively in the past decade, increasing in complexity and in evidence for efficacy. The treatment process of PAH patients cannot be considered as a mere prescription of drugs, but is characterised by a complex strategy that includes the initial evaluation of severity and the subsequent response to treatment.

The current treatment strategy for PAH patients can be divided into three main steps:

- (1) The initial approach includes general measures (physical activity and supervised rehabilitation, pregnancy, birth control and post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to treatments, genetic counselling and travel), supportive therapy (oral anticoagulants, diuretics, O2, digoxin), referral to expert centres and acute vasoreactivity testing for the indication of chronic CCB therapy.
- (2) The second step includes initial therapy with high-dose CCB in vasoreactive patients or drugs approved for PAH in non-vasoreactive patients according to the prognostic risk (Table 13) of the patient and the grade of recommendation and level of evidence for each individual compound or combination of compounds.

- (3) The third part is related to the response to the initial treatment strategy; in the case of an inadequate response, the role of combinations of approved drugs and lung transplantation are proposed.

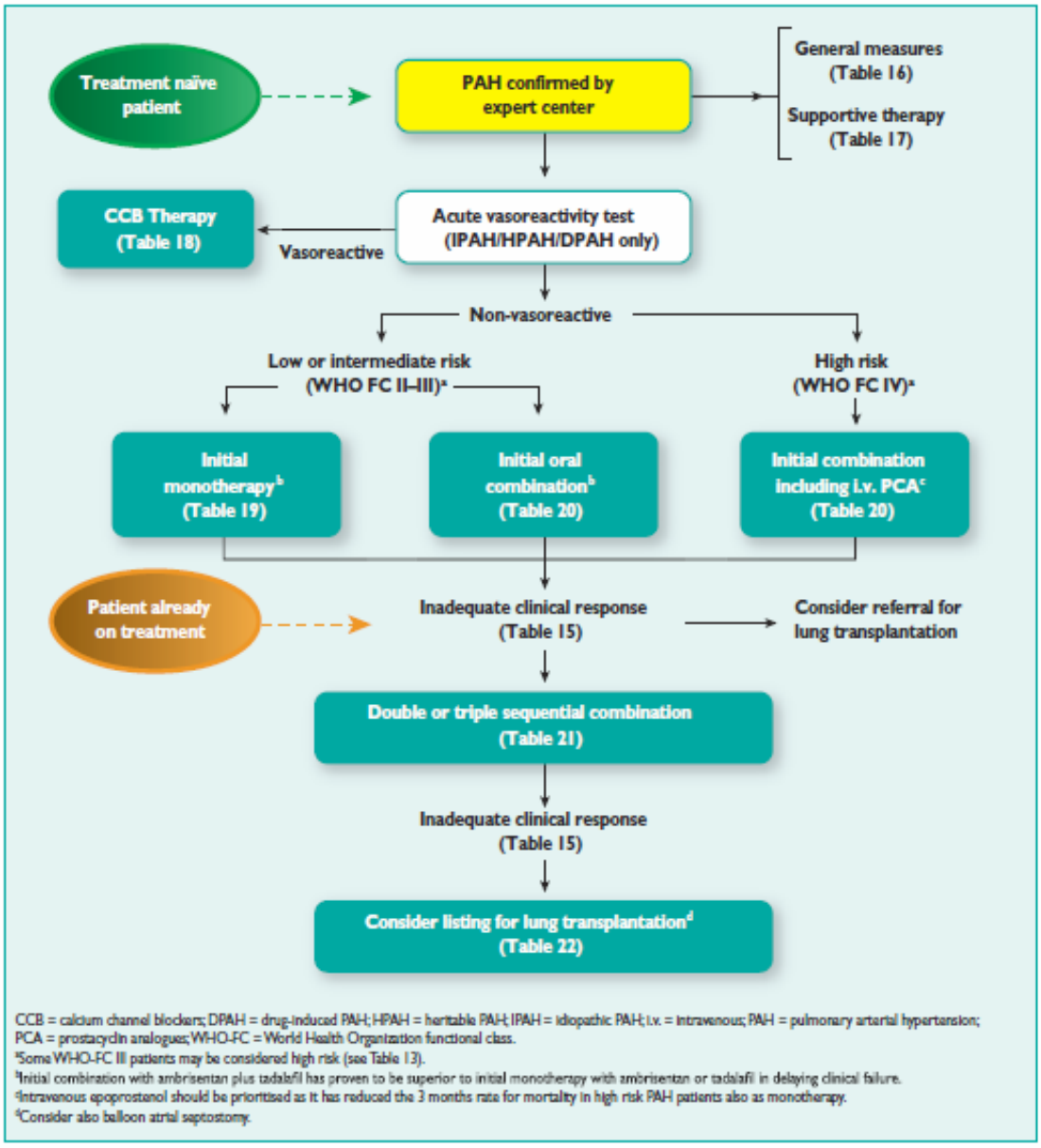

Figure 2 Evidence based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only; see description in the text).

6.3.2 Supportive therapy

Table 17 Recommendations for supportive therapy

Recommendations	Class[a]	Level[b]	Ref.[c]
Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention	I	C	178
Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)[d]	I	C	179
Oral anticoagulant treatment may be considered in patients with IPAH, HPAH and PAH due to use of anorexigens	IIb	C	84,171, 175–177
Correction of anaemia and/or iron status may be considered in PAH patients	IIb	C	184
The use of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, beta-blockers and ivabradine is not recommended in patients with PAH unless required by co-morbidities (i.e. high blood pressure, coronary artery disease or left heart failure)	III	C	

HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; O_2 = oxygen; PAH = pulmonary arterial hypertension; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]See also recommendations for PAH associated with congenital cardiac shunts.

6.3.3 Specific drug therapy

Table 18 Recommendations for calcium channel blocker therapy in patients who respond to the acute vasoreactivity test

Recommendations	Class[a]	Level[b]	Ref.[c]
High doses of CCBs are recommended in patients with IPAH, HPAH and DPAH who are responders to acute vasoreactivity testing	I	C	84,85
Close follow-up with complete reassessment after 3–4 months of therapy (including RHC) is recommended in patients with IPAH, HPAH and DPAH treated by high doses of CCBs	I	C	84,85
Continuation of high doses of CCBs is recommended in patients with IPAH, HPAH and DPAH in WHO-FC I or II with marked haemodynamic improvement (near normalization)	I	C	84,85
Initiation of specific PAH therapy is recommended in patients in WHO-FC III or IV or those without marked haemodynamic improvement (near normalization) after high doses of CCBs	I	C	84,85
High doses of CCBs are not indicated in patients without a vasoreactivity study or non-responders unless standard doses are prescribed for other indications (e.g. Raynaud's phenomenon)	III	C	

CCB = calcium channel blocker; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; RV = right ventricular; WHO-FC = World Health Organization functional class.

Table 19 Recommendations for efficacy of drug monotherapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. The sequence is by pharmacological group, by rating and by alphabetical order

Measure/treatment			Class[a]-Level[b]						Ref.[c]
			WHO-FC II		WHO-FC III		WHO-FC IV		
Calcium channel blockers			I	C[d]	I	C[d]	-	-	84,85
Endothelin receptor antagonists	Ambrisentan		I	A	I	A	IIb	C	194
	Bosentan		I	A	I	A	IIb	C	196–200
	Macitentan[e]		I	B	I	B	IIb	C	201
Phosphodiesterase type 5 inhibitors	Sildenafil		I	A	I	A	IIb	C	205–208
	Tadalafil		I	B	I	B	IIb	C	211
	Vardenafil[g]		IIb	B	IIb	B	IIb	C	212
Guanylate cyclase stimulators	Riociguat		I	B	I	B	IIb	C	214
Prostacyclin analogues	Epoprostenol	Intravenous[e]	-	-	I	A	I	A	220–222
	Iloprost	Inhaled	-	-	I	B	IIb	C	229–231
		Intravenous[g]	-	-	IIa	C	IIb	C	232
	Treprostinil	Subcutaneous	-	-	I	B	IIb	C	233
		Inhaled[g]	-	-	I	B	IIb	C	237
		Intravenous[f]	-	-	IIa	C	IIb	C	234
		Oral[g]	-	-	IIb	B	-	-	238–240
	Beraprost[g]		-	-	IIb	B	-	-	218
IP receptor agonists	Selexipag (oral)[g]		I	B	I	B	-	-	241,248

EMA = European Medicines Agency; PAH = pulmonary arterial hypertension; RCT = randomized controlled trial; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Only in responders to acute vasoreactivity tests = class I, for idiopathic PAH, heritable PAH and PAH due to drugs; class IIa, for conditions associated with PAH.
[e]Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality.
[f]In patients not tolerating the subcutaneous form.
[g]This drug is not approved by the EMA at the time of publication of these guidelines.

Table 20 Recommendations for efficacy of initial drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Ambrisentan + tadalafil[d]	I	B	I	B	IIb	C	247
Other ERA + PDE-5i	IIa	C	IIa	C	IIb	C	-
Bosentan + sildenafil + i.v. epoprostenol	-	-	IIa	C	IIa	C	246
Bosentan + i.v. epoprostenol	-	-	IIa	C	IIa	C	198, 245
Other ERA or PDE-5i + s.c. treprostinil			IIb	C	IIb	C	-
Other ERA or PDE-5i + other i.v. prostacyclin analogues			IIb	C	IIb	C	-

ERA = endothelin receptor antagonist; i.v. = intravenous; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; s.c. = subcutaneous; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical failure as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).

Table 21 Recommendations for efficacy of sequential drug combination therapy for pulmonary arterial hypertension (group 1) according to World Health Organization functional class. Sequence is by rating and by alphabetical order

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Macitentan added to sildenafil[d]	I	B	I	B	IIa	C	201
Riociguat added to bosentan	I	B	I	B	IIa	C	214
Selexipag[e] added to ERA and/or PDE-5i[d]	I	B	I	B	IIa	C	241, 248
Sildenafil added to epoprostenol	–	–	I	B	IIa	B	209
Treprostinil inhaled added to sildenafil or bosentan	IIa	B	IIa	B	IIa	C	237
Iloprost inhaled added to bosentan	IIb	B	IIb	B	IIb	C	230, 231
Tadalafil added to bosentan	IIa	C	IIa	C	IIa	C	211
Ambrisentan added to sildenafil	IIb	C	IIb	C	IIb	C	249
Bosentan added to epoprostenol	–	–	IIb	C	IIb	C	250
Bosentan added to sildenafil	IIb	C	IIb	C	IIb	C	251, 252
Sildenafil added to bosentan	IIb	C	IIb	C	IIb	C	252
Other double combinations	IIb	C	IIb	C	IIb	C	–
Other triple combinations	IIb	C	IIb	C	IIb	C	–
Riociguat added to sildenafil or other PDE-5i	III	B	III	B	III	B	215

EMA = European Medicines Agency; ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Time to clinical worsening as primary endpoint in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined).
[e]This drug was not approved by the EMA at the time of publication of these guidelines.

Table 22 Recommendations for efficacy of intensive care unit management, balloon atrial septostomy and lung transplantation for pulmonary arterial hypertension (group 1) according to World Health Organization functional class

Measure/ treatment	Class[a]-Level[b]						Ref.[c]
	WHO-FC II		WHO-FC III		WHO-FC IV		
Hospitalization in ICU is recommended in PH patients with high heart rate (>110 beats/min), low blood pressure (systolic blood pressure <90 mmHg), low urine output and rising lactate levels due or not due to co-morbidities	–	–	–	–	I	C	257
Inotropic support is recommended in hypotensive patients			I	C	I	C	
Lung transplantation is recommended soon after inadequate clinical response on maximal medical therapy	–	–	I	C	I	C	270
BAS may be considered where available after failure of maximal medical therapy	–	–	IIb	C	IIb	C	253, 254

BAS = Balloon atrial septostomy; ICU = intensive care unit; PH = pulmonary hypertension; WHO-FC = World Health Organization functional class.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 07.05.2018

#	Suchfrage
1	MeSH descriptor: [Hypertension, Pulmonary] explode all trees
2	(pulmonary near/6 hypertension):ti,ab,kw (Word variations have been searched)
3	(CTEPH):ti,ab,kw (Word variations have been searched)
4	#1 or #2 or #3
5	#4 Publication Year from 2013 to 2018
6	#5 in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 07.05.2018

#	Suchfrage
1	pulmonary hypertension[MeSH Terms]
2	("pulmonary hypertension"[Title/Abstract]) OR "pulmonary arterial hypertension"[Title/Abstract]
3	CTEPH[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
6	(#5) AND ("2013/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 07.05.2018

#	Suchfrage
1	pulmonary hypertension[MeSH Terms]
2	("pulmonary hypertension"[Title/Abstract]) OR "pulmonary arterial hypertension"[Title/Abstract]
3	CTEPH[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*[Title])
6	(#5) AND ("2013/05/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT retracted publication[ptyp]

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