American Heart Journal Plus: Cardiology Research and Practice 46 (2024) 100466

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Review article

An in-depth evaluation of the efficacy and safety of various treatment modalities for chronic thromboembolic pulmonary hypertension: A systematic review and network meta-analysis

Noha Rami Ismail [a,b], Hamdy A. Makhlouf [a,c], Atef Hassan [a,d], Ahmed Elshahat [a,d], Mohamed Abdelfatah Abdellatif [a,b], Abdelmoemen Esam Rezk [a,e], Abdelrahman Mady [a,d], Rashad G. Mohamed [a,f], Hanady Mohammad Elfeky [a,g], Ahmed Abdelaziz [a,d,*]

[a] Medical Research Group of Egypt (MRGE), Negida Academy, Arlington, MA, USA
[b] Faculty of Medicine, Zagazig University, Zagazig, Egypt
[c] Faculty of Medicine, Minia University, Egypt
[d] Faculty of Medicine Al-Azhar University, Cairo, Egypt
[e] Faculty of Medicine, 6th of October University, Cairo, Egypt
[f] Mansoura Manchester Program for Medical Education, Faculty of Medicine, Mansoura University, Egypt
[g] Department of Critical Care Medicine, Menoufia University, Menoufia, Egypt

ARTICLE INFO

Keywords:
Chronic thromboembolic pulmonary hypertension
CTEPH
PADN
BPA
Meta-analysis

ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a major risk for pulmonary hypertension with poor prognosis. Limited data is available on the optimal treatment of choice. We aimed to comprehensively assess the efficacy and safety of CTEPH targeted therapies and update the evidence.

Methods: We searched PubMed, Scopus, and the Cochrane library up to December 2023 to include randomized controlled trials comparing different therapies in patients with CTEPH. Primary outcomes were 6-minute walk distance (6 MWD), pulmonary vascular resistance (PVR), and mean pulmonary artery pressure (mPAP). While secondary outcomes were the mean right atrial pressure (mRAP), Borg dyspnea score, cardiac output (CO), cardiac index, adverse events, and all-cause mortality.

Results: Fourteen RCTs comprising 1047 patients were included in this network meta-analysis. Regarding 6 MWD, PADN (MD=113.59, 95% CI: 53.80; 173.39), BPA (MD=48.84, 95% CI: 27.99; 69.69), riociguat (MD=42.59, 95% CI: 22.01; 63.18), treprostinil (MD=41.60, 95% CI: 17.07; 66.13), and macitentan (MD=34.00, 95% CI: 3.50; 64.50) were favored compared to placebo. In terms of PVR, BPA (MD=-392.19, 95% CI: -571.77; -212.62), treprostinil (MD=-287.20, 95% CI: -475.63; -98.77), PADN (MD=-280.61, 95% CI: -506.69; -54.52), bosentan (MD=-176.00, 95% CI: -340.91; -11.09), and riociguat (MD=-171.61, 95% CI: -298.40; -44.81) displayed statistically significant results.

Conclusion: Current therapeutic modalities are effective in terms of improving exercise capacity, pulmonary hemodynamics, and reducing adverse events and all-cause mortality. Overall, BPA and PADN were superior to all other targeted medications in the studied outcomes.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease that is considered one of the major causes of severe pulmonary arterial hypertension (PAH) [1]. It is characterized by dislodged thromboembolic obstruction in the pulmonary arteries and progressive elevation of pulmonary artery pressure [2]. The overall incidence of CTEPH after acute pulmonary embolism is 2.82% [3]. Multiple factors play a role in the mechanism of CTEPH, including small vessel disease, chronic organized thrombus, and the resultant right ventricular dysfunction [4]. Incomplete resolution and organization of the thrombus lead to impaired blood flow. Subsequently, vascular arteriopathy is induced by high pressure and shear stress due to redistribution of blood in patent pulmonary arteries, which results in

* Corresponding author at: Medical Research Group of Egypt (MRGE), Negida Academy, Arlington, MA, Egypt.
E-mail address: ahmedmhmd0144@gmail.com (A. Abdelaziz).

https://doi.org/10.1016/j.ahjo.2024.100466
Received 27 March 2024; Received in revised form 20 September 2024; Accepted 23 September 2024
Available online 24 September 2024

endothelial dysfunction and eventually vascular remodelling [5]. Such events lead to progressive elevation of pulmonary vascular resistance (PVR), which predisposes patients to right-sided heart failure and death [6].

There are several therapeutic approaches to CTEPH, including surgical, interventional, and medical therapies. Both the European Society of Cardiology (ESC)/European Respiratory Society (ERS) and American guidelines recommend pulmonary endarterectomy (PEA) as the gold standard treatment for CTEPH [7–9]. However, it is estimated that up to 50% of patients are considered inoperable [10]. Fortunately, there is increasing evidence for the efficacy of PEA alternatives. Balloon pulmonary angioplasty (BPA) is one of the proposed techniques, as reported by Zhang *et al.*, to have a higher survival rate, improved exercise capacity, and fewer complications than PEA [11].

Furthermore, several medical therapies have been developed for the management of CTEPH and residual PAH. For instance, soluble guanylate cyclase (sGC) stimulator (riociguat) is the first approved medical therapy for CTEPH patients and has shown significant improvement in hemodynamic parameters in patients with inoperable or persistent PAH, as reported in some studies [12,13]. Other medications include endothelin receptor antagonists (ERAs), which antagonize the vasoconstrictive and proliferative actions on vascular smooth muscles mediated by Endothelin-1 [14]. In addition, pulmonary artery denervation (PADN) is a novel therapy directed towards reducing sympathetic nervous system activation, which can be used in the treatment of residual PAH after PEA [15,16].

Although alternatives to PEA are being increasingly used, little information exists regarding the optimum therapy. To our knowledge, there is a single previously published network meta-analysis (NMA) that evaluated the efficacy and safety of 7 pulmonary vasodilators [17]. Therefore, we conducted a comprehensive NMA to update the evidence and provide evidence-based guidelines to recommend the optimum treatment modality for patients with CTEPH.

2. Methods

We conducted this NMA in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) extension statement for reporting of systematic reviews incorporating NMAs [18]. The steps were done in strict accordance with the Cochrane Handbook of Systematic Reviews and Meta-analysis of Interventions (version 5.1.0) [19]. The study is registered in PROSPERO: **CRD42023459975**

2.1. Eligibility criteria

We included only randomized controlled trials (RCTs) that met the following criteria: (1) participants: study subjects were adults aged >18 years with CTEPH, (2) intervention and comparator: medical therapies including endothelin receptor antagonists (ERAs) (bosentan, ambrisentan, and macitentan), prostanoid analogs (iloprost, and treprostinil),

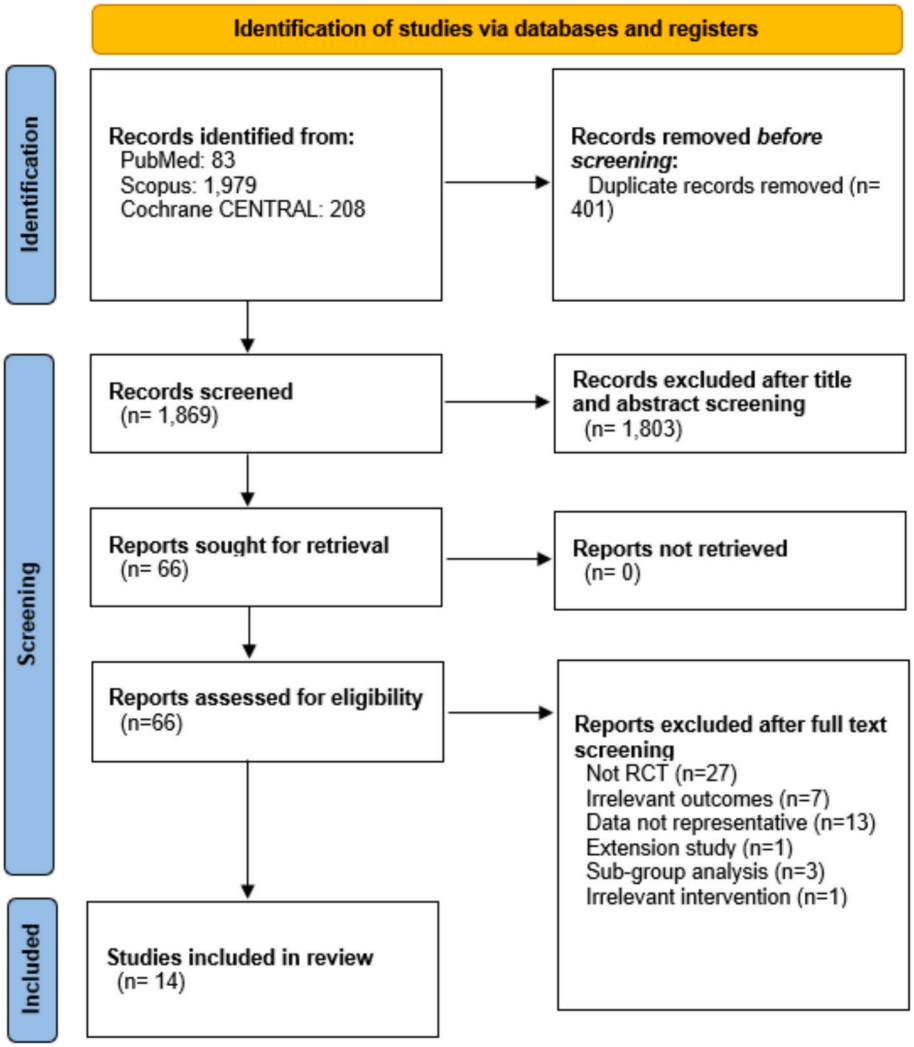

Fig. 1. PRISMA flow diagram showing the two-phase screening process.

Table 1
Baseline and clinical characteristics of the patients in trials of CTEPH.

Reference	Multicenter	Intervention	Sample size	Age (Mean ± SD)	Male Sex n (%)	Intervention dose	Previous PEA	Follow-up duration
Kramm 2005	Single center	Iloprost	11	54 ± 17	7 (63.6%)	25 μg	11 (100%)	Until hospital discharge
		Placebo	11	56 ± 13	7 (63.6%)		11 (100%)	
Jaïs 2008	Multicenter	Bosentan	77	63 ± 12.9	22 (28.6%)	62.5 mg to 125 mg twice daily	22 (28.6%)	16 Week
		Placebo	80	63.1 ± 10.3	33 (41.2%)		22 (27.5%)	
Suntharalingam 2008	Single center	Sildenafil	9	49.9 ± 13.1	2 (22%)	40 mg thrice daily	2 (22%)	12 weeks
		Placebo	10	60.0 ± 14.4	7 (70%)		7 (70%)	
Reesink 2010	Single center	Bosentan	13	67 ± 8	3 (29%)	62.5 mg to 125 mg twice daily	0 (0%)	16 weeks
		Placebo	12	64 ± 10	4 (34%)		0 (0%)	
Ghofrani 2013	Multi center	Riociguat	173	59 ± 14	55 (32%)	0.5 mg to 2.5 mg thrice daily	52 (30%)	16 weeks
		Placebo	88	59 ±13	34 (39%)		20 (23%)	
Ghofrani 2018	Multi center	Macitentan	40	58.2 ± 14.0	14 (35%)	10 mg once daily	0 (0%)	24 weeks
		Placebo	40	56.9 ± 13.9	15 (38%)		0 (0%)	
Escribano-Subias 2019	Multi center	Ambrisentan	17	61.2 ± 13.4	9 (53%)	5 mg once daily	0 (0%)	16 weeks
		Placebo	16	59.8 ± 9.0	6 (37%)		0 (0%)	
Sadushi-Kolici 2019	Multi center	High-dose treprostinil	53	68 ± 11.2	34 (64%)	30 ng/kg/min	3 (6%)	24 weeks
		Low- dose of treprostinil	52	61 ± 14.6	22 (42%)	3 ng/kg/min	5 (10%)	
Aoki 2020	Single center	Riociguat	10	64 ± 11	1 (10%)	up to 7.5 mg once daily	NR	24 weeks
		Placebo	11	66 ± 8	1 (9%)		NR	
Romanov 2020	Single center	PADN	25	48 ± 14	12 (48%)	N/A	100%	48 weeks
		Riociguat + sham PADN	25	47 ± 14	13 (52%)	0.5 mg to 2.5 mg thrice daily	100%	
Tanabe 2020	Multicenter	Selexipag	25	58 ± 15	8 (32.0%)	100 μg to 800 μg twice daily	3 (12%)	17 weeks
		Placebo	9	60 ± 5	2 (22.2%)		1 (11.1%)	
Ogo 2022	Multicenter	Selexipag	39	66.3 ± 11.1	10 (25.6%)	200 μg to 1600 μg twice daily	5 (12.8%)	20 week
		Placebo	39	68.3 ± 9.6	10 (25.6%)		5 (12.8%)	
Jaïs 2022	Multicenter	BPA	52	68.1 ± 9.4	26 (50%)	N/A	0 (0%)	26 weeks
		Riociguat	53	66.8 ± 10.5	26 (49%)	1 mg to 2.5 mg thrice daily	0 (0%)	
Kawakami 2022	Multicenter	BPA	31	68.0 ± 9.1	7 (22.6%)	N/A	0 (0%)	48 weeks
		Riociguat	26	65.7 ± 10.9	3 (11.5%)	1 mg to 2.5 mg thrice daily	0 (0%)	

prostacyclin receptor agonists (selexipag), phosphodiesterase-5 inhibitor (PDE5-i) (sildenafil), and soluble guanylate cyclase (sGC) stimulators (riociguat), procedures including pulmonary endarterectomy (PEA), pulmonary artery denervation (PADN), and balloon pulmonary angioplasty (BPA), or placebo, (3) outcome: 6-minute walk distance (6 MWD), pulmonary hemodynamics, adverse events, and all-cause mortality. We excluded non-English studies and studies including PAH patients with any World Health Organization (WHO) group other than Group 4 (CTEPH) according to the updated clinical classification of pulmonary hypertension [20].

2.2. Primary and secondary outcomes

The primary outcomes of interest were 6-minute walk distance (6 MWD), pulmonary vascular resistance (PVR), and mean pulmonary artery pressure (mPAP). The secondary outcomes were the mean right atrial pressure (mRAP), Borg dyspnea score, cardiac output (CO), cardiac index, adverse events, and all-cause mortality.

2.3. Literature search

We performed a comprehensive search of several databases, including the Cochrane Central Library, PubMed, and Scopus. The databases were searched from inception until December 2023. We conducted our search based on the following keywords: ("Chronic thromboembolic pulmonary hypertension OR "CTEPH") AND ("riociguat" OR "soluble guanylate cyclase stimulators" OR "sGC stimulators" OR "sildenafil" OR "phosphodiesterase-5 inhibitor" OR "PDE5-I" OR "prostacyclin" OR "iloprost" OR "treprostinil" OR "prostanoid analogs" OR "selexipag" OR "prostacyclin receptor agonists" OR "bosentan" OR "ambrisentan" OR "macitentan" OR "endothelin receptor antagonists" OR "ERAs" OR "Balloon pulmonary angioplasty" OR "BPA" OR "Pulmonary artery denervation" OR "PADN" OR "pulmonary endarterectomy" OR "PEA"). A detailed search strategy for each database is provided in ***Supplementary Table 1***. In addition, we performed a manual search of the reference lists of the relevant studies and reviews.

2.4. Study screening and selection

Three authors independently reviewed the search results. Titles and abstracts were first screened for eligibility, followed by a full-text screening of the included studies. We used Rayaan software in to screen the articles and remove duplicates. Discrepancies were discussed until a consensus was reached.

2.5. Data extraction

Data were extracted using a standardized data abstraction form. The extracted data included: (1) last name of the first author, (2) year of publication, (3) setting, (4) intervention and dose, (5) sample size, and (6) follow-up duration, (7) baseline patient characteristics (age, male sex, and previous PEA).

2.6. Risk of bias assessment

We used the Cochrane Collaboration's tool 2 to assess the quality of each RCT [21]. Two authors independently assessed the outcomes of interest across 5 domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results, and overall bias. For each domain, we rated the risk of bias as low, high, or some concerns. Discrepancies were resolved through discussion.

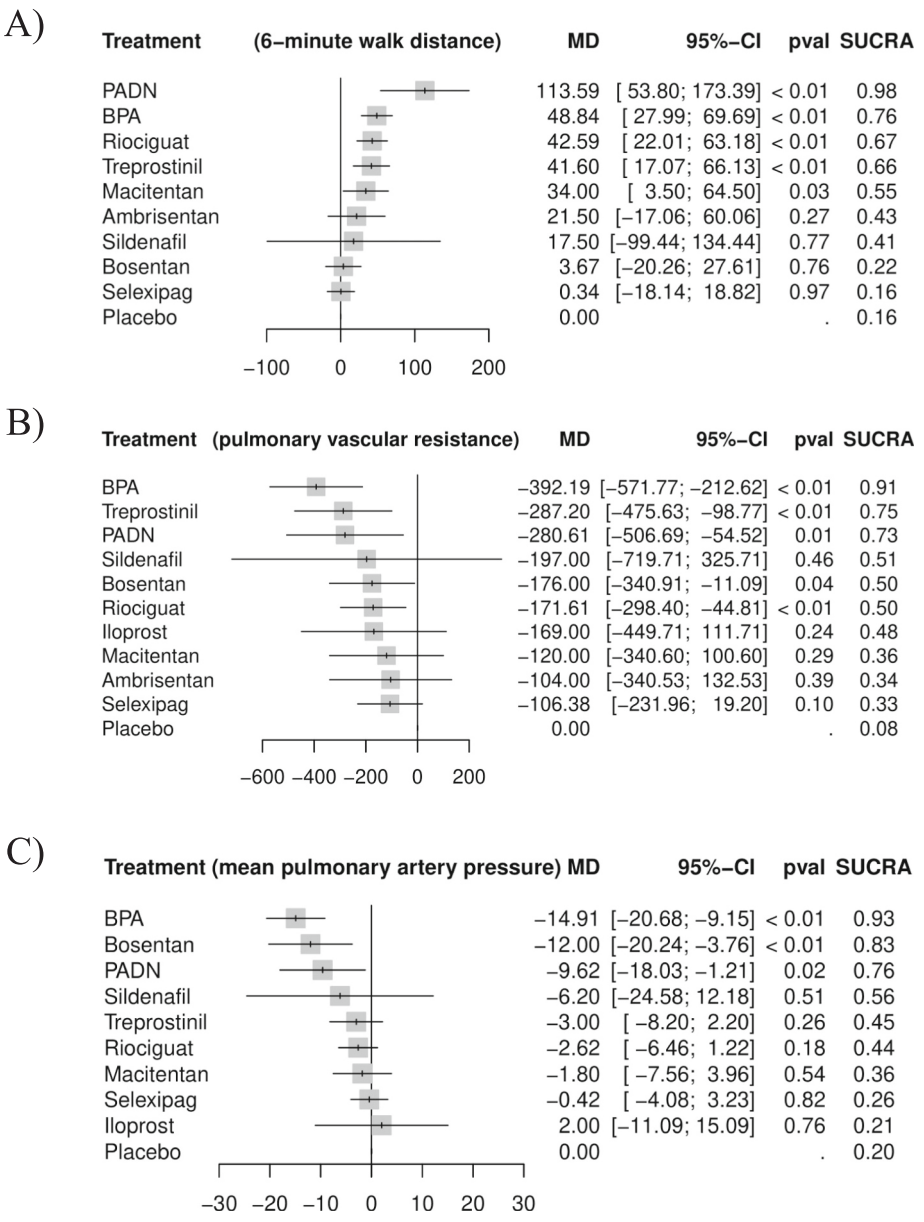

Fig. 2. Forest plot for each primary outcome assessing the efficacy. A) 6-minute walk distance; B) Pulmonary vascular resistance; C) Mean pulmonary artery pressure.

2.7. Data analysis

Analysis was conducted in R software [22] and Figs. were produced using the package netmeta [23]. We conducted a network meta-analysis using a frequentist effects model to compare the efficacy of multiple treatment options. In contrast to traditional pairwise meta-analyses, this model permits the assessment of multiple interventions simultaneously and makes indirect comparisons between different outcomes, despite the lack of direct head-to-head comparisons.

The accuracy of the overall network evidence for the effect of this specific treatment was improved by including head-to-head studies comparing one treatment to another. Continuous variables were analyzed as mean difference (MD), and dichotomous variables were analyzed as risk ratio (RR). 95% CI was used to predict statistical significance. The interval containing 0 for MD and 1 for RR indicated no significant difference.

Heterogeneity was evaluated by chi-squared test, with significant heterogeneity defined as $P<0.1$ and $I^2 \geq 50\%$. A random effects model was utilized to account for the heterogeneity in the analysis. To rank the interventions based on their effectiveness for each outcome, we used the surface under cumulative ranking (SUCRA) approach. The SUCRA approach has a value index that begins at 0% (least effective) and ends at 100% (most effective). This approach provides a comparative measure of intervention performance [24].

3. Results

3.1. Study selection

A total of 2,270 potentially relevant articles were identified from the electronic databases. We eliminated 401 duplicates, followed by 1,803 articles in the first phase of the title and abstract screening. A total of 66 articles were reviewed for full text. Of these, only 14 met our criteria and were included in the analysis [25–38]. Fig. 1 shows the PRISMA flow diagram.

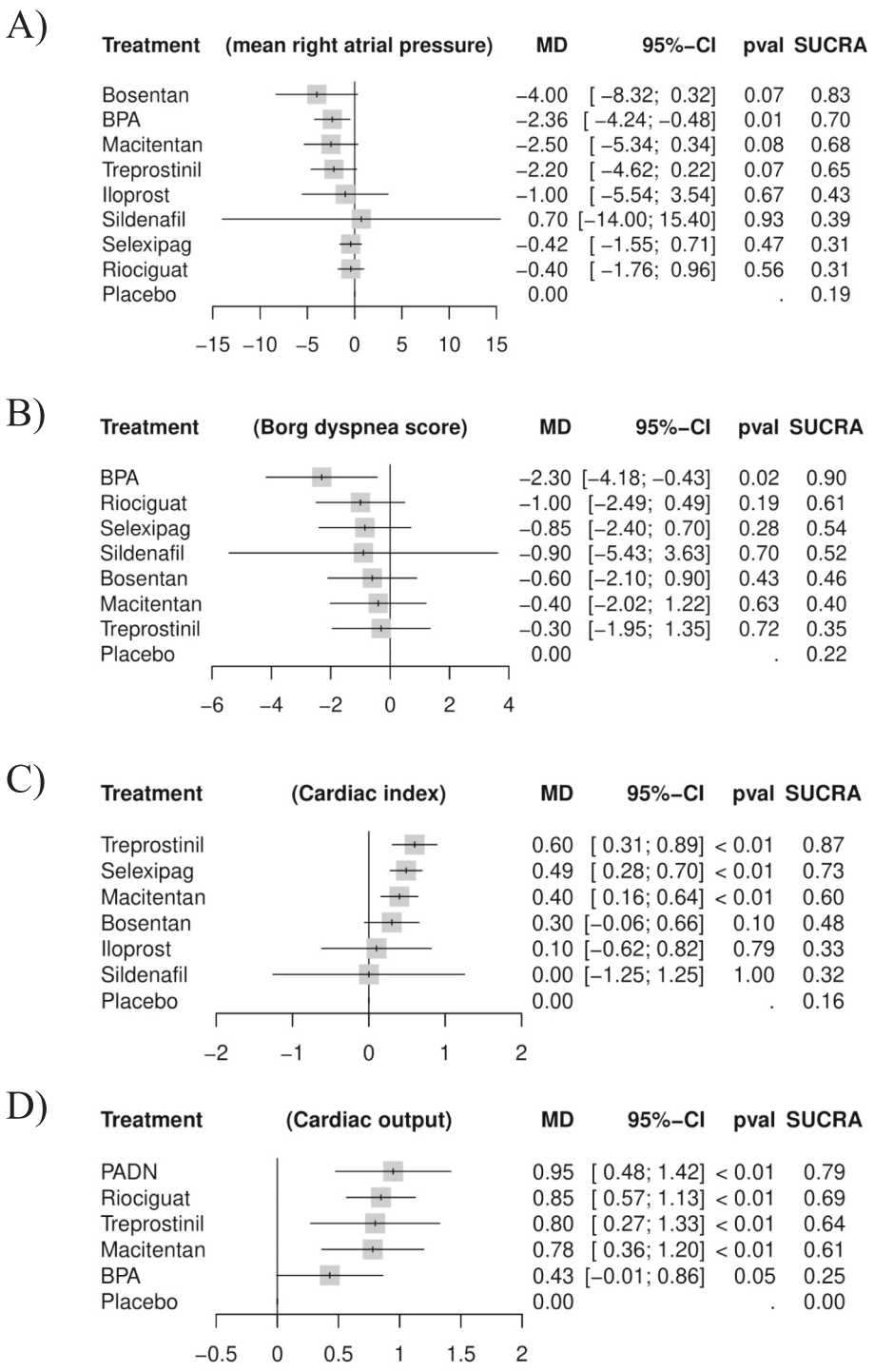

Fig. 3. Forest plot for each secondary outcome assessing the efficacy. A) Mean right atrial pressure; B) Borg dyspnea score; C) Cardiac index; D) Cardiac output.

3.2. Study characteristics

Our study included 14 RCTs with a total of 1047 patients, ranging from 19 to 261 per study. Therapies assessed included riociguat, selexipag, macitentan, bosentan, ambrisentan, treprostinil, iloprost, sildenafil, BPA, and PADN. No RCTs evaluated PEA; hence, PEA was not included in our analysis. Of the included trials, the group receiving medical therapy was compared to the placebo in 11 trials [27–33,35–38], 2 trials compared BPA to riociguat [25,26], and one trial compared PADN to riociguat [34]. Table 1 presents the characteristics of the included RCTs published between 2005 and 2022. The outcomes of interest reported in each study are presented in Supplementary Table 2. Figs. 2-4 present the direct comparisons for each outcome. Net league Tables 2 and 3 show the effect estimates of different treatments.

3.3. Risk of bias assessment

Fig. 5 shows the graph and summary of the risk of bias assessment for the included studies. All the studies exhibited a low risk of bias in terms of random sequence generation and missing outcome data. Eight studies showed a low risk of bias in terms of deviation from the intended

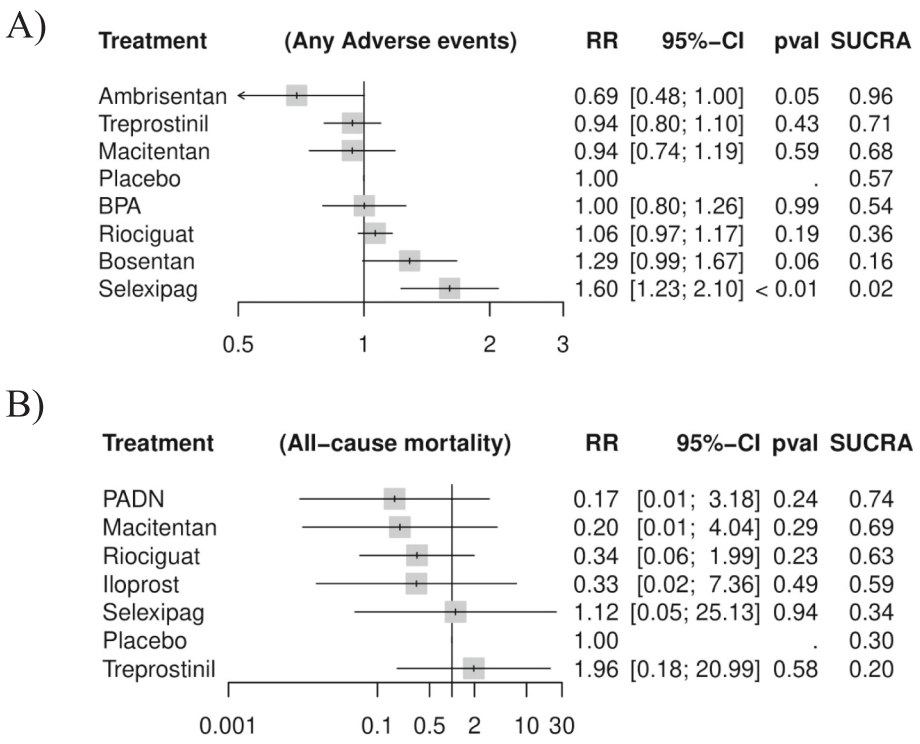

Fig. 4. Forest plot for each secondary outcome assessing the safety. A) Any adverse events; B) All-cause mortality.

interventions [29–32,34–37]. Measurement of the outcome was adequately reported in 5 studies [28,29,31,34,38]. Only 3 studies showed some concerns regarding the selection of the reported result [27,30,38]. Apart from 3 studies [29,31,34], all studies showed some concerns regarding overall bias.

3.4. Primary outcomes

Figs. 6-8 illustrate the network of comparisons for each outcome. Most of the studies were directly linked to placebo, as shown in the network geometry.

3.4.1. Six-minute walk distance

Thirteen studies reported the 6 MWD outcome, comprising 1025 patients. The treatment comparison groups consisted of 10 nodes representing 9 different therapies and the placebo, as shown in Fig. 6A. The analysis results showed that PADN (MD=113.59, 95% CI: 53.80; 173.39), BPA (MD=48.84, 95% CI: 27.99; 69.69), riociguat (MD=42.59, 95% CI: 22.01; 63.18), treprostinil (MD=41.60, 95% CI: 17.07; 66.13), and macitentan (MD=34.00, 95% CI: 3.50; 64.50) displayed statistically significant results compared with placebo, as shown in Fig. 2A and Table 2. Other therapies did not demonstrate any statistically significant results when compared with placebo. This is further indicated by the SUCRA rankings in Table 4, which show that PADN exhibited relatively greater efficacy than the other interventions (98%), followed by BPA (76%), riociguat (67%), treprostinil (66%), and macitentan (55%). There was no significant heterogeneity within pairwise comparisons (I^2=0%, p=0.7634).

3.4.2. Pulmonary vascular resistance

Thirteen studies reported the PVR outcome, including 1022 patients. The treatment comparison groups consisted of 11 nodes representing 10 different therapies and a placebo, as shown in Fig. 6B. Statistically significant results were only observed for BPA (MD=-392.19, 95% CI: -571.77; -212.62), treprostinil (MD=-287.20, 95% CI: -475.63; -98.77), PADN (MD=-280.61, 95% CI: -506.69; -54.52), bosentan (MD=-176.00, 95% CI: -340.91; -11.09), and riociguat (MD=-171.61, 95% CI: -298.40; -44.81) when compared with placebo, as shown Fig. 2B and Table 2. Compared with placebo, no significant differences were observed between the other treatments. As shown in Table 4, the SUCRA values indicated the superiority of BPA (91%) over other interventions, followed by treprostinil (75%), PADN (73%), bosentan (50%), and riociguat (50%). There was significant heterogeneity within pairwise comparisons (I^2=59.6%, p=0.0595).

3.4.3. Mean pulmonary artery pressure

Twelve studies reported the mPAP outcome, including 857 patients. The treatment comparison groups consisted of 10 nodes representing 9 different therapies and a placebo, as shown in Fig. 6C. The analysis results showed that BPA (MD=-14.91, 95% CI: -20.68; -9.15), bosentan (MD=-12.00, 95% CI: -20.24; -3.76), and PADN (MD=-9.62, 95% CI: -18.03; -1.21) performed significantly better than placebo, as demonstrated in Fig. 2C and Table 2. BPA topped the ranking (93%), followed by bosentan (83%), and PADN (76%), according to the SUCRA results, as shown in Table 4. There was significant heterogeneity within pairwise comparisons (I^2=55.4%; p=0.0810).

3.4.4. Sensitivity analysis

We performed a sensitivity analysis by excluding Jaïs 2022 [26], as all reported changes from baseline were analysed with an analysis of covariance (ANCOVA) model, with the treatment and baseline value as covariates and revealed minor fluctuation in the effect size with no significant differences regarding primary outcomes, as shown in Supplementary Fig. 1.

3.5. Secondary outcomes

3.5.1. Mean right atrial pressure

The analysis results revealed that only BPA (MD=-2.36, 95% CI: -4.24; -0.48) had statistically significant results when compared to the placebo, as shown in Fig. 3A and Table 2. Regarding SUCRA values, bosentan (83%) had the highest ranking, followed by BPA (70%) and

Table 2
The league table shows the effect estimate of treatments in outcomes assessing the efficacy outcomes. Significant results are in bold.

6-Minute Walk Distance MD (95%CI)									
Ambrisentan	.	.	.	.	21.50 (-17.06; 60.06)	.	.	.	.
17.83 (-27.56; 63.21)	Bosentan	.	.	.	3.67 (-20.26; 27.61)	.	.	.	.
-27.34 (-71.17; 16.50)	**-45.16 (-76.91; -13.42)**	BPA	.	.	.	**6.24 (2.93; 9.56)**	.	.	.
-12.50 (-61.66; 36.66)	-30.33 (-69.10; 8.44)	14.84 (-22.11; 51.79)	Macitentan	.	**34.00 (3.50; 64.50)**	.	.	.	.
-92.09 (-163.24; -20.94)	**-109.92 (-174.33; -45.51)**	**-64.76 (-120.99; -8.52)**	**-79.59 (-146.72; -12.47)**	PADN	.	**71.00 (14.86; 127.14)**	.	.	.
21.50 (-17.06; 60.06)	3.67 (-20.26; 27.61)	**48.84 (27.99; 69.69)**	**34.00 (3.50; 64.50)**	**113.59 (53.80; 173.39)**	Placebo	**-42.59 (-63.18; -22.01)**	-0.34 (-18.82; 18.14)	-17.50 (-134.44; 99.44)	**-41.60 (-66.13; -17.07)**
-21.09 (-64.80; 22.62)	**-38.92 (-70.49; -7.35)**	**6.24 (2.93; 9.56)**	-8.59 (-45.39; 28.20)	**71.00 (14.86; 127.14)**	**-42.59 (-63.18; -22.01)**	Riociguat	.	.	.
21.16 (-21.60; 63.92)	3.34 (-26.90; 33.57)	**48.50 (20.64; 76.36)**	33.66 (-2.00; 69.32)	**113.26 (50.67; 175.84)**	-0.34 (-18.82; 18.14)	**42.26 (14.59; 69.92)**	Selexipag	.	.
4.00 (-119.14; 127.14)	-13.83 (-133.19; 105.54)	31.34 (-87.45; 150.13)	16.50 (-104.36; 137.36)	96.09 (-35.25; 227.44)	-17.50 (-134.44; 99.44)	25.09 (-93.65; 143.83)	-17.16 (-135.56; 101.23)	Sildenafil	.
-20.10 (-65.80; 25.60)	**-37.93 (-72.20; -3.65)**	7.24 (-24.96; 39.43)	-7.60 (-46.74; 31.54)	**71.99 (7.36; 136.63)**	**-41.60 (-66.13; -17.07)**	0.99 (-31.03; 33.02)	**-41.26 (-71.97; -10.55)**	-24.10 (-143.59; 95.39)	Treprostinil

Pulmonary Vascular Resistance MD (95%CI)										
Ambrisentan	.	.	.	.	.	-104.00 (-292.41; 84.41)	.	.	.	.
72.00 (-133.53; 277.53)	Bosentan	.	.	.	.	**-176.00 (-258.13; -93.87)**	.	.	.	.
342.94 (132.14; 553.74)	**270.94 (145.69; 396.19)**	BPA	.	.	.	.	**-235.81 (-304.95; -166.67)**	.	.	.
65.00 (-241.34; 371.34)	-7.00 (-262.14; 248.14)	**-277.94 (-537.34; -18.54)**	Iloprost	.	.	-169.00 (-410.55; 72.55)	.	.	.	.
16.00 (-236.41; 268.41)	-56.00 (-242.97; 130.97)	**-326.94 (-519.69; -134.19)**	-49.00 (-343.21; 245.21)	Macitentan	.	-120.00 (-287.96; 47.96)	.	.	.	.
216.13 (-16.77; 449.04)	144.13 (-15.53; 303.80)	-126.81 (-265.97; 12.36)	151.13 (-126.53; 428.80)	200.13 (-16.57; 416.84)	PADN	.	-109.00 (-229.77; 11.77)	.	.	.
-104.00 (-292.41; 84.41)	**-176.00 (-258.13; -93.87)**	**-446.94 (-541.50; -352.38)**	-169.00 (-410.55; 72.55)	-120.00 (-287.96; 47.96)	**-320.13 (-457.06; -183.21)**	Placebo	**211.13 (146.63; 275.64)**	**98.56 (40.84; 156.27)**	197.00 (-305.76; 699.76)	**287.20 (164.50; 409.90)**
107.13 (-92.01; 306.28)	35.13 (-69.30; 139.57)	**-235.81 (-304.95; -166.67)**	42.13 (-207.88; 292.15)	91.13 (-88.79; 271.06)	-109.00 (-229.77; 11.77)	**211.13 (146.63; 275.64)**	Riociguat	.	.	.
-5.44 (-202.49; 191.61)	-77.44 (-177.83; 22.94)	**-348.38 (-459.16; -237.60)**	-70.44 (-318.80; 177.91)	-21.44 (-199.05; 156.16)	**-221.58 (-370.16; -72.99)**	**98.56 (40.84; 156.27)**	**-112.58 (-199.13; -26.02)**	Selexipag	.	.
93.00 (-443.91; 629.91)	21.00 (-488.43; 530.43)	-249.94 (-761.52; 261.64)	28.00 (-529.78; 585.78)	77.00 (-453.08; 607.08)	-123.13 (-644.21; 397.94)	197.00 (-305.76; 699.76)	-14.13 (-521.02; 492.75)	98.44 (-407.62; 604.51)	Sildenafil	.
183.20 (-41.64; 408.04)	111.20 (-36.45; 258.85)	**-159.74 (-314.65; -4.83)**	118.20 (-152.73; 389.13)	167.20 (-40.81; 375.21)	-32.93 (-216.79; 150.92)	**287.20 (164.50; 409.90)**	76.07 (-62.56; 214.69)	**188.64 (53.04; 324.24)**	90.20 (-427.32; 607.72)	Treprostinil

Mean Pulmonary Artery Pressure MD (95%CI)									
Bosentan	.	.	.	.	**-12.00 (-19.06; -4.94)**	.	.	.	.

(*continued on next page*)

Table 2 (*continued*)

Mean Pulmonary Artery Pressure MD (95%CI)									
4.68 (-3.16; 12.52)	BPA	.	.	.	.	**-12.67 (-15.56; -9.77)**	.	.	.
-14.00 (-28.25; 0.25)	**-18.68 (-31.52; -5.84)**	Iloprost	.	.	2.00 (-10.38; 14.38)	.	.	.	.
-10.20 (-18.27; -2.13)	**-14.88 (-20.06; -9.71)**	3.80 (-9.18; 16.78)	Macitentan	.	-1.80 (-5.70; 2.10)	.	.	.	.
-0.98 (-10.53; 8.56)	-5.67 (-12.47; 1.14)	13.02 (-0.93; 26.96)	9.22 (1.71; 16.72)	PADN	.	**-7.00 (-13.16; -0.84)**	.	.	.
-12.00 (-19.06; -4.94)	**-16.68 (-20.09; -13.28)**	2.00 (-10.38; 14.38)	-1.80 (-5.70; 2.10)	**-11.02 (-17.43; -4.60)**	Placebo	**4.02 (2.22; 5.81)**	0.47 (-1.24; 2.17)	6.20 (-11.68; 24.08)	**3.00 (0.00; 6.00)**
-7.98 (-15.27; -0.70)	**-12.67 (-15.56; -9.77)**	6.02 (-6.50; 18.53)	2.22 (-2.07; 6.51)	**-7.00 (-13.16; -0.84)**	**4.02 (2.22; 5.81)**	Riociguat	.	.	.
-11.53 (-18.80; -4.27)	**-16.22 (-20.03; -12.41)**	2.47 (-10.03; 14.96)	-1.33 (-5.59; 2.92)	**-10.55 (-17.19; -3.91)**	0.47 (-1.24; 2.17)	**-3.55 (-6.03; -1.07)**	Selexipag	.	.
-5.80 (-25.02; 13.42)	-10.48 (-28.68; 7.72)	8.20 (-13.55; 29.95)	4.40 (-13.90; 22.70)	-4.82 (-23.81; 14.18)	6.20 (-11.68; 24.08)	2.18 (-15.78; 20.15)	5.73 (-12.23; 23.69)	Sildenafil	.
-9.00 (-16.67; -1.33)	**-13.68 (-18.22; -9.14)**	5.00 (-7.74; 17.74)	1.20 (-3.72; 6.12)	**-8.02 (-15.10; -0.93)**	**3.00 (0.00; 6.00)**	-1.02 (-4.51; 2.48)	2.53 (-0.92; 5.99)	-3.20 (-21.33; 14.93)	Treprostinil

Mean Right Atrial Pressure MD (95%CI)								
Bosentan	.	.	.	-4.00 (-8.32; 0.32)	.	.	.	.
-1.64 (-6.35; 3.07)	BPA	.	.	.	**-1.96 (-3.26; -0.66)**	.	.	.
-3.00 (-9.26; 3.26)	-1.36 (-6.28; 3.55)	Iloprost	.	-1.00 (-5.54; 3.54)	.	.	.	.
-1.50 (-6.67; 3.67)	0.14 (-3.27; 3.54)	1.50 (-3.85; 6.85)	Macitentan	-2.50 (-5.34; 0.34)	.	.	.	.
-4.00 (-8.32; 0.32)	**-2.36 (-4.24; -0.48)**	-1.00 (-5.54; 3.54)	-2.50 (-5.34; 0.34)	Placebo	0.40 (-0.96; 1.76)	0.42 (-0.71; 1.55)	-0.70 (-15.40; 14.00)	2.20 (-0.22; 4.62)
-3.60 (-8.13; 0.93)	**-1.96 (-3.26; -0.66)**	-0.60 (-5.34; 4.14)	-2.10 (-5.25; 1.05)	0.40 (-0.96; 1.76)	Riociguat	.	.	.
-3.58 (-8.04; 0.88)	-1.94 (-4.14; 0.25)	-0.58 (-5.26; 4.10)	-2.08 (-5.14; 0.98)	0.42 (-0.71; 1.55)	0.02 (-1.75; 1.79)	Selexipag	.	.
-4.70 (-20.02; 10.62)	-3.06 (-17.88; 11.76)	-1.70 (-17.09; 13.69)	-3.20 (-18.17; 11.77)	-0.70 (-15.40; 14.00)	-1.10 (-15.86; 13.66)	-1.12 (-15.87; 13.62)	Sildenafil	.
-1.80 (-6.75; 3.15)	-0.16 (-3.23; 2.90)	1.20 (-3.94; 6.34)	-0.30 (-4.03; 3.43)	2.20 (-0.22; 4.62)	1.80 (-0.98; 4.58)	1.78 (-0.89; 4.45)	2.90 (-12.00; 17.80)	Treprostinil

Borg Dyspnea Score MD (95%CI)							
Bosentan	.	.	-0.60 (-1.20; 0.00)	.	.	.	.
2.09 (1.25; 2.94)	BPA	.	.	**-1.69 (-1.80;-1.59)**	.	.	.
-0.20 (-1.25; 0.85)	**-2.29 (-3.33; -1.25)**	Macitentan	-0.40 (-1.26; 0.46)	.	.	.	.
-0.60 (-1.20; 0.00)	**-2.69 (-3.29; -2.10)**	-0.40 (-1.26; 0.46)	Placebo	**1.00 (0.42; 1.58)**	**0.85 (0.13; 1.57)**	0.90 (-3.42; 5.22)	0.30 (-0.62; 1.22)
0.40 (-0.44; 1.24)	**-1.69 (-1.80; -1.59)**	0.60 (-0.44; 1.64)	**1.00 (0.42; 1.58)**	Riociguat	.	.	.
0.25 (-0.69; 1.19)	**-1.84 (-2.78; -0.91)**	0.45 (-0.67; 1.57)	**0.85 (0.13; 1.57)**	-0.15 (-1.08; 0.78)	Selexipag	.	.
0.30 (-4.06; 4.66)	-1.79 (-6.15; 2.56)	0.50 (-3.90; 4.90)	0.90 (-3.42; 5.22)	-0.10 (-4.46; 4.26)	0.05 (-4.33; 4.43)	Sildenafil	.
-0.30 (-1.40; 0.80)	**-2.39 (-3.49; -1.30)**	-0.10 (-1.36; 1.16)	0.30 (-0.62; 1.22)	-0.70 (-1.79; 0.39)	-0.55 (-1.72; 0.62)	-0.60 (-5.01; 3.81)	Treprostinil

Cardiac index MD (95%CI)						
Bosentan	.	.	0.30 (-0.06; 0.66)	.	.	.
0.20 (-0.60; 1.00)	Iloprost	.	0.10 (-0.62; 0.82)	.	.	.
-0.10 (-0.53; 0.33)	-0.30 (-1.06; 0.46)	Macitentan	**0.40 (0.16; 0.64)**	.	.	.
0.30 (-0.06; 0.66)	0.10 (-0.62; 0.82)	**0.40 (0.16; 0.64)**	Placebo	**-0.49 (-0.70; -0.28)**	0.00 (-1.25; 1.25)	**-0.60 (-0.89; -0.31)**
-0.19 (-0.60; 0.23)	-0.39 (-1.14; 0.36)	-0.09 (-0.41; 0.23)	-0.49 (-0.70; -0.28)	Selexipag	.	.
0.30 (-1.00; 1.60)	0.10 (-1.35; 1.55)	0.40 (-0.88; 1.68)	-0.00 (-1.25; 1.25)	0.49 (-0.78; 1.76)	Sildenafil	.
-0.30 (-0.76; 0.16)	-0.50 (-1.28; 0.28)	-0.20 (-0.58; 0.18)	-0.60 (-0.89; -0.31)	-0.11 (-0.47; 0.25)	-0.60 (-1.89; 0.69)	Treprostinil

Cardiac Output MD (95%CI)					
BPA	.	.	.	**-0.42 (-0.75; -0.09)**	.

(*continued on next page*)

Table 2 (*continued*)

Cardiac Output MD (95%CI)					
-0.35 (-0.95; 0.25)	Macitentan	.	**0.78 (0.36; 1.20)**	.	.
-0.52 (-1.02; -0.02)	-0.17 (-0.80; 0.46)	PADN	.	0.10 (-0.28; 0.48)	.
0.43 (-0.01; 0.86)	**0.78 (0.36; 1.20)**	**0.95 (0.48; 1.42)**	Placebo	**-0.85 (-1.13; -0.57)**	**-0.80 (-1.33; -0.27)**
-0.42 (-0.75; -0.09)	-0.07 (-0.57; 0.44)	0.10 (-0.28; 0.48)	**-0.85 (-1.13; -0.57)**	Riociguat	.
-0.37 (-1.06; 0.31)	-0.02 (-0.69; 0.65)	0.15 (-0.56; 0.85)	-0.80 (-1.33; -0.27)	0.05 (-0.55; 0.65)	Treprostinil

macitentan (68%), as shown in Table 4. There was no significant heterogeneity within pairwise comparisons (I^2=0%, p=0.7554).

3.5.2. Borg dyspnea score

The analysis results showed that only BPA (MD=-2.30, 95% CI: -4.18; -0.43) produced a statistically significant difference compared with the placebo, as presented in Fig. 3B and Table 2. According to the SUCRA rankings in Table 4, BPA (90%) was the highest-ranking intervention, followed by riociguat (61%), and selexipag (54%). There was significant heterogeneity within pairwise comparisons (I^2=63.6%; p=0.0972).

3.5.3. Cardiac index

The analysis results exhibited a statistically significant difference only for treprostinil (MD=0.60, 95% CI: 0.31; 0.89), selexipag (MD=0.49, 95% CI: 0.28; 0.70), and macitentan (MD=0.40, 95% CI: 0.16; 0.64) when compared with the placebo, as shown in Fig. 3C and Table 2. The SUCRA values presented in Table 4 confirmed these findings, with treprostinil (87%), selexipag (73%), and macitentan (60%) having the highest rankings. There was no significant heterogeneity within pairwise comparisons (I^2=0%; p=0.972).

3.5.4. Cardiac output

The analysis found that, except for BPA (MD=0.43, 95% CI: -0.01; 0.86), PADN, riociguat, treprostinil, and macitentan were all significantly more effective than the placebo, as shown in Fig. 3D and Table 2. Regarding the SUCRA values presented in Table 4, PADN, (79%) riociguat (69%), and treprostinil (64%) were the treatments with the highest improvement in terms of CO. There was no significant heterogeneity within pairwise comparisons (I^2=0%; p=0.8304)

3.5.5. Adverse events

There was no significant difference between the studied treatments and placebo; except for selexipag which exhibited higher risk of adverse events compared to placebo (RR=1.60, 95% CI: 1.23; 2.10), as indicated in Fig. 4A and Table 3. However, the SUCRA values in Table 4 showed that ambrisentan (96%) was most likely to be effective, followed by treprostinil (71%), and macitentan (68%). There was no significant heterogeneity within pairwise comparisons (I^2=0%; p=0.4886).

3.5.6. All-cause mortality

Moreover, there was no significant difference between all studied treatments and placebo in terms of all-cause mortality, as shown in Fig. 4B and Table 3. However, the SUCRA values in Table 4 showed that PADN (74%) had the highest score, followed by macitentan (69%), and riociguat (63%).

4. Discussion

CTEPH is a progressive condition that poses a substantial health risk. The treatment of choice for CTEPH is pulmonary endarterectomy (PEA) [7], although its use is limited by a number of conditions, including peripheral lesions, high PVR, and increased surgical risk [39,40]. Notably, a significant percentage of individuals still experience recurrent pulmonary arterial hypertension (PAH) even following PEA [41]. Hence, there are emerging treatment options to address these complexities.

To the best of our knowledge, there is only one previously published network meta-analysis that evaluated only 7 different CTEPH drugs. Our NMA included 3 additional treatment options: selexipag, pulmonary artery denervation (PADN), and Balloon pulmonary angioplasty (BPA). Furthermore, we reported the following additional outcomes: mean pulmonary artery pressure, mean right atrial pressure, Borg dyspnea score, cardiac index, CO, adverse events, and all-cause mortality. Hence, the scope of our study extends beyond previous network meta-analysis to evaluate the relative efficacy and safety of a wider range of interventions, including 14 trials with 1047 patients randomized to 10 intervention arms. We ranked them in terms of the 6-minute walk distance (6 MWD), pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP), mean right atrial pressure (mRAP), Borg dyspnea score, cardiac index, cardiac output (CO), adverse events, and all-cause mortality.

Table 3
The league table shows the effect estimate of treatments in outcomes assessing the safety outcomes. Significant results are in bold.

Adverse events RR (95%CI)							
Ambrisentan	.	.	.	0.69 (0.48; 1.00)	.	.	.
0.54 (0.34; 0.85)	Bosentan	.	.	1.29 (0.99; 1.67)	.	.	.
0.69 (0.44; 1.07)	1.28 (0.91; 1.82)	BPA	.	.	0.94 (0.76; 1.16)	.	.
0.74 (0.47; 1.15)	1.37 (0.97; 1.95)	1.07 (0.77; 1.49)	Macitentan	0.94 (0.74; 1.19)	.	.	.
0.69 (0.48; 1.00)	1.29 (0.99; 1.67)	1.00 (0.80; 1.26)	0.94 (0.74; 1.19)	Placebo	0.94 (0.86; 1.03)	**0.62 (0.48; 0.82)**	1.07 (0.91; 1.25)
0.65 (0.44; 0.95)	1.21 (0.92; 1.59)	0.94 (0.76; 1.16)	0.88 (0.68; 1.14)	0.94 (0.86; 1.03)	Riociguat	.	.
0.43 (0.27; 0.68)	0.80 (0.55; 1.17)	**0.62 (0.44; 0.89)**	**0.58 (0.41; 0.84)**	**0.62 (0.48; 0.82)**	**0.66 (0.50; 0.88)**	Selexipag	.
0.74 (0.49; 1.10)	1.37 (1.01; 1.86)	1.07 (0.81; 1.41)	1.00 (0.75; 1.33)	1.07 (0.91; 1.25)	1.13 (0.94; 1.36)	1.71 (1.25; 2.33)	Treprostinil

All-cause mortality RR (95%CI)						
Iloprost	.	.	0.33 (0.02; 7.36)	.	.	.
1.67 (0.02; 124.49)	Macitentan	.	0.20 (0.01; 4.04)	.	.	.
1.97 (0.03; 139.51)	1.18 (0.02; 78.47)	PADN	.	0.50 (0.05; 5.17)	.	.
0.33 (0.02; 7.36)	0.20 (0.01; 4.04)	0.17 (0.01; 3.18)	Placebo	2.95 (0.50; 17.32)	0.89 (0.04; 20.12)	0.51 (0.05; 5.45)
0.98 (0.03; 34.75)	0.59 (0.02; 19.29)	0.50 (0.05; 5.17)	2.95 (0.50; 17.32)	Riociguat	.	.
0.30 (0.00; 24.03)	0.18 (0.00; 13.54)	0.15 (0.00; 10.91)	0.89 (0.04; 20.12)	0.30 (0.01; 10.90)	Selexipag	.
0.17 (0.00; 8.37)	0.10 (0.00; 4.68)	0.09 (0.00; 3.75)	0.51 (0.05; 5.45)	0.17 (0.01; 3.33)	0.57 (0.01; 28.48)	Treprostinil

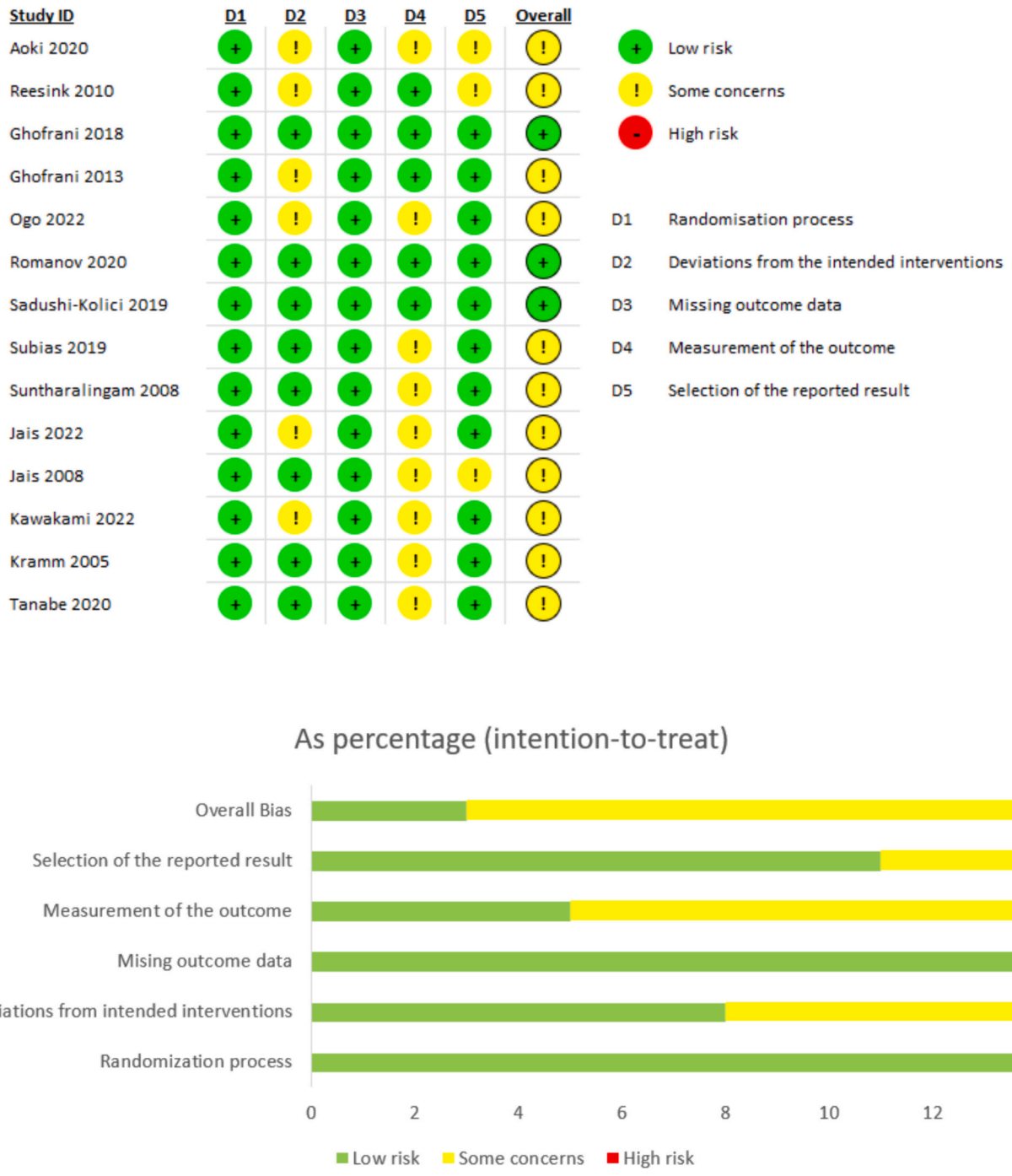

Fig. 5. Risk of bias graph and risk of bias summary.

Our NMA displayed results comparable to those of previous NMA [17]. In terms of increasing 6 MWD, Chen *et al.*, reported statistically significant results with riociguat, treprostinil, and macitentan. These findings were in line with ours. Nevertheless, PADN and BPA were included in our analysis and showed the most significant improvement in this regard. The results of the previous NMA demonstrated that treprostinil, riociguat, bosentan, and iloprost significantly reduced PVR. These results aligned with ours only in terms of treprostinil, riociguat, and bosentan. However, according to our results, BPA and PADN continued to show significant improvement in terms of decreasing PVR.

According to the SUCRA rankings, the results of our analysis showed that PADN was the most effective in improving 6 MWD, CO, and all-cause mortality. BPA performed best for decreasing PVR, mPAP, and Borg dyspnea score. Moreover, bosentan was superior to others in reducing mRAP, while treprostinil was shown to be more effective in improving cardiac index. In terms of low adverse events, ambrisentan was more beneficial than others. Based on these findings, it appears that different therapies may offer benefits in terms of certain clinical outcomes.

CTEPH Treatment options are continuously evolving. Newer interventions are being explored to manage patients who are ineligible for PEA or have residual PAH after PEA. With regards to PADN, it can serve as a potential therapeutic procedure of residual PAH as it targets sympathetic nervous system activation [42]. Activation of sympathetic nervous system and renin-angiotensin-aldosterone system produce circulating neurohormone transmitters which are a significant

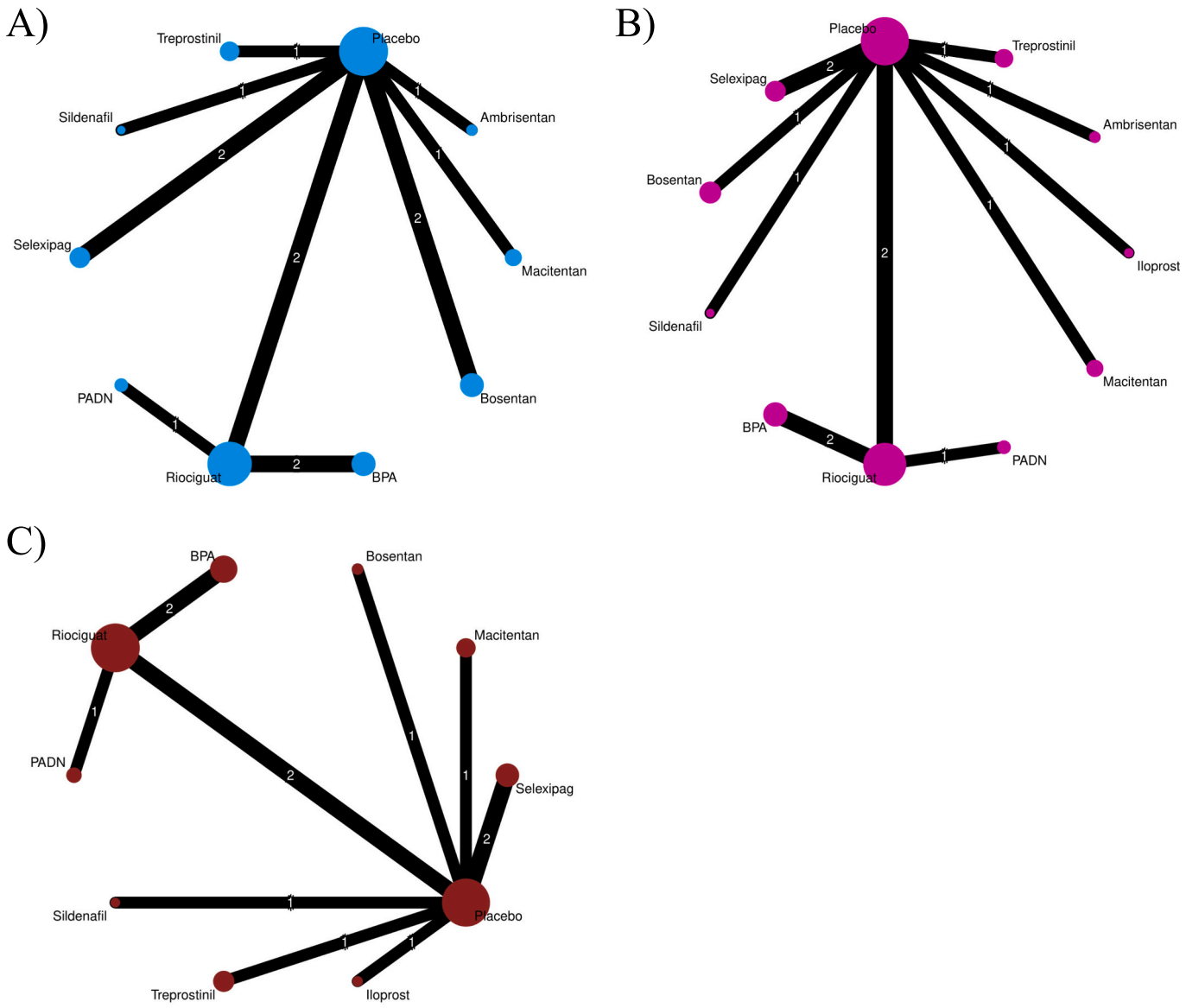

Fig. 6. Network diagram for the primary outcomes assessing the efficacy in RCTs of CTEPH treatments. Each node represents an intervention that has been tested in trials; the size of the nodes is proportional to the number of patients that have received the intervention; and the thickness of the connecting lines is proportional to the number of trials. A) 6-minute walk distance; B) Pulmonary vascular resistance; C) Mean pulmonary artery pressure.

contributor to the pathogenesis and progression of PAH [43,44]. Results from previous pairwise meta-analyses published by ZUO *et al.*, Zheng *et al.*, and Salazar *et al.*, were in line with our findings as they showed that PADN demonstrated improvements in 6 MWD, CO, and a reduction in mPAP, and PVR [15,45,46].

According to the 2022 European Society of Cardiology/European Respiratory Society (ECS/ERS) and American guidelines, BPA is an emerging option for ineligible patients for PEA or with residual PAH after PEA [7–9], which was previously used for distal lesion disease [47]. In addition, several pairwise meta-analyses analyzed the efficacy of BPA against or following PEA [48–50], where BPA exhibited promising results in terms of improving clinical and hemodynamic parameters. These results align with ours in terms of 6 MWD, PVR, mPAP and mRAP. Therefore, BPA is deemed a viable option.

In the context of prostacyclin and its analogs, results from Chen *et al.*, displayed the potential efficacy of treprostinil and iloprost in terms of improving 6 MWD and pulmonary hemodynamics. Their leading role is hypothesized to be due to its engagement in additional pathways other than those associated with G-protein (Gs), linked with adenylate cyclase, which restricts the proliferation of muscle cells in the pulmonary artery [51]. Bosentan, ambrisentan, and macitentan are endothelin receptor antagonists (ERAs), which function by inhibiting the binding of endothelin, a vasoconstrictive peptide, to its receptors on smooth muscle cells leading to vasodilation [52]. The results from a previous meta-analysis found that bosentan was effective in improving cardiac index and reducing PVR. In addition, they also found that bosentan displayed no statistical significance in terms of mPAP and improving 6 MWD [53]. Although these results were in line with ours in terms of 6 MWD and PVR, our results were comparable in terms of cardiac index and mPAP, as bosentan displayed no significant improvement in cardiac index, but significantly reduced mPAP.,. Regarding macitentan, Chen *et al.* found that it was superior to other ERAs and has significantly improved 6 MWD, which was not in line with our results [17]. As for ambrisentan, it was not favored in any of the outcomes as shown in our analysis, except for potential results in terms of adverse events.

Targeting the nitric oxide (NO)/soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP) pathway is a plausible treatment strategy since patients with PAH have decreased endothelial cell-

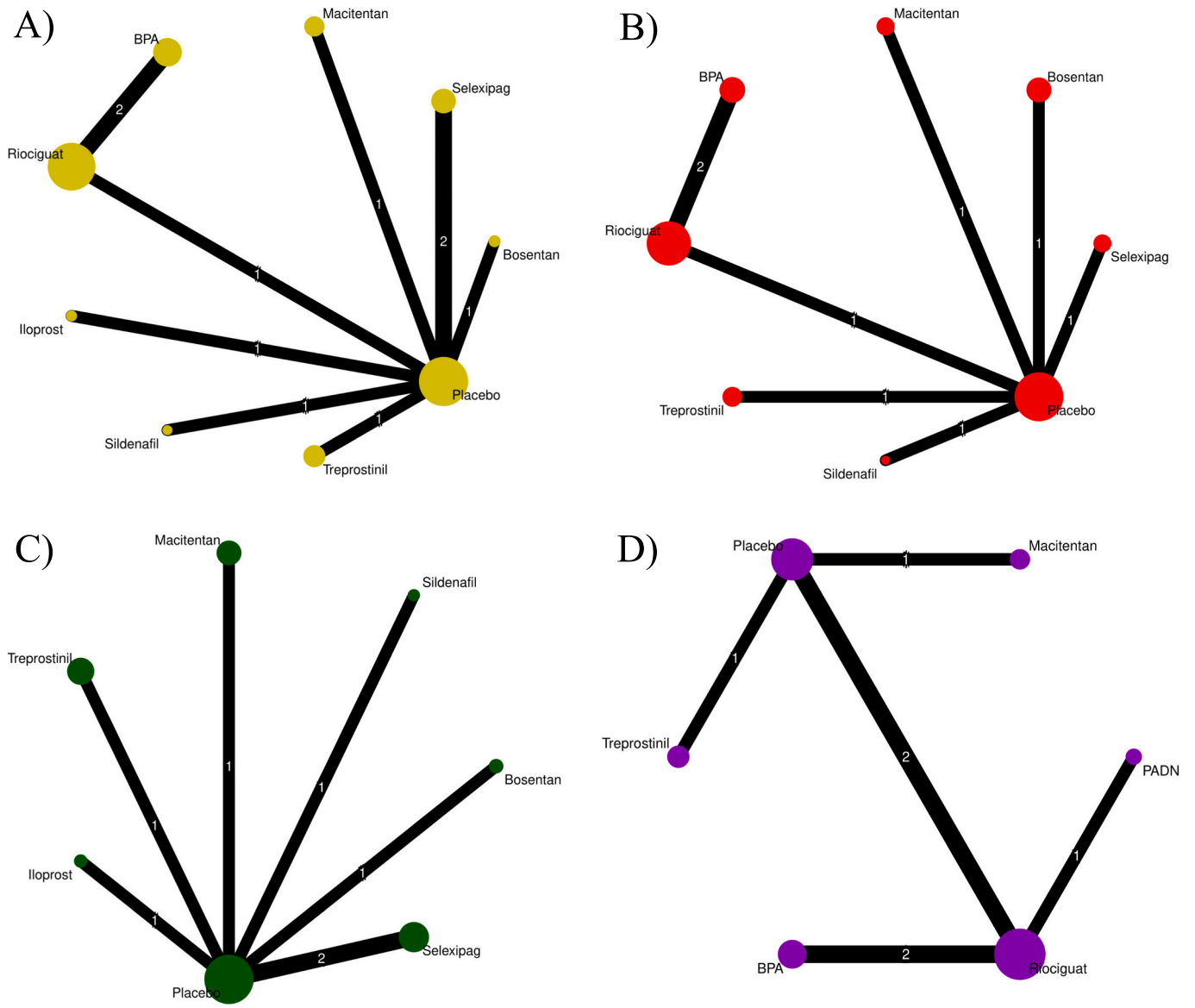

Fig. 7. Network diagram for the secondary outcomes assessing the efficacy in RCTs of CTEPH treatments. Each node represents an intervention that has been tested in trials; the size of the nodes is proportional to the number of patients that have received the intervention; and the thickness of the connecting lines is proportional to the number of trials. A) Mean right atrial pressure; B) Borg dyspnea score; C) Cardiac index; D) Cardiac output.

derived nitric oxide (NO) production [54]. Riociguat accomplishes this through a dual mechanism of action, it sensitizes sGC to endogenous NO and directly activates sGC receptors without the need for NO, which has the effects of vasorelaxation and antiproliferative activity [55,56]. Several studies revealed that riociguat proved to be an effective treatment [57–60]. These results aligned with ours in terms of improving 6 MWD, CO, and decreasing PVR. In terms of sildenafil, it did not display any significant results, whereas selexipag showed significant improvement only in cardiac index.

4.1. Limitations

By incorporating a wider range of interventions and results, our study expands on prior research and enables a more thorough comparison. However, a few limitations need to be taken into account. Heterogeneity may be influenced by variations in several factors. Initially, different RCTs had different inclusion criteria. Hence, different groups of patients were included, such as (1) patients who underwent previous PEA but had recurrent or persistent PAH, (2) inoperable patients, (3) patients who underwent BPA, and (4) patients who received concomitant PAH-targeted therapies. Additionally, bias could have been introduced because of the relatively small number of comparison trials between some therapies. For instance, only one RCT was included for each of ambrisentan and sildenafil with a relatively small sample size, so their full potential is yet to be explored. Additionally, one study used low-dose subcutaneous treprostinil (3 ng/kg per min) but was considered a placebo in our study [31] because it was expected to have limited clinical effects [61]. In addition, studies that stated that mortality was not related to the study treatment or that there were no adverse events leading to withdrawal from the study were not included in the assessment of all-cause mortality, which may have resulted in overestimation or underestimation of the effects of the drugs reported in these studies. This also applies to the evaluation of adverse events, since serious and less serious adverse events were included and assessed together in one outcome. Also, there was no source of inconsistency, as our study did not have any closed loops; hence, we did not evaluate consistency. Finally, the range of follow-up times at which the outcomes were assessed was different between the included trials, which can impact the

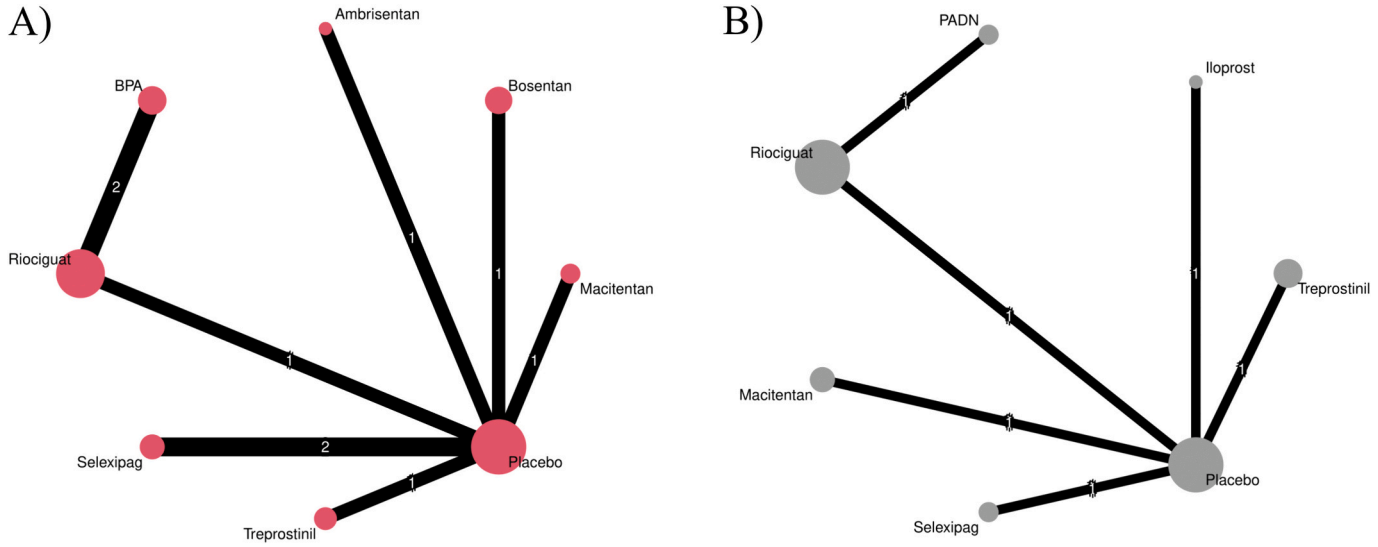

Fig. 8. Network diagram for the secondary outcomes assessing the safety in RCTs of CTEPH treatments. Each node represents an intervention that has been tested in trials; the size of the nodes is proportional to the number of patients that have received the intervention; and the thickness of the connecting lines is proportional to the number of trials. A) Adverse events; B) All-cause mortality.

Table 4
Ranking of different therapies for CTEPH using SUCRA values.

Intervention	6 MWD (%)	PVR (%)	mPAP (%)	mRAP (%)	Borg dyspnea score (%)	CI (%)	CO (%)	Adverse events (%)	All-cause mortality (%)
Placebo	16	8	20	19	22	16	0	57	30
Bosentan	22	50	83	83	46	48	—	16	—
Sildenafil	41	51	56	39	52	32	—	—	—
Riociguat	67	50	44	31	61	—	69	36	63
Macitentan	55	36	36	68	40	60	61	68	69
Ambrisentan	43	34	—	—	—	—	—	96	—
Treprostinil	66	75	45	65	35	87	64	71	20
BPA	76	91	93	70	90	—	25	54	—
PADN	98	73	76	—	—	—	79	—	74
Selexipag	16	33	26	31	54	73	—	2	34
Iloprost	—	48	21	43	—	33	—	—	59

comparability of the outcomes.

Despite these drawbacks, this study provides insightful information regarding the relative efficacy of various CTEPH therapies, aiding clinicians in making wise treatment choices. Further investigation and randomized controlled trials are necessary to improve these findings and to offer more specific recommendations for patient treatment as CTEPH management progresses. Nevertheless, this study offers important data regarding the relative efficacy of various CTEPH treatments, which can be used by clinicians to select the most appropriate course of treatment.

4.2. Conclusion

In conclusion, our study suggests that the current therapeutic modalities are effective in terms of improving exercise capacity, pulmonary hemodynamics, and reducing adverse events and all-cause mortality, which is supported by current practice guideline recommendations. However, the degree can vary among therapies. The results of the previous NMA suggested that treprostinil and riociguat were superior drugs. Nevertheless, this was not the case in the present analysis. Based on our results, BPA and PADN provided the most promising efficacy and safety outcomes. Further RCTs are encouraged to continue the assessment of various CTEPH therapies, and identifying the optimal treatment for patients should be a key component of future clinical practice.

4.3. Impact on daily practice

CTEPH is a serious pulmonary vascular disease and is one of the leading causes of pulmonary arterial hypertension. Several therapeutic options are available for the treatment of CTEPH. Our NMA comprises 14 RCTs and has analyzed 10 different treatments. According to the SUCRA rankings, our results favor PADN in the management of residual pulmonary hypertension after PEA. Furthermore, BPA has shown remarkable results as a promising alternative to PEA, as well as in the management of residual pulmonary hypertension following PEA. Overall, the results of our analysis expand our understanding of the available CTEPH treatment options and provide valuable insight into the possible relative effectiveness of PADN and BPA as treatment options for CTEPH.

Ethical approval

not required.

Funding

there was no funding available.

CRediT authorship contribution statement

Noha Rami Ismail: Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Hamdy A. Makhlouf:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Atef Hassan:** Writing – original draft, Visualization, Validation, Project administration. **Ahmed Elshahat:** Writing – review &

editing, Visualization, Validation, Software, Resources, Project administration. **Mohamed Abdelfatah Abdellatif:** Validation, Software, Resources, Project administration, Methodology. **Abdelmoemen Esam Rezk:** Writing – original draft, Visualization, Validation, Formal analysis, Conceptualization. **Abdelrahman Mady:** Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Rashad G. Mohamed:** Writing – original draft, Software, Formal analysis, Data curation, Conceptualization. **Hanady Mohammad Elfeky:** Writing – review & editing, Visualization, Methodology, Investigation, Funding acquisition, Conceptualization. **Ahmed Abdelaziz:** Writing – review & editing, Validation, Supervision, Software, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100466.

References

[1] M.M. Hoeper, E. Mayer, G. Simonneau, L.J. Rubin, Chronic thromboembolic pulmonary hypertension, Circulation 113 (16) (2006) 2011–2020, https://doi.org/10.1161/CIRCULATIONAHA.105.602565. Apr 25. PMID: 16636189.

[2] I.M. Lang, M. Madani, Update on chronic thromboembolic pulmonary hypertension, Circulation 130 (6) (2014) 508–518, https://doi.org/10.1161/CIRCULATIONAHA.114.009309. Aug 5. PMID: 25092279.

[3] W. Pang, Z. Zhang, Z. Wang, K. Zhen, M. Zhang, Y. Zhang, Q. Gao, S. Zhang, X. Tao, J. Wan, W. Xie, Z. Zhai, Higher Incidence of Chronic Thromboembolic Pulmonary Hypertension After Acute Pulmonary Embolism in Asians Than in Europeans: A Meta-Analysis, Front Med (Lausanne). 26 (8) (2021), https://doi.org/10.3389/fmed.2021.721294. PMID: 34765615; PMCID: PMC8575791, 721294. Oct.

[4] N.H. Kim, Group 4 Pulmonary Hypertension: Chronic Thromboembolic Pulmonary Hypertension: Epidemiology, Pathophysiology, and Treatment, Cardiol. Clin. 34 (3) (2016) 435–441, https://doi.org/10.1016/j.ccl.2016.04.011. Aug. PMID: 27443139.

[5] G. Simonneau, A. Torbicki, P. Dorfmüller, N. Kim, The pathophysiology of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (143) (2017), https://doi.org/10.1183/16000617.0112-2016. PMID: 28356405; PMCID: PMC9488693, 160112. Mar 29.

[6] Klok FA, Delcroix M, Bogaard HJ. Chronic thromboembolic pulmonary hypertension from the perspective of patients with pulmonary embolism. J. Thromb. Haemost. 2018Jun; 16(6): 1040-1051. doi: https://doi.org/10.1111/jth.14016. Epub 2018 May 8. PMID: 29608809.

[7] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S; ESC/ERS Scientific Document Group 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618-3731. doi: 10.1093/eurheartj/ehac237. Erratum in: Eur Heart J. 2023 Apr 17;44(15):1312. PMID: 36017548.

[8] D.B. Badesch, S.H. Abman, G. Simonneau, L.J. Rubin, V.V. McLaughlin, Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines, Chest 131 (6) (2007) 1917–1928, https://doi.org/10.1378/chest.06-2674. Jun. PMID: 17565025.

[9] N.H. Kim, M. Delcroix, D.P. Jenkins, R. Channick, P. Dartevelle, P. Jansa, I. Lang, M.M. Madani, H. Ogino, V. Pengo, E. Mayer, Chronic thromboembolic pulmonary hypertension, J. Am. Coll. Cardiol. 62 (25 Suppl) (2013) D92–D99, https://doi.org/10.1016/j.jacc.2013.10.024. Dec 24. PMID: 24355646.

[10] Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011Nov 1;124(18):1973-81. doi: https://doi.org/10.1161/CIRCULATIONAHA.110.015008. Epub 2011 Oct 3. PMID: 21969018.

[11] L. Zhang, Y. Bai, P. Yan, T. He, B. Liu, S. Wu, Z. Qian, C. Li, Y. Cao, M. Zhang, Balloon pulmonary angioplasty vs. pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis, Heart Fail. Rev. 26 (4) (2021) 897–917, https://doi.org/10.1007/s10741-020-10070-w. Jul. Epub 2021 Feb 5. PMID: 33544306.

[12] Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, Weissmann N, Mück W, Unger S, Wensing G, Schermuly RT, Ghofrani HA. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur. Respir. J. 2009Apr;33(4):785-92. doi: https://doi.org/10.1183/09031936.00039808. Epub 2009 Jan 7. PMID: 19129292.

[13] Simonneau G, D'Armini AM, Ghofrani HA, Grimminger F, Hoeper MM, Jansa P, Kim NH, Wang C, Wilkins MR, Fritsch A, Davie N, Colorado P, Mayer E. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2). Eur. Respir. J. 2015May;45(5):1293-302. doi: https://doi.org/10.1183/09031936.00087114. Epub 2014 Nov 13. PMID: 25395036.

[14] M. Correale, A. Ferraretti, I. Monaco, D. Grazioli, M. Di Biase, N.D. Brunetti, Endothelin-receptor antagonists in the management of pulmonary arterial hypertension: where do we stand? Vasc. Health Risk Manag. 4 (14) (2018) 253–264, https://doi.org/10.2147/VHRM.S133921. PMID: 30323613; PMCID: PMC6174907. Oct.

[15] W. Zuo, N. Liu, Y. Xiao, Y. Xie, Q. Liu, Meta-Analysis of Pulmonary Artery Denervation for Treatment of Pulmonary Hypertension, Braz. J. Cardiovasc. Surg. 37 (4) (2022) 554–565, https://doi.org/10.21470/1678-9741-2020-0533. PMID: 35976208; PMCID: PMC9423798. Aug 16.

[16] H. Zhang, S.L. Chen, Pulmonary Artery Denervation: Update on Clinical Studies, Curr. Cardiol. Rep. 21 (10) (2019) 124, https://doi.org/10.1007/s11886-019-1203-z. Sep 5. PMID: 31486924.

[17] Y. Chen, F. Li, J. Luo, J. Chen, P. Luo, J. Li, Comparative Efficacy and Safety of Targeted Therapies for Chronic Thromboembolic Pulmonary Hypertension: A Systematic Review and Network Meta-Analysis, Can. Respir. J. 1 (2021) (2021), https://doi.org/10.1155/2021/1626971. PMID: 34512819; PMCID: PMC8426079, 1626971. Sep.

[18] B. Hutton, G. Salanti, D.M. Caldwell, A. Chaimani, C.H. Schmid, C. Cameron, J. P. Ioannidis, S. Straus, K. Thorlund, J.P. Jansen, C. Mulrow, F. Catalá-López, P. C. Gøtzsche, K. Dickersin, I. Boutron, D.G. Altman, D. Moher, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations, Ann. Intern. Med. 162 (11) (2015) 777–784, https://doi.org/10.7326/M14-2385. Jun 2. PMID: 26030634.

[19] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29 [cited 2022 Dec 4];372. Available from: https://pubmed.ncbi.nlm.nih.gov/33782057/.

[20] Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013Dec 24;62(25 Suppl):D34-41. doi: 10.1016/j.jacc.2013.10.029. Erratum in: J Am Coll Cardiol. 2014 Feb 25;63(7):746. Erratum in: J. Am. Coll. Cardiol. 2014 Feb 25;63(7):746. PMID: 24355639.

[21] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C. J. Cates, H.Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernán, S. Hopewell, A. Hróbjartsson, D.R. Junqueira, P. Jüni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I. R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 28 (366) (2019), https://doi.org/10.1136/bmj.l4898 l4898. Aug. PMID: 31462531.

[22] D. Bates, M. Maechler, B. Bolker, S. Walker, Fitting Linear Mixed-Effects Models Using lme4, J. Stat. Softw. 67 (1) (2015) 1–48, https://doi.org/10.18637/jss.v067.i01.

[23] S. Balduzzi, G. Rücker, A. Nikolakopoulou, T. Papakonstantinou, G. Salanti, O. Efthimiou, G. Schwarzer, netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods, J. Stat. Softw. 106 (2) (2023) 1–40, https://doi.org/10.18637/jss.v106.i02.

[24] L. Mbuagbaw, B. Rochwerg, R. Jaeschke, D. Heels-Andsell, W. Alhazzani, L. Thabane, G.H. Guyatt, Approaches to interpreting and choosing the best treatments in network meta-analyses, Syst Rev. 6 (1) (2017) 79, https://doi.org/10.1186/s13643-017-0473-z. PMID: 28403893; PMCID: PMC5389085. Apr 12.

[25] Kawakami T, Matsubara H, Shinke T, Abe K, Kohsaka S, Hosokawa K, Taniguchi Y, Shimokawahara H, Yamada Y, Kataoka M, Ogawa A, Murata M, Jinzaki M, Hirata K, Tsutsui H, Sato Y, Fukuda K. Balloon pulmonary angioplasty versus riociguat in inoperable chronic thromboembolic pulmonary hypertension (MR BPA): an open-label, randomised controlled trial. Lancet Respir. Med. 2022Oct;10(10):949-960. doi: https://doi.org/10.1016/S2213-2600(22)00171-0. Epub 2022 Aug 1. PMID: 35926544.

[26] Jaïs X, Brenot P, Bouvaist H, Jevnikar M, Canuet M, Chabanne C, Chaouat A, Cottin V, De Groote P, Favrolt N, Horeau-Langlard D, Magro P, Savale L, Prévot G, Renard S, Sitbon O, Parent F, Trésorier R, Tromeur C, Piedvache C, Grimaldi L, Fadel E, Montani D, Humbert M, Simonneau G. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. Lancet Respir. Med. 2022Oct;10(10):961-971. doi: https://doi.org/10.1016/S2213-2600(22)00214-4. Epub 2022 Aug 1. PMID: 35926542.

[27] T. Aoki, K. Sugimura, Y. Terui, S. Tatebe, S. Fukui, M. Miura, S. Yamamoto, N. Yaoita, H. Suzuki, H. Sato, K. Kozu, R. Konno, S. Miyata, K. Nochioka, K. Satoh, H. Shimokawa, Beneficial effects of riociguat on hemodynamic responses to exercise in CTEPH patients after balloon pulmonary angioplasty - A randomized controlled study, Int J Cardiol Heart Vasc. 10 (29) (2020), https://doi.org/10.1016/j.ijcha.2020.100579. PMID: 32685661; PMCID: PMC7356201, 100579. Jul.

[28] Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C; CHEST-1 Study Group, Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, N. Engl. J. Med. 369 (4) (2013) 319–329, https://doi.org/10.1056/NEJMoa1209657. Jul 25. PMID: 23883377.

[29] H.A. Ghofrani, G. Simonneau, A.M. D'Armini, P. Fedullo, L.S. Howard, X. Jaïs, D. P. Jenkins, Z.C. Jing, M.M. Madani, N. Martin, E. Mayer, K. Papadakis, D. Richard, Kim NH; MERIT study investigators. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study, Lancet Respir. Med. 5 (10) (2017 Oct) 785–794, https://doi.org/10.1016/S2213-2600(17)30305-3. Epub 2017 Sep 11, 28919201.

[30] X. Jaïs, A.M. D'Armini, P. Jansa, A. Torbicki, M. Delcroix, H.A. Ghofrani, M. M. Hoeper, I.M. Lang, E. Mayer, J. Pepke-Zaba, L. Perchenet, A. Morganti, G. Simonneau, L.J. Rubin, Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial, J. Am. Coll. Cardiol. 52 (25) (2008) 2127–2134, https://doi.org/10.1016/j.jacc.2008.08.059. Dec 16. PMID: 19095129.

[31] Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, Samarzija M, Salobir B, Klepetko W, Lindner J, Lang IM. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir. Med. 2019Mar;7(3):239-248. doi: https://doi.org/10.1016/S2213-2600(18)30367-9. Epub 2018 Nov 23. PMID: 30477763.

[32] Kramm T, Eberle B, Guth S, Mayer E. Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy. Eur. J. Cardiothorac. Surg. 2005Dec;28(6):882-8. doi: https://doi.org/10.1016/j.ejcts.2005.09.007. Epub 2005 Oct 19. PMID: 16242948.

[33] Ogo T, Shimokawahara H, Kinoshita H, Sakao S, Abe K, Matoba S, Motoki H, Takama N, Ako J, Ikeda Y, Joho S, Maki H, Saeki T, Sugano T, Tsujino I, Yoshioka K, Shiota N, Tanaka S, Yamamoto C, Tanabe N, Tatsumi K; Study Group. Selexipag for the treatment of chronic thromboembolic pulmonary hypertension. Eur. Respir. J. 2022Jul 7;60(1):2101694. doi: https://doi.org/10.1183/13993003.01694-2021. PMID: 34824052; PMCID: PMC9260121.

[34] A. Romanov, A. Cherniavskiy, N. Novikova, A. Edemskiy, D. Ponomarev, V. Shabanov, D. Losik, D. Elesin, I. Stenin, I. Mikheenko, R. Zhizhov, E. Kretov, E. Pokushalov, S.S. Po, T.V. Martynyuk, J.S. Steinberg, Pulmonary Artery Denervation for Patients With Residual Pulmonary Hypertension After Pulmonary Endarterectomy, J. Am. Coll. Cardiol. 76 (8) (2020) 916–926, https://doi.org/10.1016/j.jacc.2020.06.064. Aug 25. PMID: 32819465.

[35] P. Escribano-Subias, H. Bendjenana, P.S. Curtis, I. Lang, Noordegraaf A. Vonk, Ambrisentan for treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH), Pulm Circ. Apr-Jun;9(2):2045894019846433 (2019), https://doi.org/10.1177/2045894019846433. PMID: 30957635; PMCID: PMC6540507.

[36] Tanabe N, Fukuda K, Matsubara H, Nakanishi N, Tahara N, Ikeda S, Kishi T, Satoh T, Hirata KI, Inoue T, Kimura H, Okano Y, Okazaki O, Sata M, Tsujino I, Ueno S, Yamada N, Yao A, Kuriyama T. Selexipag for Chronic Thromboembolic Pulmonary Hypertension in Japanese Patients - A Double-Blind, Randomized, Placebo-Controlled, Multicenter Phase II Study. Circ J. 2020Sep 25;84(10):1866-1874. doi: https://doi.org/10.1253/circj.CJ-20-0438. Epub 2020 Sep 3. PMID: 32879152.

[37] Suntharalingam J, Treacy CM, Doughty NJ, Goldsmith K, Soon E, Toshner MR, Sheares KK, Hughes R, Morrell NW, Pepke-Zaba J. Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest 2008Aug;134(2):229-236. doi: https://doi.org/10.1378/chest.07-2681. Epub 2008 Feb 8. PMID: 18263674.

[38] Reesink HJ, Surie S, Kloek JJ, Tan HL, Tepaske R, Fedullo PF, Bresser P. Bosentan as a bridge to pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. J. Thorac. Cardiovasc. Surg. 2010Jan;139(1):85-91. doi: https://doi.org/10.1016/j.jtcvs.2009.03.053. Epub 2009 May 31. PMID: 19660388.

[39] Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, Treacy C, D'Armini AM, Morsolini M, Snijder R, Bresser P, Torbicki A, Kristensen B, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Hamid AM, Jaïs X, Simonneau G. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation 2011Nov 1;124(18):1973-81. doi: https://doi.org/10.1161/CIRCULATIONAHA.110.015008. Epub 2011 Oct 3. PMID: 21969018.

[40] Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, Bresser P, Torbicki A, Mellemkjaer S, Lewczuk J, Simkova I, Barberà JA, de Perrot M, Hoeper MM, Gaine S, Speich R, Gomez-Sanchez MA, Kovacs G, Jaïs X, Ambroz D, Treacy C, Morsolini M, Jenkins D, Lindner J, Dartevelle P, Mayer E, Simonneau G. Long-Term Outcome of Patients With Chronic Thromboembolic Pulmonary Hypertension: Results From an International Prospective Registry. Circulation 2016Mar 1;133(9):859-71. doi: https://doi.org/10.1161/CIRCULATIONAHA.115.016522. Epub 2016 Jan 29. PMID: 26826181.

[41] L. Godinas, T. Verbelen, M. Delcroix, Residual pulmonary hypertension after pulmonary thromboendarterectomy: incidence, pathogenesis and therapeutic options, Ann Cardiothorac Surg. 11 (2) (2022) 163–165, https://doi.org/10.21037/acs-2021-pte-11. PMID: 35433368; PMCID: PMC9012192. Mar.

[42] M.G. Davies, D. Miserlis, J.P. Hart, Current status of pulmonary artery denervation, Front Cardiovasc Med. 3 (9) (2022), https://doi.org/10.3389/fcvm.2022.972256. PMID: 36262207; PMCID: PMC9573987, 972256. Oct.

[43] de Man FS, Tu L, Handoko ML, Rain S, Ruiter G, François C, Schalij I, Dorfmüller P, Simonneau G, Fadel E, Perros F, Boonstra A, Postmus PE, van der Velden J, Vonk-Noordegraaf A, Humbert M, Eddahibi S, Guignabert C. Dysregulated renin-angiotensin-aldosterone system contributes to pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012 Oct 15;186(8):780-9. doi: 10.1164/rccm.201203-0411OC. Epub 2012 Aug 2. PMID: 22859525; PMCID: PMC5104838.

[44] Manolis AA, Manolis TA, Apostolopoulos EJ, Apostolaki NE, Melita H, Manolis AS. The role of the autonomic nervous system in cardiac arrhythmias: The neuro-cardiac axis, more foe than friend? Trends Cardiovasc Med. 2021Jul;31(5):290-302. doi: https://doi.org/10.1016/j.tcm.2020.04.011. Epub 2020 May 17. PMID: 32434043.

[45] Zheng Z, Chen R, Sun X, Lu J, Wang D, Liu H, Chen M, Chen H, Hong C. A Meta-analysis of the efficacy of pulmonary artery denervation in the treatment of pulmonary hypertension. Heart Lung 2022 May-Jun;53:42-50. doi: https://doi.org/10.1016/j.hrtlng.2022.01.020. Epub 2022 Feb 7. PMID: 35144042.

[46] A.M. Salazar, K.S. Al-Asad, R.M. Prasad, G. Panama, S. Banga, M. Wilcox, Pulmonary Artery Denervation as a New Therapeutic Option for Pulmonary Hypertension: A Systematic Review and Meta-Analysis, Curr. Probl. Cardiol. 48 (9) (2023), https://doi.org/10.1016/j.cpcardiol.2023.101776, 101776. Sep. Epub 2023 Apr 29. PMID: 37121454.

[47] Moriarty JM, Khan SN, Kao SD, Saggar R. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. Cardiovasc. Intervent. Radiol. 2018Dec;41(12):1826-1839. doi: https://doi.org/10.1007/s00270-018-2012-2. Epub 2018 Jul 23. PMID: 30039506.

[48] Kennedy MK, Kennedy SA, Tan KT, de Perrot M, Bassett P, McInnis MC, Thenganatt J, Donahoe L, Granton J, Mafeld S. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: A Systematic Review and Meta-analysis. Cardiovasc. Intervent. Radiol. 2023Jan;46(1):5-18. doi: https://doi.org/10.1007/s00270-022-03323-8. Epub 2022 Dec 6. PMID: 36474104.

[49] Tanabe N, Kawakami T, Satoh T, Matsubara H, Nakanishi N, Ogino H, Tamura Y, Tsujino I, Ogawa A, Sakao S, Nishizaki M, Ishida K, Ichimura Y, Yoshida M, Tatsumi K. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: A systematic review. Respir. Investig. 2018Jul;56(4):332-341. doi: https://doi.org/10.1016/j.resinv.2018.03.004. Epub 2018 Jul 3. PMID: 30008295.

[50] Zoppellaro G, Badawy MR, Squizzato A, Denas G, Tarantini G, Pengo V. Balloon Pulmonary Angioplasty in Patients With Chronic Thromboembolic Pulmonary Hypertension - A Systematic Review and Meta-Analysis. Circ. J. 2019Jul 25;83(8):1660-1667. doi: https://doi.org/10.1253/circj.CJ-19-0161. Epub 2019 Jun 21. PMID: 31231116.

[51] L.H. Clapp, P. Finney, S. Turcato, S. Tran, L.J. Rubin, A. Tinker, Differential effects of stable prostacyclin analogs on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery, Am. J. Respir. Cell Mol. Biol. 26 (2) (2002) 194–201, https://doi.org/10.1165/ajrcmb.26.2.4695. Feb. PMID: 11804870.

[52] J.J. Maguire, A.P. Davenport, Endothelin receptors and their antagonists, Semin. Nephrol. 35 (2) (2015) 125–136, https://doi.org/10.1016/j.semnephrol.2015.02.002. PMID: 25966344; PMCID: PMC4437774. Mar.

[53] Chen X, Zhai Z, Huang K, Xie W, Wan J, Wang C. Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: A systemic review and meta-analysis. Clin. Respir. J. 2018Jun;12(6):2065-2074. doi: https://doi.org/10.1111/crj.12774. Epub 2018 Feb 22. PMID: 29393580.

[54] A. Giaid, D. Saleh, Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension, N. Engl. J. Med. 333 (4) (1995) 214–221, https://doi.org/10.1056/NEJM199507273330403. Jul 27. PMID: 7540722.

[55] H.A. Ghofrani, F. Grimminger, Soluble guanylate cyclase stimulation: an emerging option in pulmonary hypertension therapy, Eur. Respir. Rev. 18 (111) (2009) 35–41, https://doi.org/10.1183/09059180.00011112. Mar. PMID: 20956121.

[56] D. Khaybullina, A. Patel, T. Zerilli, Riociguat (adempas): a novel agent for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, P T. 39 (11) (2014) 749–758. Nov. PMID: 25395817; PMCID: PMC4218670.

[57] Wang L, Zhu L, Wu Y, Li Q, Liu H. Riociguat therapy for pulmonary hypertension: a systematic review and meta-analysis. Ann Palliat Med. 2021Oct;10(10):11117-11128. doi: 10.21037/apm-21-2656. PMID: 34763472.

[58] M. Ying, J. Song, S. Gu, R. Zhao, M. Li, Efficacy and safety of riociguat in the treatment of chronic thromboembolic pulmonary arterial hypertension: A meta-analysis, Medicine (Baltimore) 100 (22) (2021), https://doi.org/10.1097/MD.0000000000026211. PMID: 34087896; PMCID: PMC8183702 e26211. Jun 4.

[59] Wang W, Wen L, Song Z, Shi W, Wang K, Huang W. Balloon pulmonary angioplasty vs riociguat in patients with inoperable chronic thromboembolic pulmonary hypertension: A systematic review and meta-analysis. Clin Cardiol. 2019Aug;42(8):741-752. doi: https://doi.org/10.1002/clc.23212. Epub 2019 Jun 12. Erratum in: Clin. Cardiol. 2020 Mar;43(3):315-316. PMID: 31188483; PMCID: PMC6671827.

[60] Wardle AJ, Seager MJ, Wardle R, Tulloh RM, Gibbs JS. Guanylate cyclase stimulators for pulmonary hypertension. Cochrane Database Syst. Rev. 2016Aug 2;2016(8):CD011205. doi: https://doi.org/10.1002/14651858.CD011205.pub2. PMID: 27482837; PMCID: PMC8502073.

[61] Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ; 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. 165 (6) (2002) 800–804, https://doi.org/10.1164/ajrccm.165.6.2106079. Mar 15. PMID: 11897647.