Cardiology in the Young

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Pulmonary vasodilator therapies in pulmonary arterial hypertension associated with CHD: a systematic review and network meta-analysis

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Abstract

The optimal treatment strategy using pulmonary vasodilators in pulmonary arterial hypertension associated with CHD (PAH-CHD) remains controversial. We aimed to compare the efficacy and safety of pulmonary vasodilators in PAH-CHD. PubMed and EMBASE databases were searched through May 2022 and a network meta-analysis was conducted. The primary outcomes were mean difference of changes in 6-minute walk distance, NYHA functional class, and N-terminal pro-brain natriuretic peptide. The secondary outcomes included pulmonary vascular resistance, mean pulmonary arterial pressure, and resting oxygen saturation. We identified 14 studies, yielding 807 patients with PAH-CHD. Bosentan and sildenafil were associated with a significant increase in 6-minute walk distance from baseline compared with placebo (MD 48.92 m, 95% CI 0.32 to 97.55 and MD 59.70 m, 95% CI 0.88 to 118.53, respectively). Bosentan, sildenafil, and combination of bosentan and sildenafil were associated with significant improvement in NYHA functional class compared with placebo (MD −0.33, 95% CI −0.51 to −0.14, MD −0.58, 95% CI −0.75 to −0.22 and MD −0.62, 95% CI −0.92 to −0.31, respectively). Bosentan and sildenafil were also associated with significant improvements in secondary outcomes. These findings were largely confirmed in the subgroup analysis. Various adverse events were reported; however, serious adverse event rates were relatively low (4.8–8.7%), including right heart failure, acute kidney injury, respiratory failure, hypotension, and discontinuation of pulmonary vasodilators. In conclusion, bosentan and sildenafil were the most effective in improving prognostic risk factor such as 6-minute walk distance and NYHA class. Overall, pulmonary vasodilators were well tolerated in PAH-CHD.

Introduction

Pulmonary arterial hypertension (PAH) is a severe complication of CHD[1] with an estimated incidence of 5 to 10%.[2] Pulmonary arterial hypertension associated with CHD (PAH-CHD) is often caused by left-to-right shunting defects or obstructive left heart disease.[3] Unfortunately, the management of PAH-CHD is challenging because of limited prospective registry studies in PAH-CHD, heterogeneity of the underlying CHD, and variability in pulmonary haemodynamics. The most recent update from the 6th World Symposium on Pulmonary Hypertension proposed updates in paediatric PAH epidemiology, including classification of PAH-CHD.[4,5] CHD with left-to-right shunts has been classified in group 1.4.4 "Congenital heart disease", including patients with operable and inoperable CHD, Eisenmenger syndrome and post-operative cardiac defects. Pulmonary hypertension with complex CHD is categorised in group 5.4 "Complex CHD", including patients with segmental pulmonary hypertension and unoperated or operated single ventricle.[6,7] Patients with single ventricle physiology remains a difficult group to define as these patients have variable pulmonary blood flow at different stages of palliation and have a wide range of pulmonary vascular disease after the Fontan procedure.[8] PAH has a direct impact on morbidity and mortality in these various types of CHD patients. Thus, an appropriate pulmonary hypertension therapy is crucial to improve the quality of life and prognosis in patients with PAH-CHD.

There are four groups of pulmonary vasodilators as targeted therapies for PAH, including endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogues, and soluble guanylate cyclase stimulators.[9,10] The use of targeted pulmonary therapies is based on the data extrapolated from studies in PAH patients and data on the comparison of pulmonary vasodilators in the different setting of PAH-CHD are lacking. Most studies on the use of pulmonary vasodilators in PAH-CHD have been published for adult Eisenmenger syndrome.[11–14] In patients with Eisenmenger syndrome, bosentan, and macitentan, the dual endothelin receptor antagonist, as well as sildenafil and tadalafil, phosphodiesterase type 5 inhibitors, have been demonstrated to improve exercise capacity and haemodynamics. Despite the small number of patients, several studies have been reported on the efficacy of pulmonary vasodilators such as bosentan, sildenafil, tadalafil selexipag, and riociguat in corrected or uncorrected CHD patients with PAH.[15–19] In addition, beneficial haemodynamic effects as well as improvements in markers of exercise capacity have been reported in patients with Fontan circulation on bosentan, ambrisentan, and sildenafil.[20–24] However, studies comparing the efficacy of different pulmonary vasodilators in each type of PAH-CHD are scarce. Furthermore, the selection of the appropriate pulmonary vasodilators for this population with different haemodynamic characteristics remains controversial. Herein, we aimed to improve the quality of life and reduce risk for adverse outcomes in PAH-CHD patients and thus conducted a network meta-analysis to compare the safety and efficacy of various pulmonary vasodilators in PAH-CHD.

Materials and methods

Search strategy

The current network meta-analysis is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] All studies that investigated the impact of pulmonary vasodilators on efficacy and safety outcomes in patients with PAH-CHD were identified using a two-level search strategy. First, PubMed and EMBASE were searched comprehensively from inception to May 16, 2022 using web-based search engines. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses.

The search terms included pulmonary hypertension OR pulmonary arterial hypertension OR PH OR PAH, congenital heart disease OR congenital heart defects OR CHD, endothelin receptor antagonist OR ERA OR bosentan OR ambrisentan O R macitentan OR phosphodiesterase-5 inhibitor OR PDE-5 inhibitor OR sildenafil OR tadalafil OR prostacyclin analogue OR selexipag OR soluble guanylate cyclase stimulator OR riociguat. Two independent and blinded authors (J.Y. and T.K.) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria. Any discrepancies were resolved by discussion and consensus.

Inclusion and/or exclusion criteria

Studies which met the following criteria were included: (1) the study was published in peer-reviewed journals, (2) the design was a comparative study of patients with PAH-CHD who received different pulmonary vasodilators or placebo/no pulmonary vasodilators; and (3) the study reported either 6-minute walk distance (6MWD), NYHA functional class, N-terminal pro-brain natriuretic peptide (NT-proBNP), mean pulmonary arterial pressure, pulmonary vascular resistance, or oxygen saturation measured by pulse oximetry (SpO_2) as efficacy outcomes at baseline and follow-up time point. No restriction to publication language was applied.

Outcomes

The primary efficacy outcomes were mean difference of changes in 6MWD, NYHA functional class, and NT-proBNP from baseline to follow-up, which were included as main parameters in comprehensive risk assessment in the most recent 2022 ESC/ERS Guidelines.[26] The secondary efficacy outcomes included mean difference of changes in haemodynamic parameters such as pulmonary vascular resistance (dynes·sec·cm^{-5} = Wood units × 80) and mean pulmonary arterial pressure as well as SpO_2 to evaluate the efficacy of different pulmonary vasodilators. Changes in these parameters were measured from baseline to follow-up. Mean difference was calculated as the difference in mean values between the specified follow-up and baseline. In addition, adverse events and side effects were extracted to assess the safety outcomes of pulmonary vasodilators, including death, clinical worsening, and any symptoms. We investigated bosentan versus ambrisentan versus macitentan versus sildenafil versus tadalafil versus selexipag versus riociguat versus combination of bosentan and sildenafil versus placebo or no pulmonary vasodilators since these medication and combination were previously studied. Other parameters extracted were author, number of patients, age, sex, follow-up period, type of CHD, and comorbidities. Disagreements regarding the extracted data were resolved through discussion and consensus of a third author (H.T.).

Risk of bias assessment

To assess the risk of bias, we used the Cochrane Collaboration risk of bias tool for randomised controlled trials[27] and the Newscastle–Ottawa Assessment Scale for observational studies.[28] A publication bias was assessed by Egger's test and Funnel plots.[29] Two investigators (J.Y. and T.K.) reviewed the studies and judged selection, comparability, and outcomes.

Statistical analysis

For each study, the adjusted hazard ratio and associated 95% confidence interval were extracted. The mean difference of change in mean mean pulmonary arterial pressure, pulmonary vascular resistance, SpO_2, 6MWD, NYHA functional class, and NT-proBNP levels between treatment arms were synthesised for comparison. Considering the potential heterogeneity among the included studies, the effect estimate was pooled using the random-effect model for the analysis. We performed a network meta-analysis using R "netmeta" 3.6.2 package (R Foundation for Statistical Computing, Vienna, Austria).[30] Within the framework, I^2 and Q statistics, which represent the proportion of total variation in study estimates that is due to heterogeneity, were used to quantify heterogeneity.[31] The I^2 statistic represents the proportion of variability that is not attributable to chance. I^2 values were interpreted as follows: <25% indicating low, 25–50% moderate, and >50% high heterogeneity.[32] The Q statistic is the sum of a statistic for heterogeneity, and a statistic for inconsistency, which represents the variability of treatment effect between direct and

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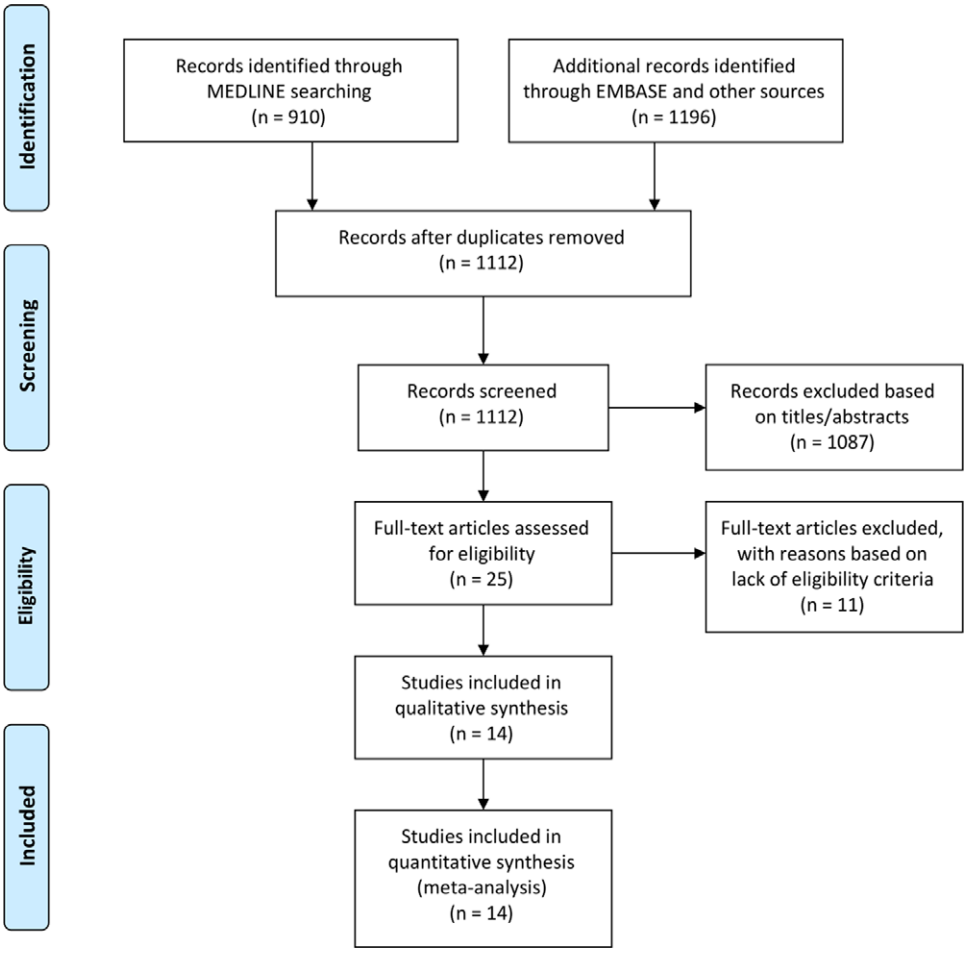

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection.

indirect comparisons at the meta-analytic level. Potential publication bias was assessed by the Funnel plots and Egger's linear regression test. Subgroup analyses were performed in Eisenmenger syndrome patients, other patients with biventricular circulation (CHD-PH), and Fontan patients as well as by excluding studies in Fontan patients with pulmonary hypertension.

Results

Among the 1112 articles retrieved following database and manual searches, 14 studies fulfilled eligibility criteria, enrolling a total of 807 patients with PAH-CHD (Fig 1).[11–24] Eleven randomised controlled trials and three observational studies were identified. The study and patient characteristics are summarised in Table 1. The follow-up period ranged from 1 day to 24 months. The risk of bias assessment is shown in Supplementary Fig S1 and Supplementary Table.

Structure of the network meta-analysis

The characteristics of the network of pulmonary vasodilators used in analysis are shown in Fig 2. We compared the following treatment strategies of pulmonary vasodilators: bosentan, ambrisentan, macitentan, sildenafil, tadalafil, selexipag, riociguat, combination therapy of bosentan and sildenafil, and placebo.

Primary efficacy outcome

Bosentan and sildenafil were associated with a significant increase in 6MWD from baseline compared with placebo (MD 48.92 m, 95% CI 0.32 to 97.55 and MD 59.70 m, 95% CI 0.88 to 118.53, respectively) (Table 2 and Fig 3). There was no significant difference in change of 6MWD from baseline between bosentan, macitentan, sildenafil, tadalafil, selexipag, reiociguat, and combination of bosentan and sildenafil. This analysis had high heterogeneity (I^2: 62.9%; p = 0.06) and significant inconsistency (p = 0.01).

Bosentan, sildenafil, and combination of bosentan and sildenafil were associated with significant improvement in NYHA functional class compared with placebo (MD −0.33, 95% CI −0.51 to −0.14, MD −0.58, 95% CI −0.75 to −0.22 and MD −0.62, 95% CI −0.92 to −0.31, respectively) (Table 2 and Fig 4). There was no significant heterogeneity (I^2: 0.0%; p = 0.38) and no significant inconsistency (p = 0.56) in this analysis.

Riociguat 1.5 mg was associated with a significant decrease in NT-proBNP levels compared with placebo (MD −826.00 pg/mL, 95% CI −1499.08 to −152.92) (Table 2 and Fig 5). Furthermore, riociguat 1.5 mg was associated with a significant improvement in change of NT-proBNP levels compared with bosentan, selexipag, riociguat 2.5 mg, and combination of bosentan and sildenafil. There was no significant heterogeneity (I^2: 0.0%; p = 0.94) in this analysis.

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Table 1. Characteristics of the included studies

Author	Year	Treatment Comparison	Classification of PH	Study Design	Follow-up (months)	No. of Patients
Galiè et al.[11]	2006	Bosentan Placebo	ES	RCT	4	37 17
Iversen et al.[12]	2010	Bosentan Bosentan + Sildenafil	ES	RCT	6	10 9
Mukhopadhyay et al.[13]	2011	Tadalafil Placebo	ES	RCT	1.5	14 14
Gatzoulis et al.[14]	2019	Macitentan Placebo	ES	RCT	4	114 112
Rosenkranz et al.[15]	2015	Riociguat 2.5 mg Riociguat 1.5 mg Placebo	CHD-PH	RCT	3	15 8 12
van Riel AC et al.[16]	2016	Bosentan Sildenafil	CHD-PH	Observational	12	45 29
Negoi et al.[17]	2017	Bosentan Sildenafil Bosentan + Sildenafil Placebo	CHD-PH	Observational	24	7 13 3 32
Clavé et al.[18]	2019	Sildenafil Tadalafil	CHD-PH	Observational	3	16 15
Beghetti et al.[19]	2019	Selexipag Placebo	CHD-PH	RCT	6.5	60 50
Giardini et al.[20]	2008	Sildenafil Placebo	Fontan	RCT	1 day	18 9
Schuuring et al.[21]	2014	Bosentan Placebo	Fontan	RCT	6	32 16
Hebert et al.[22]	2014	Bosentan Placebo	Fontan	RCT	3	36 39
Shang et al.[23]	2016	Bosentan Placebo	Fontan	RCT	24	5 4
Hill et al.[24]	2020	Ambrisentan Placebo	Fontan	RCT	3 day	13 3

Author	Age (years)	Men (%)	SpO_2 (%)	SpO_2 change (%)	mPAP (mmHg)	mPAP change (mmHg)	PVR (dyne•sec•cm^{-5})	PVR (Wood units)
Galiè et al.[11]	37.2 ± 12.0 44.2 ± 8.5	38.0 41.0	82.4 ± 5.3 83.6 ± 5.1	NA NA	77.8 ± 15.2 72.1 ± 19.4	−5.0 ± 9.7 0.5 ± 5.8	3425.1 ± 1410.5 2870.0 ± 1209.3	42.8 ± 17.6 35.9 ± 15.1
Iversen et al.[12]	NA NA	NA NA	NA NA	2.9 −1.8	NA NA	NA NA	NA NA	NA NA
Mukhopadhyay et al.[13]	NA NA	NA NA	NA NA	2.6 ± 3.4 0.9 ± 2.5	NA NA	NA NA	NA NA	NA NA
Gatzoulis et al.[14]	33.0 (12.0–82.0) 31.0 (13.0–62.0)	28.1 39.3	84.3 ± 5.6 85.2 ± 5.1	1.1 0.2	77.5 ± 11.6 79.0 ± 15.8	−6.4 ± 8.2 −3.5 ± 9.6	2821.0 ± 1321.0 2776.0 ± 1455.0	35.3 ± 16.5 34.7 ± 18.2

Table 1. (*Continued*)

Author	PVR change (dyne•sec•cm^{-5})	PVR change (Wood units)	6MWD (meters)	6MWD change (meters)	NYHA functional class	NYHA functional class change	NT-proBNP (pg/mL)	NT-proBNP change (pg/mL)
Rosenkranz et al.[15]	15.0 ± 14.0 41.0 ± 15.0 40.0 ± 16.0	13.0 25.0 17.0	NA NA NA	NA NA NA	59.0 ± 21.0 67.0 ± 19.0 61.0 ± 23.0	−4.0 ± 7.0 −3.0 ± 10 1.0 ± 8.0	1130.0 ± 664.0 1047.0 ± 564.0 1313.0 ± 763.0	14.1 ± 8.3 13.1 ± 7.1 16.4 ± 9.5
van Riel AC et al.[16]	47.0 ± 14.0 41.0 ± 14.0	31.0 31.0	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
Negoi et al.[17]	NA NA NA NA	NA NA NA NA	84.8 ± 7.4 91.6 ± 3.8 78.0 ± 19.8 92.9 ± 4.9	4.2 ± 7.1 −0.3 ± 6.1 12.5 ± 17.9 −3.1 ± 4.8	61.7 ± 9.2 56.7 ± 9.9 NA 51.4 ± 12.4	−2.7 ± 9.2 −5.2 ± 10.7 NA 2.2 ± 15.6	NA NA NA NA	NA NA NA NA
Clavé et al.[18]	26.6 (17.4–40.0) 30.3 (19.7–43.1)	43.8 20.0	90.0 (86.0–92.0) 81.0 (77.0–89.0)	0.0 ± 5.3 5.0 ± 8.0	NA NA	−2.3 ± 7.4 1.4 ± 6.7	NA NA	NA NA
Beghetti et al.[19]	40.2 ± 15.4 40.3 ± 14.8	23.3 16.0	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
Giardini et al.[20]	22.2 ± 5.2 23.8 ± 4.5	44 33.0	90.0 ± 6.0 91.0 ± 6.0	0.0 0.0	NA NA	NA NA	NA NA	NA NA
Schuuring et al.[21]	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
Hebert et al.[22]	20.3 ± 7.5 19.7 ± 6.6	58.0 62.0	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
Shang et al.[23]	8.1 ± 2.3 11.1 ± 4.1	NA NA	NA NA	NA NA	10.8 ± 2.4 13.8 ± 1.5	1.0 ± 2.6 1.5 ± 1.4	NA NA	NA NA
Hill et al.[24]	35.0 ± 7.0 48.0 ± 21.0	54.0 67.0	NA NA	NA NA	16.8 ± 2.9 14.3 ± 1.1	−1.2 0.0	184.0 ± 72.0 144.0 ± 48.0	2.3 ± 0.9 1.8 ± 0.6
Galiè et al.[11]	−316.9 ± 841.2 155.1 ± 552.5	−4.0 ± 10.5 1.9 ± 6.9	331.9 ± 82.8 366.4 ± 67.6	43.4 ± 49.3 −9.7 ± 74.0	NA NA	NA NA	NA NA	NA NA
Iversen et al.[12]	−608.0 ± 389.1 −0.2 ± 389.1	−7.6 ± 4.9 −0.2 ± 4.9	NA NA	21.1 7.9	NA NA	−0.26 −0.13	NA NA	2.2 −9.9
Mukhopadhyay et al.[13]	38.4 −165.6	0.5 −2.1	357.8 ± 73.3 357.8 ± 73.3	46.4 ± 31.6 11 ± 15.6	NA NA	NA NA	NA NA	NA NA
Gatzoulis et al.[14]	−410.0 ± 752.0 79.0 ± 491.0	−5.1 ± 9.4 1.0 ± 6.0	368.7 ± 74.5 380.3 ± 76.3	18.3 ± 84.4 19.7 ± 53	NA NA	NA NA	693.0 ± 1135.5 893.0 ± 2320.8	−88.0 ± 537.2 72.0 ± 1253.5
Rosenkranz et al.[15]	−250.0 ± 410.0 −126.0 ± 368.0 −66.0 ± 632.0	−3.1 ± 5.1 −1.6 ± 4.6 −0.8 ± 7.9	369.0 ± 78.0 391.0 ± 59.0 360.0 ± 59.0	39.0 ± 60.0 43.0 ± 54.0 0.0 ± 42.0	NA NA NA	NA NA NA	761.0 ± 1172.0 1352.0 ± 1350.0 1573.0 ± 1775.0	−164.0 ± 317.0 −872.0 ± 1147.0 −46.0 ± 697.0
van Riel AC et al.[16]	NA NA	NA NA	395.0 ± 137.0 312.0 ± 121.0	49.0 ± 119.2 122.0 ± 100.5	NA NA	NA NA	NA NA	NA NA
Negoi et al.[17]	NA NA	NA NA	440.0 ± 127.0 330.0 ± 140.0	75.0 ± 115.4 49.0 ± 119.3	3.0 ± 0.6 2.9 ± 0.3	−0.6 ± 0.6 −0.3 ± 0.4	NA NA	NA NA

(*Continued*)

Table 1. (*Continued*)

Author	PVR change (dyne•sec•cm^{-5})	PVR change (Wood units)	6MWD (meters)	6MWD change (meters)	NYHA functional class	NYHA functional class change	NT-proBNP (pg/mL)	NT-proBNP change (pg/mL)
	NA NA	NA NA	340.0 ± 84.8.0 397.0 ± 55.1	−55.0 ± 156 23.0 ± 58.9	3.0 ± 0.1 2.5 ± 0.8	−0.3 ± 0.6 0.4 ± 0.7	NA NA	NA NA
Clavé et al.[18]	NA NA	NA NA	484.0 (410.0–523.0) 480.0 (462.0–510.0)	37.0 ± 67.2 60.0 ± 39.5	NA NA	NA NA	NA NA	NA NA
Beghetti et al.[19]	NA NA	NA NA	379.0 (346.0–431.0) 369.0 (320.0–423.0)	11.0 ± 41.0 2.0 ± 56.0	NA NA	NA NA	286.0 (98.0–649.0) 426.0 (151.0–1280.0)	−4.0 ± 104.0 −11.0 ± 139.0
Giardini et al.[20]	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA
Schuuring et al.[21]	NA NA	NA NA	NA NA	NA NA	NA NA	MD −0.2, 95% CI −0.7 to 0.3	274.0 (35.0–1463.0) 275.0 (35.0–1463.0)	−4.5 2.6
Hebert et al.[22]	NA NA	NA NA	NA NA	NA NA	NA NA	MD −0.2, 95% CI −0.5 to 0.0	12.2 (6.3–25.3) 15.5 (7.0–24.4)	40.0 −7.0
Shang et al.[23]	NA NA	NA NA	377.0 ± 41.3 403.0 ± 53.6	91.2 ± 38.6 −32.4 ± 42.9	NA NA	MD −0.8, 95% CI −1.5 to −0.1	NA NA	NA NA
Hill et al.[24]	−40.0 −20.0	−0.5 −0.3	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA

Abbreviations: *6MWD* 6-minute walk distance, *CHD-PH* CHD-associated pulmonary hypertension, *CI* confidence interval, *ES* Eisenmenger syndrome, *MD* mean difference, *mPAP* mean pulmonary arterial pressure, *NA* not available, *No.* number, *NTproBNP* N-terminal pro brain natriuretic peptide, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *RCT* randomised controlled trial, *SpO_2* oxygen saturation.

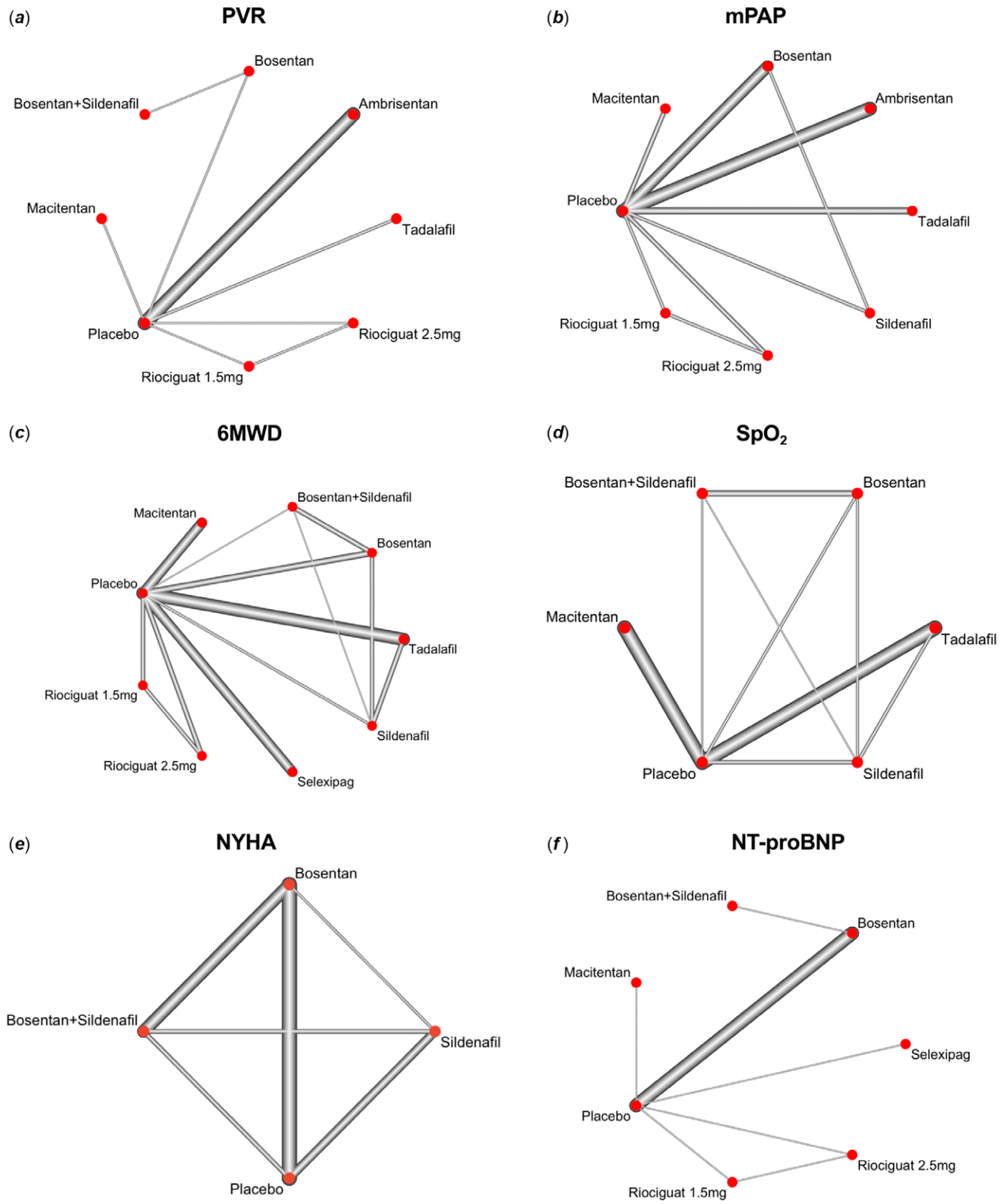

Figure 2. Network of pulmonary vasodilator comparisons. The width of the lines between pulmonary vasodilator strategies reflects the number of studies available for each comparison. (***a***) PVR, (***b***) mPAP, (***c***) 6MWD, (***d***) SpO_2, (***e***) NYHA, (***f***) NT-proBNP. 6MWD, 6-minute walk distance; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; SpO_2, resting oxygen saturation.

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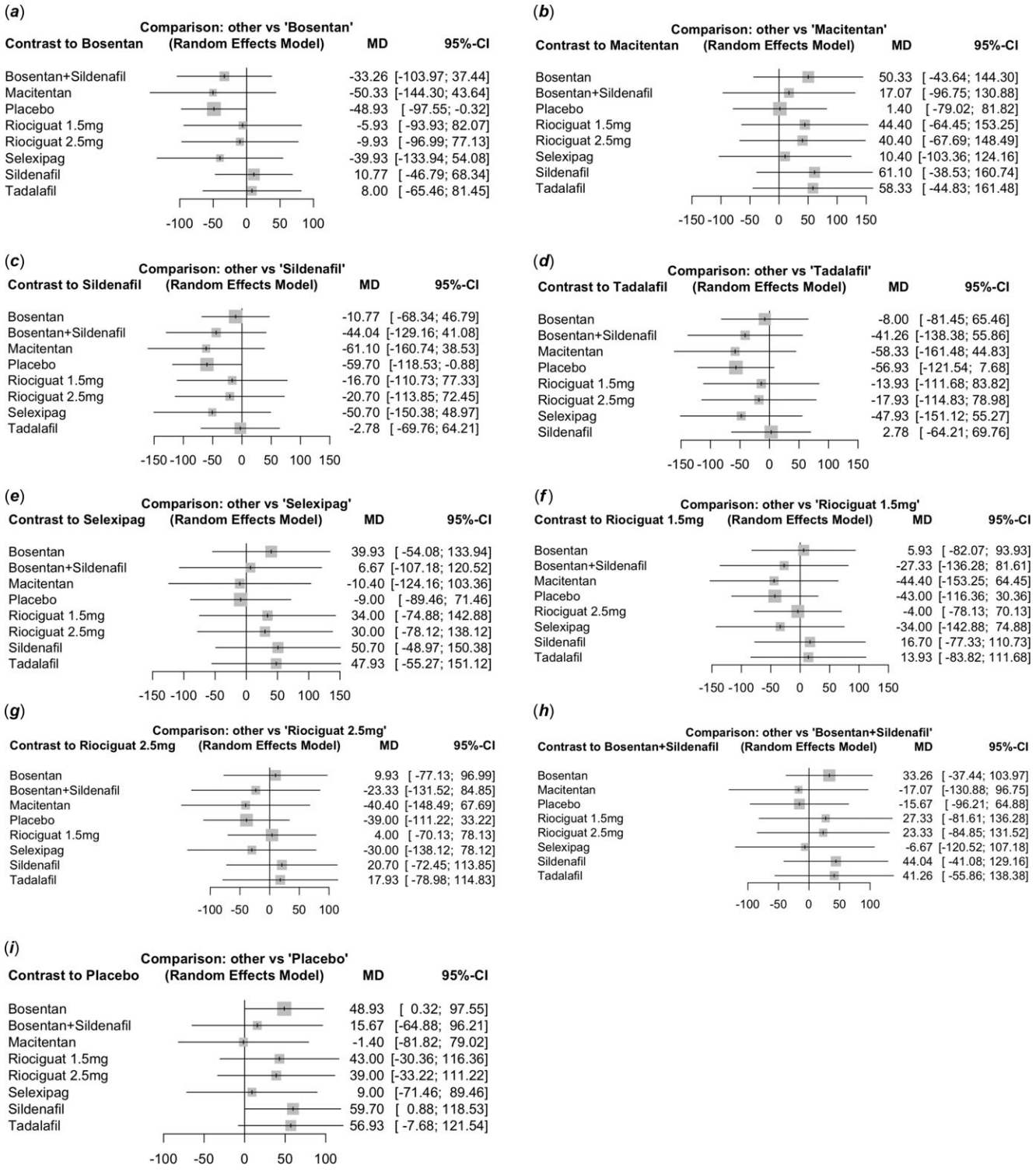

Figure 3. Effect of pulmonary vasodilators on the primary efficacy outcome (6MWD). Forest plots for the comparisons among pulmonary vasodilators (random effects model): (***a***) versus bosentan; (***b***) versus macitentan; (***c***) versus sildenafil; (***d***) versus tadalafil; (***e***) versus selexipag; (***f***) versus riociguat 1.5 mg; (***g***) versus riociguat 2.5 mg; (***h***) versus bosentan+sildenafil; (***i***) versus placebo. 6MWD, 6-minute walk distance; CI, confidence interval; MD, mean difference.

Secondary efficacy outcomes

Pulmonary vascular resistance was significantly decreased in bosentan (MD −472.0 dynes·sec·cm^{-5}, 95% CI −906.8 to −37.1 [MD −5.9 Wood units, 95% CI −11.3 to −0.5]), macitentan (MD −489.0 dynes·sec·cm^{-5}, 95% CI −899.8 to −78.2 [MD −6.1 Wood units, 95% CI −11.2 to −1.0]) and tadalafil (MD −584.0 dynes·sec·cm^{-5}, 95% CI −866.2 to −301.8 [MD −7.3 Wood units, 95% CI −10.8 to −3.8]) compared with placebo (Supplementary Fig S2). Bosentan, macitentan, and tadalafil were associated with a significant decrease in pulmonary vascular resistance compared

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Table 2. Network meta-analysis comparing the primary efficacy outcomes of pulmonary vasodilators for PAH-CHD.

	Efficacy in improving 6MWD (m)								
Efficacy in improving NYHA functional class	Bosentan	33.26 (−37.44 to 103.97)	50.33 (−43.64 to 144.30)	5.93 (−82.07 to 93.93)	9.93 (−77.13 to 96.99)	39.93 (−54.08 to 133.94)	−10.77 (−68.34 to 46.79)	−8.00 (−81.45 to 65.46)	48.93 (0.32 to 97.55)
	0.16 (−0.06 to 0.37)	Bosenttan + sildenafil	17.07 (−96.75 to 130.88)	−27.33 (−136.28 to 81.61)	−23.33 (−131.52 to 84.85)	6.67 (−107.18 to 120.52)	−44.04 (−129.16 to 41.08)	−41.26 (−138.38 to 55.86)	15.67 (−64.88 to 96.21)
			Macietntan	−44.40 (−153.25 to 64.45)	−40.40 (−148.49 to 67.69)	−10.40 (−124.16 to 103.36)	−61.10 (−160.74 to 38.53)	−58.33 (−161.48 to 44.83)	−1.40 (−81.82 to 79.02)
				Riociguat 1.5 mg	4.00 (−70.13 to 78.13)	−9.00 (−89.46 to 71.46)	−16.70 (−110.73 to 77.33)	−13.93 (−111.68 to 83.82)	43.00 (−30.36 to 116.36)
					Riociguat 2.5 mg	30.00 (−78.12 to 138.12)	−20.70 (−113.85 to 72.45)	−17.93 (−114.83 to 78.98)	39.00 (−33.22 to 111.22)
						Selexipag	−50.70 (−150.38 to 48.97)	−47.93 (−151.12 to 55.27)	9.00 (−71.46 to 89.46)
	0.29 (−0.05 to 0.62)	0.13 (−0.23 to 0.49)					Sildenafil	2.78 (−64.21 to 69.76)	59.70 (0.88 to 118.53)
								Tadalafil	56.93 (−7.68 to 121.54)
	−0.33 (−0.51 to −0.14)	−0.48 (−0.75 to −0.22)					−0.62 (−0.92 to −0.31)		Placebo

Efficacy in improving NT-proBNP (pg/mL)	Bosentan								
	0.16 (−0.06 to 0.37)	Bosenttan + sildenafil							
	158.10 (−94.16 to 410.36)	170.10 (−85.28 to 425.47)	Macietntan						
	824.10 (151.01 to 1497.18)	836.10 (161.84 to 1510.36)	666.00 (−52.80 to 1384.80)	Riociguat 1.5 mg					
	116.10 (−291.75 to 523.95)	128.10 (−281.68 to 537.88)	−42.00 (−521.54 to 437.54)	−708.00 (−1371.47 to −44.53)	Riociguat 2.5 mg				
	−8.90 (−55.60 to 37.80)	3.10 (−58.25 to 64.45)	−167.00 (−423.52 to 89.52)	−833.00 (−1507.70 to −158.3)	−125.00 (−535.50 to 285.50)	Selexipag			
	−1.90 (−4.10 to 0.29)	10.10 (−29.75 to 49.95)	−160.00 (−412.25 to 92.25)	−826.00 (−1499.08 to −152.92)	−118.00 (−525.84 to 289.84)	7.00 (−39.65 to 53.65)	Placebo		

Mean difference of changes from baseline to follow-up and 95% confidence interval are shown.
Abbreviations: *6MWD* 6-minute walk distance, *NTproBNP* N-terminal pro brain natriuretic peptide

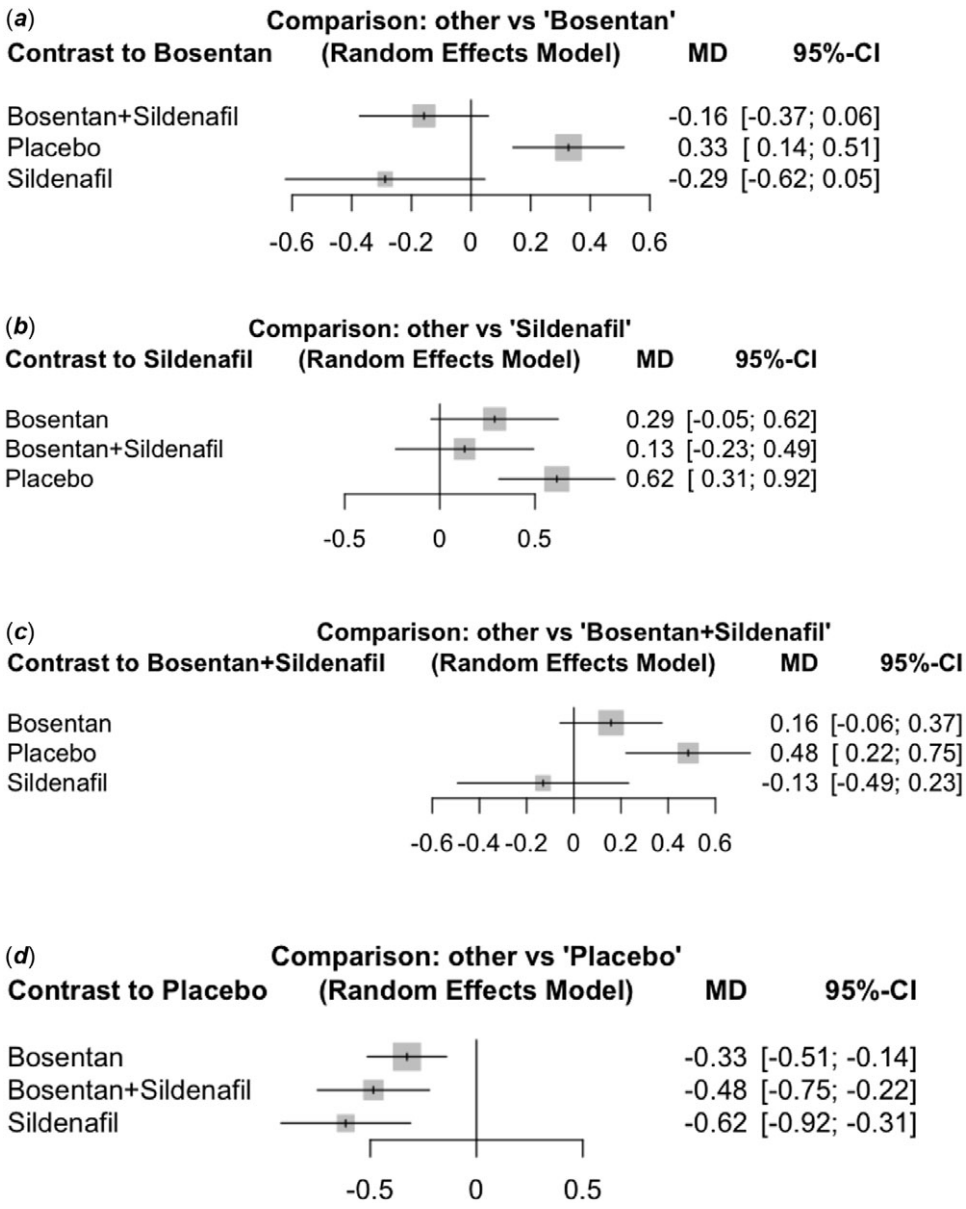

Figure 4. Effect of pulmonary vasodilators on the secondary efficacy outcome (NYHA functional class). Forest plots for the comparisons among pulmonary vasodilators (random effects model): (***a***) versus bosentan; (***b***) versus sildenafil; (***c***) versus bosentan + sildenafil; (***d***) versus placebo. CI, confidence interval; MD, mean difference.

with ambrisentan (MD −448.0 dynes·sec·cm^{-5}, 95% CI −887.2 to −8.8 [MD −5.6 Wood units, 95% CI −11.1 to −0.1], MD −465.0 dynes·sec·cm^{-5}, 95% CI −880.3 to −49.7 [MD −5.8 Wood units, 95% CI −11.0 to −0.6], and MD −560.0 dynes·sec·cm^{-5}, 95% CI −848.7 to −271.3 [MD −7.0 Wood units, 95% CI −10.6 to −3.4], respectively). In addition, tadalafil were associated with a significant reduction in pulmonary vascular resistance than riociguat 1.5 mg (MD −524.0 dynes·sec·cm^{-5}, 95% CI −978.7 to −69.4 [MD −6.6 Wood units, 95% CI −12.2 to −0.9]). There was no significant heterogeneity (I^2: 0.0%; p = 0.00) and no significant inconsistency (p = 1.0) in this analysis.

Sildenafil was associated with a significant decrease in mean pulmonary arterial pressure from baseline compared with placebo (MD −6.2 mmHg, 95% CI −12.2 to −0.2) (Fig S3). There was no significant difference in change of mean pulmonary arterial pressure from baseline between bosentan, ambrisentan, macitentan, sildenafil, tadalafil, and riociguat. There was no significant heterogeneity (I^2: 0.0%; p = 0.17) and no significant inconsistency (p = 0.89) in this analysis.

Bosentan, tadalafil, and combination of bosentan and sildenafil were associated with a significant increase in peripheral blood oxygen saturation as assessed by SpO_2 compared to placebo (MD 6.7, 95% CI 2.6 to 10.9, MD 1.9, 95% CI 0.8 to 3.1, and MD 11.6, 95% CI 6.7 to 16.4, respectively) (Fig S4). Bosentan was associated with a significant increase in SpO_2 compared to macitentan, sildenafil, or tadalafil (MD 5.8, 95% CI 1.5 to 10.1, MD 5.8, 95% CI 1.6 to 10.1 and MD 4.8, 95% CI 0.5 to 9.0, respectively). Furthermore, combination therapy of bosentan and sildenafil was significantly more effective in improving SpO_2 compared with bosentan, macitentan, sildenafil, and tadalafil monotherapies (MD 4.9, 95% CI 2.1 to 7.6, MD 10.7, 95% CI 5.7 to 15.7, MD 10.7, 95% CI 5.8 to 15.7, MD 9.6%, and 95% CI 4.7 to 14.6, respectively). There was no significant difference in change of SpO_2 between macitentan, tadalafil, and sildenafil. There was

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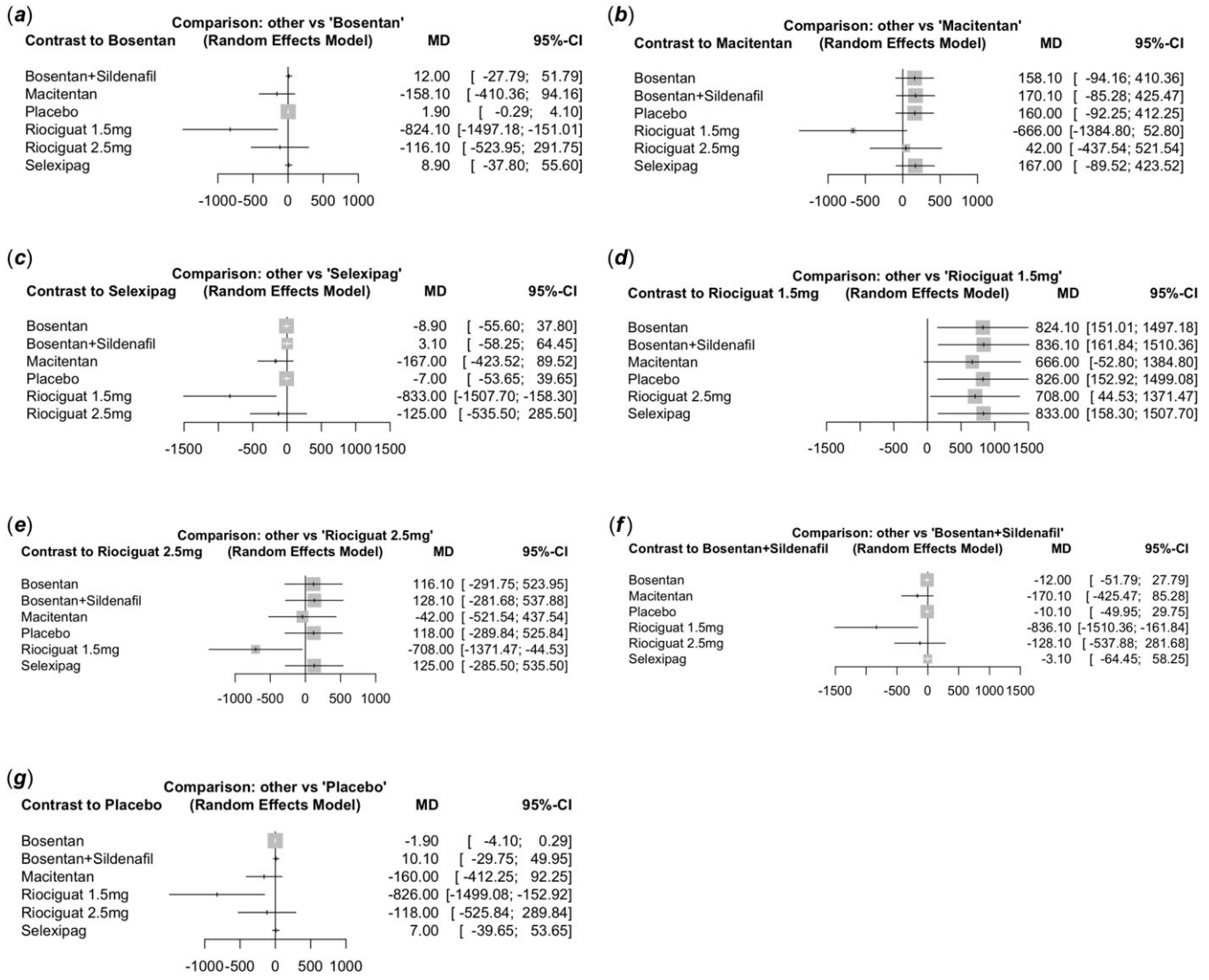

Figure 5. Effect of pulmonary vasodilators on the secondary efficacy outcome (NT-proBNP). Forest plots for the comparisons among pulmonary vasodilators (random effects model): (***a***) versus bosentan; (***b***) versus bosentan+sildenafil; (***c***) versus placebo. CI, confidence interval; MD, mean difference; NT-proBNP, N-terminal pro brain natriuretic peptide.

no significant heterogeneity (I^2: 0.0%; p = 0.74) and no significant inconsistency (p = 0.39) in this analysis.

Safety outcomes

Nine of the studies reported adverse events in bosentan (29.5%), macitentan (66.7%), sildenafil (5.6%), tadalafil (28.9%), selexipag (95.0%), riociguat (87.0%), combination of bosentan and sildenafil (20.0%), and placebo (54.3%), including headache, palpitation, back pain, nausea, itching, peripheral oedema, fatigue, flushing, dizziness, and liver dysfunction. Serious adverse events, such as right heart failure, acute kidney injury, liver function abnormalities, respiratory failure, hypotension, discontinuation of pulmonary vasodilators, were seen in bosentan (4.8%), macitentan (6.1%), and riociguat (8.7%), similar to placebo (8.5%).

Subgroup analyses

The subgroup analyses in Eisenmenger syndrome patients, other patients with biventricular circulation (CHD-PH), and Fontan patients as well as excluding patients with Fontan circulation showed similar results (Supplementary Fig S5-20). Bosentan and combination of bosentan and sildenafil were associated with significant improvement in 6MWD compared with placebo in Eisenmenger syndrome patients. In CHD-PH patients, bosentan, sildenafil, and combination of bosentan and sildenafil were associated with significant improvement in NYHA functional class compared with placebo, while tadalafil and riociguat were associated with significant improvement in 6MWD or NT-proBNP, which is not consistent with the main result. Bosentan was associated with significant improvement in 6MWD compared with placebo in Fontan patients. Bosentan, sildenafil, and combination of bosentan and sildenafil were associated with significant improvement in NYHA functional class compared with placebo when excluding Fontan patients. However, 6MWD was significantly improved in tadalafil compared with placebo, which is also inconsistent with the main result.

Publication bias

A significant publication bias in each outcome was not detected by using funnel plots and Egger's test (Supplementary Fig S21).

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Discussion

This systematic review and network meta-analysis comprehensively reviewed published articles and described the efficacy and safety of pulmonary vasodilators in patients with PAH-CHD. We demonstrated that bosentan and sildenafil were ranked best in terms of the efficacy on primary outcomes such as 6MWD and NYHA functional class. While various adverse effects were identified, serious adverse event rates were relatively low, and overall pulmonary vasodilators were well tolerated.

The most recent 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension proposed comprehensive prognostic evaluation and risk assessment based on a multiparametric approach using a three-strata model to classify patients at low, intermediate, or high risk of death.[26] Although main parameters are assessed in this risk stratification, including sings of right heart failure, progression of clinical manifestations, syncope, World Health Organization functional class (WHO-FC), 6MWD, cardiopulmonary exercise testing, biomarkers such as BNP or NT-proBNP, RV function and hemodynamics, the use of WHO-FC, 6MWD, and BNP/ NT-proBNP is recommended. Several studies identified WHO-FC, 6MWD, and BNP/NT-proBNP as the strongest prognostic predictors.[33–35] Functional capacity has been shown to be associated with outcomes in patients with PAH-CHD.[36] 6MWD is the most commonly used measure of functional capacity in patients with PAH because of its simplicity and validation. Despite the disadvantage of a potentially subjective assessment, functional class is also a good predictor of survival and aids in clinician decision to initiate pulmonary vasodilator therapy for PAH-CHD.[37] In this study, we demonstrated that bosentan and sildenafil improved 6MWD compared with placebo. Moreover, NYHA class was significantly improved in bosentan, sildenafil, and combination therapy of bosentan and sildenafil compared with placebo. Furthermore, we exhibited that riociguat 1.5 mg was associated with a significant improvement in change of NT-proBNP levels compared with placebo. Collectively, our network meta-analysis demonstrated that bosentan and sildenafil were ranked best in terms of the efficacy on risk factors determining prognosis, including 6MWD and NYHA functional class. Previous studies reported that bosentan and sildenafil might have the effects of improving exercise tolerance and hemodynamic parameter in patients with different types of PAH-CHD, supporting our findings.[38–40] However, evidence on the use of pulmonary vasodilators in patients with PAH-CHD remains limited. Bosentan improved 6MWD in Eisenmenger syndrome patients with WHO-FC III.[11] Other ERAs and phosphodiesterase type 5 inhibitors have shown favourable effects on functional and haemodynamic parameters in Eisenmenger syndrome.[14,41] The efficacy of PAH therapies in patients with prevalent systemic-to-pulmonary shunts, segmental pulmonary hypertension, and Fontan circulation is not well established.[6,42–44] Given the heterogeneous patient population in PAH-CHD, further studies are warranted to compare outcomes of pulmonary vasodilators in homogeneous patient cohort of PAH-CHD.

In addition to the effect on 6MWD and NYHA functional class, we also demonstrated potential benefits of bosentan and sildenafil in improving haemodynamics such as pulmonary vascular resistance, mean pulmonary arterial pressure, and SpO_2 in patients with PAH-CHD compared to placebo. Although lower pulmonary vascular resistance and mean pulmonary arterial pressure are generally accepted to be beneficial in PAH-CHD including Fontan, the efficacy of pulmonary vasodilators on pulmonary vascular resistance and mean pulmonary arterial pressure in PAH-CHD remains controversial since there are many factors associated with pulmonary vascular resistance and mean pulmonary arterial pressure, including various anatomic lesions, non-pulsatile pulmonary blood in Fontan circulation, an abnormal vascular tone, and a variety of pulmonary vascular disease. We found that bosentan, sildenafil, macitentan, and tadalafil might be more effective in improving pulmonary vascular resistance. However, the study analysing ambrisentan in our meta-analysis was conducted in Fontan patients, and thus the small effective size of ambrisentan may reflect differences in patient population rather than the effectiveness of pulmonary vasodilators. Baseline resting SpO_2 was reported to be a reliable prognosticator in patients with Eisenmenger syndrome.[45] A deterioration in SpO_2 as well as functional capacity were reported to be associated with adverse outcome in Eisenmenger syndrome patients.[46] In our network meta-analysis, bosentan might be more effective in improving SpO_2 than other monotherapies. Although the heterogeneity of the included studies and patients needs to be considered, these findings may support the efficacy of bosentan and sildenafil in PAH-CHD.

Our network meta-analysis demonstrated that bosentan and sildenafil combination therapy might be more effective in several of the secondary outcomes than other monotherapies. Combination therapy has been becoming to play a central role in patients with PAH.[47,48] Benefits of initial combination therapy of endothelin receptor antagonist and phosphodiesterase type 5 inhibitor have been demonstrated in PAH.[47,49] In recent years, a treatment strategy called "treat and repair," in which upfront combination therapy of multiple pulmonary vasodilators are administered preoperatively and post-operatively to close the defect even in patients with a high pulmonary vascular resistance has been tried, and some reports are showing its effectiveness.[50,51] However, no consensus has been reached regarding which drugs are recommended for treating and repairing left-to-right shunting defects such as atrial septal defect and ventricular septal defect. In addition, combination therapy remains controversial in PAH-CHD because there are only few data available to support combination therapy for PAH-CHD and heterogeneity of the underlying CHD. There have been studies reporting monotherapy of current available pulmonary vasodilators such as endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, sGC stimulators, and prostacyclin analogues in PAH-CHD. Bosentan has the strongest evidence for the use in PAH-CHD, demonstrating favourable long-term outcomes as well as improvements in functional capacity and hemodynamics.[11,52] Macitentan achieves a higher affinity for the lipophilic milieu and a longer duration of action compared with bosentan and ambrisentan.[53] Phosphodiesterase type 5 inhibitor monotherapy such as sildenafil and tadalafil in patients with PAH-CHD was reported to improve functional capacity and pulmonary hemodynamics.[13,54,55] Riociguat was reported to improve pulmonary vascular resistance and exercise capacity in PAH-CHD patients and has been utilised widely for PAH-CHD lately.[15] By contrast to monotherapy, data investigating benefits of combination therapy for PAH-CHD are scarce. Combination of bosentan and sildenafil was shown to improve functional capacity and hemodynamic parameters in PAH-CHD patients in some studies, while other studies failed to demonstrate benefits.[12,56–58] Although overall pulmonary vasodilators were well tolerated in our study, combination therapy may deteriorate the patient's clinical condition in PAH-CHD, developing complications including

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pulmonary oedema, interstitial lung disease, and alveolar haemorrhage.[59] Thus, the strategy of combination therapy for patients with PAH-CHD should be considered prudently and our findings of combination therapy warrant further investigation.

Limitations

Our study has some limitations. First, there is heterogeneity of the studies included in our network meta-analysis with regards to study population, including patients with PAH due to repaired CHD, unrepaired CHD with Eisenmenger syndrome, and Fontan patients. Each group has a different haemodynamic profile and different expected response to pulmonary vasodilator therapies. Particularly in Fontan patients, mean pulmonary arterial pressure is markedly different and pulmonary vascular resistance is difficult to assess. Therefore, we performed the subgroup analyses in Eisenmenger syndrome patients, other patients with biventricular circulation, and Fontan patients as well as excluding Fontan patients, which showed similar results to our primary analysis with regards to positive impacts of bosentan and sildenafil on primary outcomes (6MWD and NYHA class). However, we could not assess the efficacy of pulmonary vasodilators separately due to a small number of included studies in each group. Second, each study contained a small number of patients, potentially leading to heterogeneity. In particular, riociguat and ambrisentan were reported in only one study, respectively. Small sample size produces larger effect sizes which are more variable than large samples size studies, limiting the statistical power of the meta-analyses. Therefore, our analyses need to be interpreted with great caution. Third, we included both children and adults with PAH-CHD in our meta-analysis, which also lead to substantial heterogeneity. The purpose of retrieving studies without age restriction was to systemically review all cases and to compare the efficacy and safety of pulmonary vasodilators in PAH-CHD patients. In the subgroup analysis, we excluded the study reporting children,[23] showing overall consistent results with the main result. Fourth, the study duration ranged from 1 day to 24 months, which also lead to substantial heterogeneity. The different lengths of follow-up may limit the validity of our network meta-analysis in the comparisons of efficacy and safety among pulmonary vasodilators. Fifth, each efficacy and safety outcome were not obtainable across the included studies. For example, pulmonary vascular resistance was reported in 6 of the 14 studies and all-cause death could not be evaluated due to limited available data. Sixth, most analyses had wide confidence intervals of pooled estimates, indicating less precise estimates and leading to concerns about the reliability of our findings. However, the robustness of our results was verified in subgroup analyses. Seventh, there is a dose–effect of each drug compared to placebo, which can be analysed by dose–effect meta-regression analysis, whereas it is difficult to compare the dose-effect of one drug with the dose–effect of another drug and to investigate which dose of one drug is compared with the dose–effect of another drug is of concern since dose and outcome are related. Therefore, dose–effects can be evaluated only for one drug each, which is not the main objective of our network meta-analysis aiming to compare multiple drug effects. Eighth, although relative change proportional to the baseline would be more appropriate to identify positive treatment effects compared to mean difference of changes since relative change proportional to the baseline is adjusted for the differences in pre-treatment values when divided by the pre-treatment values, there are many data where pre-treatment values are not available, making it difficult to examine the relative change in baseline proportionality. Lastly, our study is a network meta-analysis of trial-level data and not individual patient data, therefore lack of detailed analysis including data on underlying CHD might have contributed to our results. Further studies are needed to compare the outcomes of pulmonary vasodilators in homogeneous patient population, which will help establish optimal treatment strategies for each type of PAH-CHD.

Conclusions

This network meta-analysis showed that pulmonary vasodilator therapy in PAH-CHD appears to demonstrate largely favourable efficacy and safety with relatively low serious adverse event rates, including monotherapies and combination therapies. Bosentan and sildenafil and their combination were ranked best in terms of risk stratification factors in PAH such as 6MWD and NYHA functional class. Further comparative studies to examine outcomes of pulmonary vasodilators in each type of PAH-CHD are warranted.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S1047951123000124

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