

Supplementary Material

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Supplementary Figure S19. Effect of pulmonary vasodilators on the primary efficacy outcome (NYHA functional class) of subgroup analysis in Fontan patients.

Supplementary Figure S20. Effect of pulmonary vasodilators on the primary efficacy outcome (NT-proBNP) of subgroup analysis in Fontan patients.

Supplementary Figure S21. Funnel plot for each analysis. (A) PVR; (B) mPAP; (C) 6MWD; (D) SpO₂; (E) NYHA; (F) NT-proBNP

Supplementary Table. Quality assessment of observational studies based on Newcastle-Ottawa Scale (NOS) score (range, 1-9).

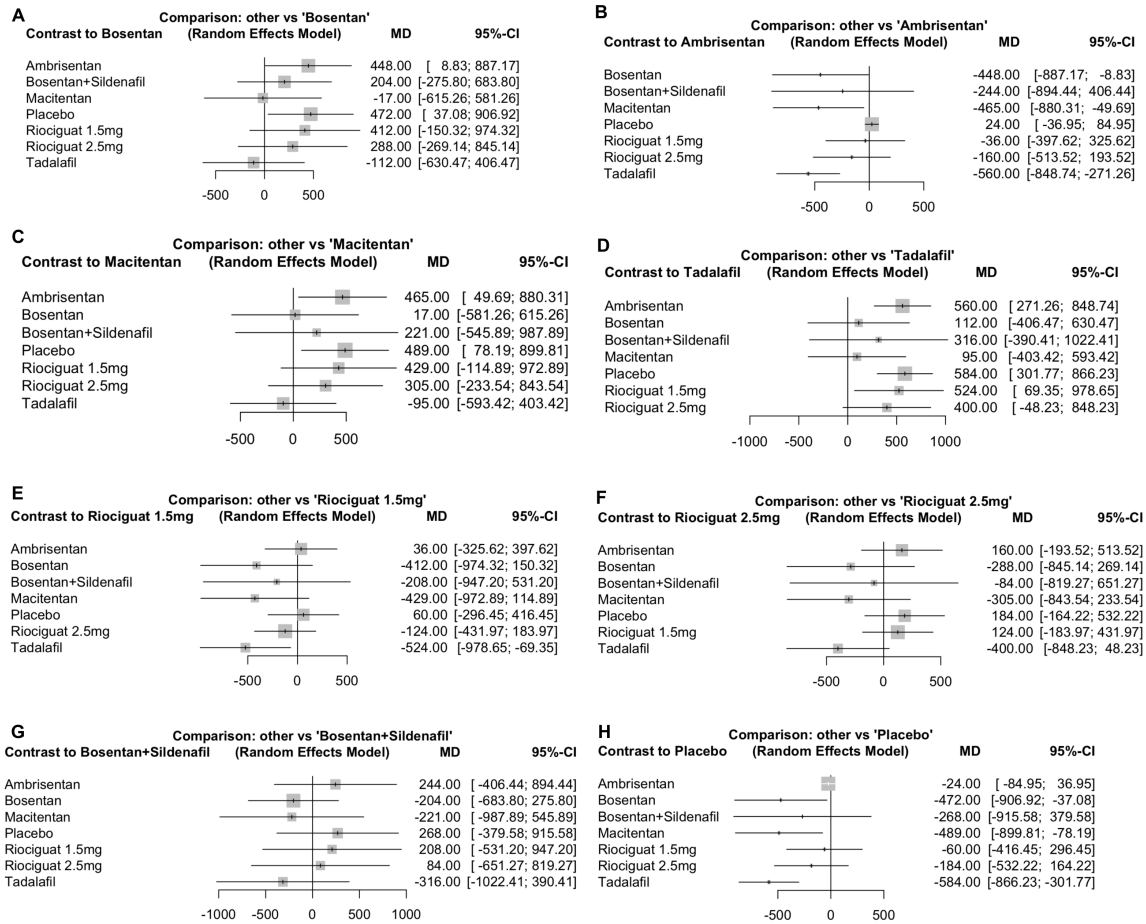
Supplementary Figure S1. Risk of bias summary according to the Cochrane Collaboration

Manual. Yellow: unclear risk; Green: low risk.

	Randomization sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Galiè et al. [11]	+	+	+	+	+	+
Iversen et al. [12]	+	+	+	+	+	+
Mukhopadhyay et al. [13]	+	+	+	?	+	+
Gatzoulis et al. [14]	+	+	+	+	+	+
Rosenkranz et al. [15]	+	+	+	?	-	+
Beghetti et al. [19]	+	+	+	+	+	+
Giardini et al. [20]	+	+	?	?	+	+
Schuuring et al. [21]	+	+	?	+	+	+
Hebert et al. [22]	+	+	+	?	+	+
Shang et al. [23]	+	+	+	?	+	+
Hill et al. [24]	+	?	+	?	+	+

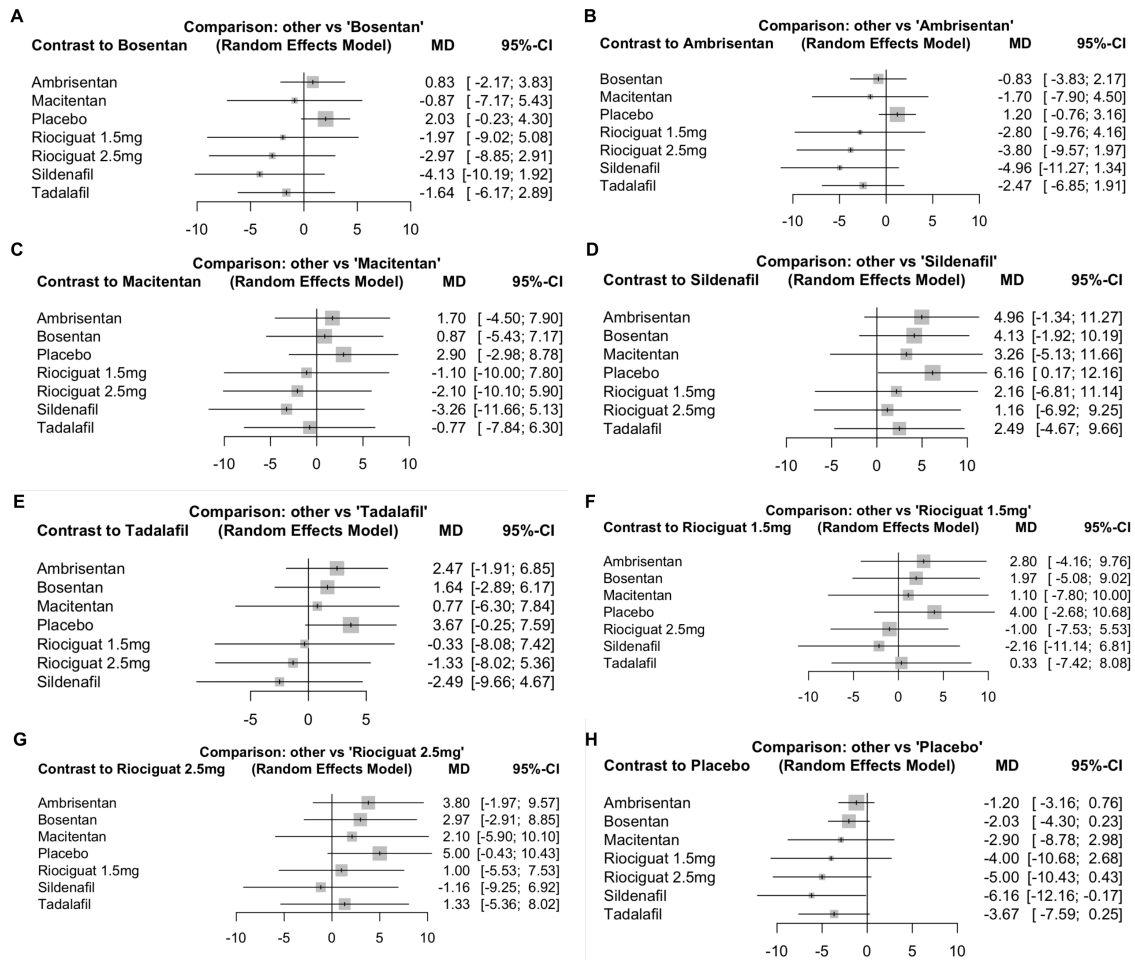
Supplementary Figure S2. Effect of pulmonary vasodilators on the primary efficacy outcome (PVR).

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus ambrisentan; (C) versus macitentan; (D) versus tadalafil; (E) versus riociguat 1.5 mg; (F) versus riociguat 2.5 mg; (G) versus bosentan+sildenafil; (H) versus placebo. CI, confidence interval; MD, mean difference; PVR, pulmonary vascular resistance.



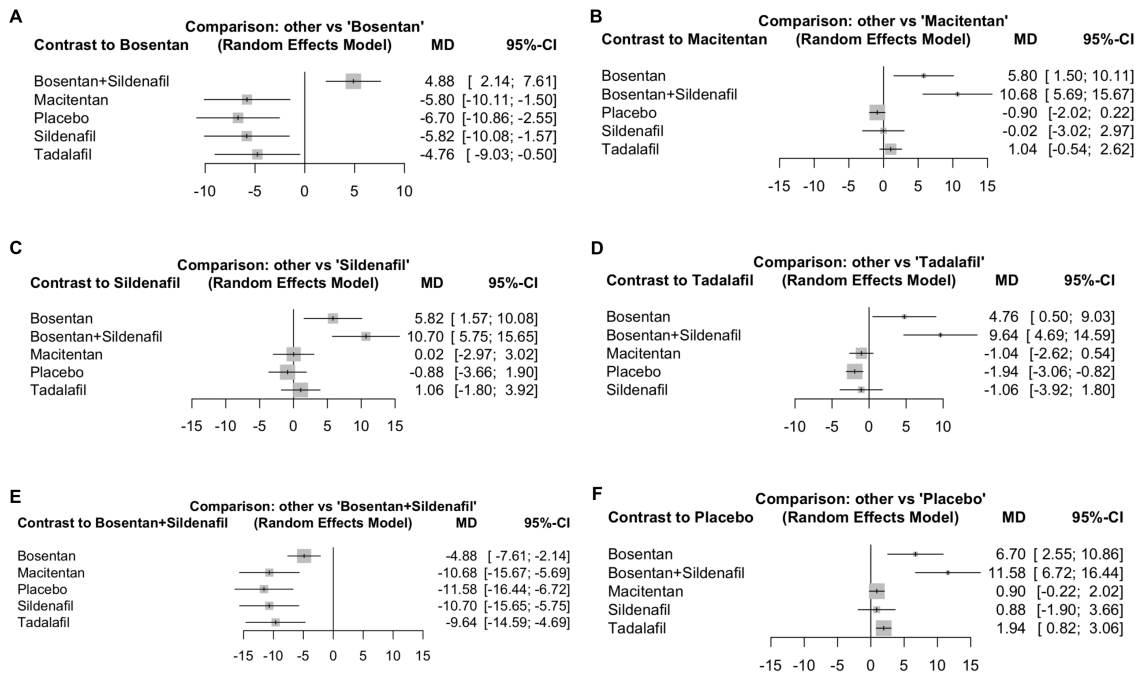
Supplementary Figure S3. Effect of pulmonary vasodilators on the secondary efficacy outcome (mPAP).

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus ambrisentan; (C) versus macitentan; (D) versus sildenafil; (E) versus tadalafil; (F) versus riociguat 1.5 mg; (G) versus riociguat 2.5 mg; (H) versus placebo. CI, confidence interval; MD, mean difference; mPAP, mean pulmonary arterial pressure.



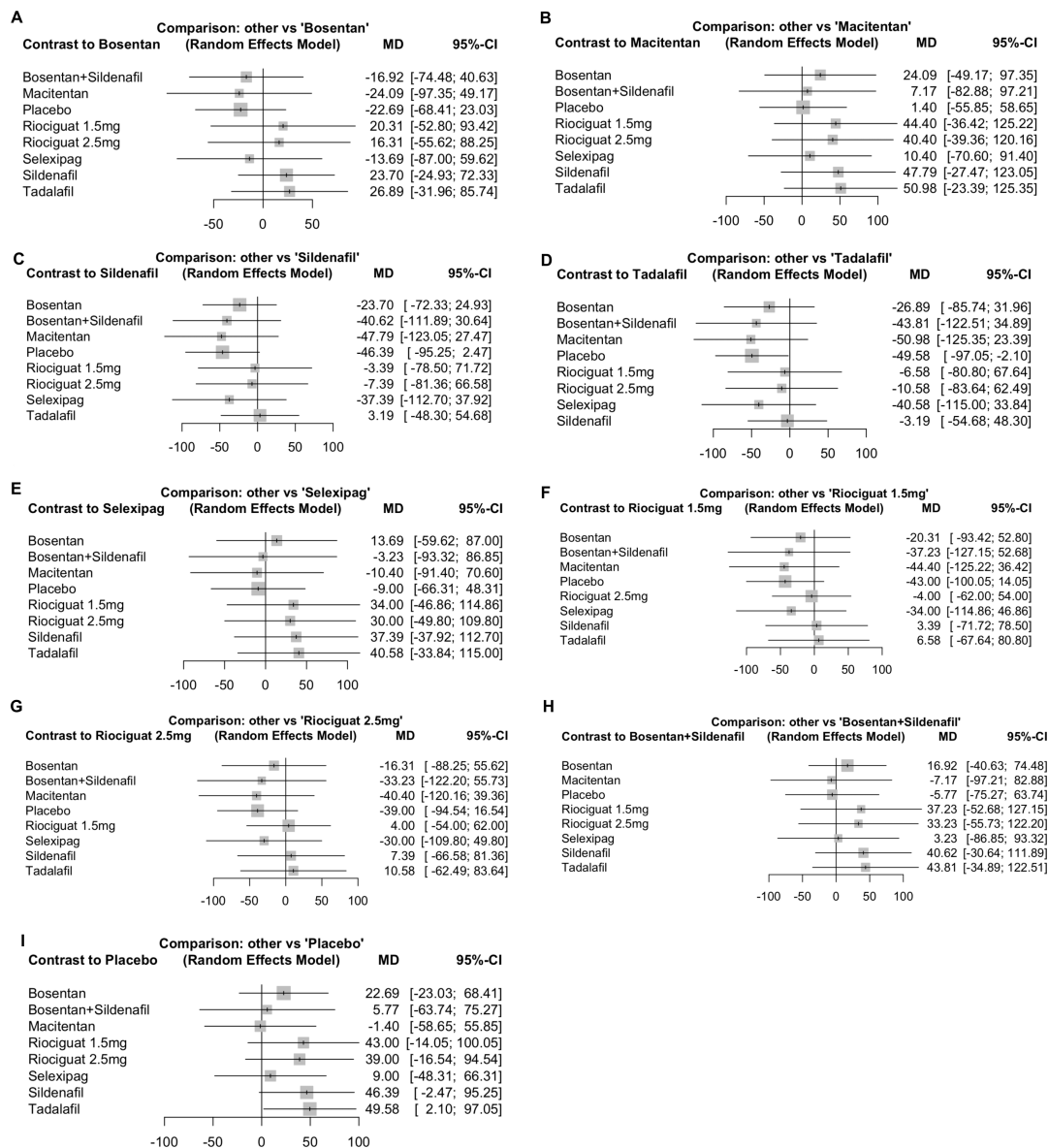
Supplementary Figure S4. Effect of pulmonary vasodilators on the secondary efficacy outcome (SpO₂).

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 bosentan+sildenafil; (F) versus placebo. CI, confidence interval; MD, mean difference; SpO₂, resting oxygen saturation.



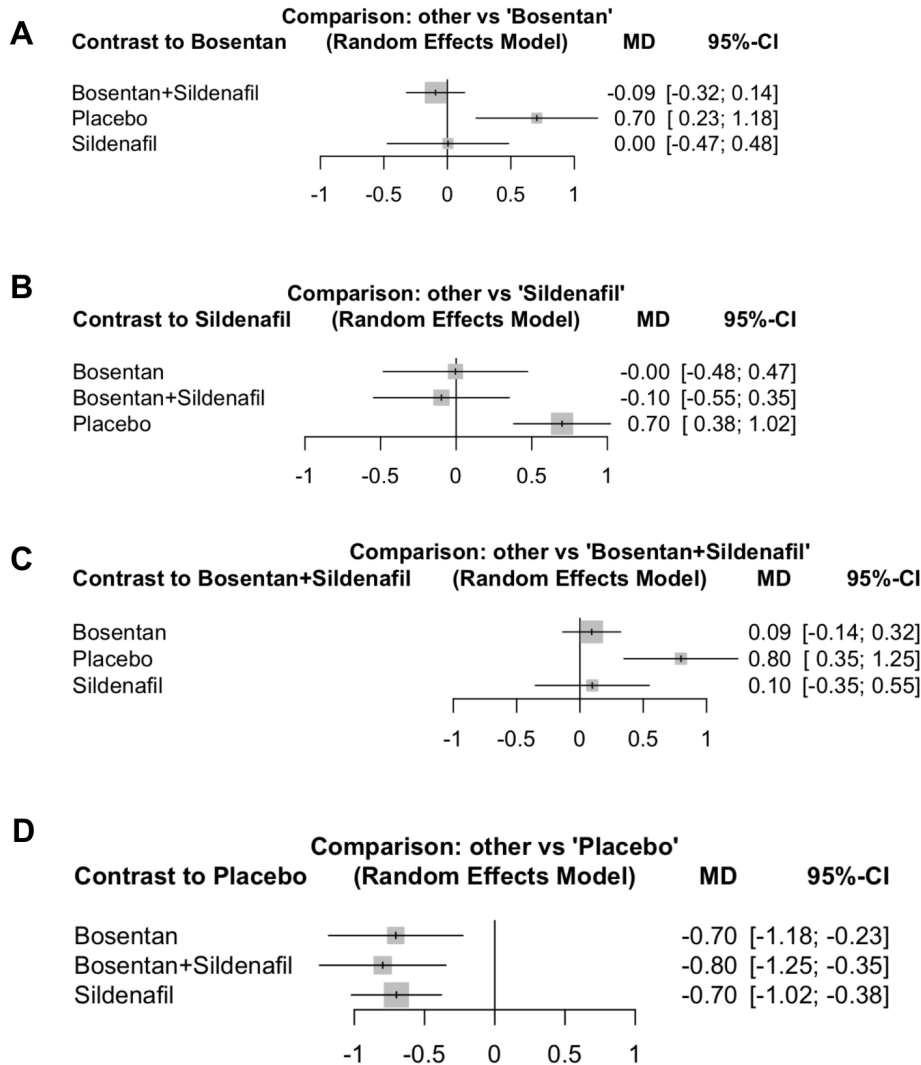
Supplementary Figure S5. Effect of pulmonary vasodilators on the secondary efficacy outcome (6MWD) of sensitivity analysis excluding Fontan patients.

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.



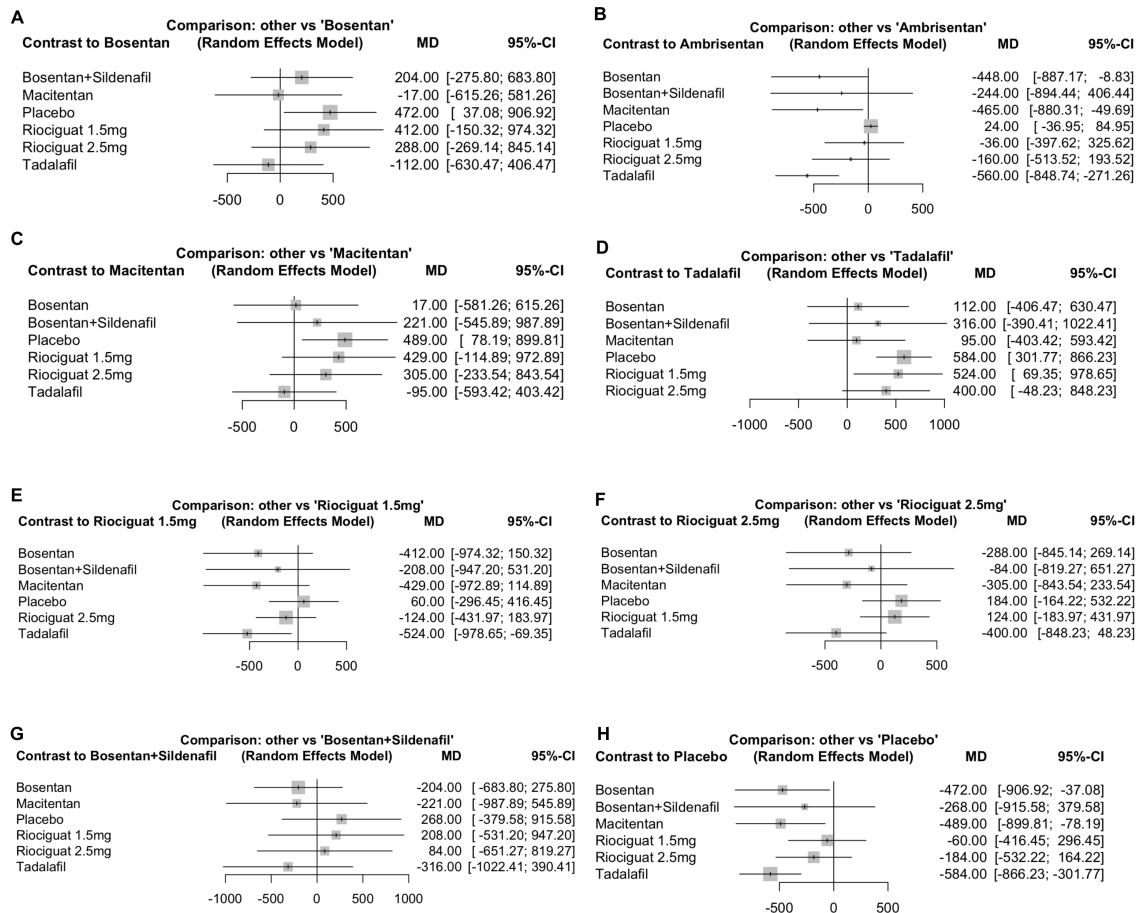
Supplementary Figure S6. Effect of pulmonary vasodilators on the secondary efficacy outcome (NYHA functional class) of sensitivity analysis excluding Fontan patients.

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; NYHA, New York Heart Association.



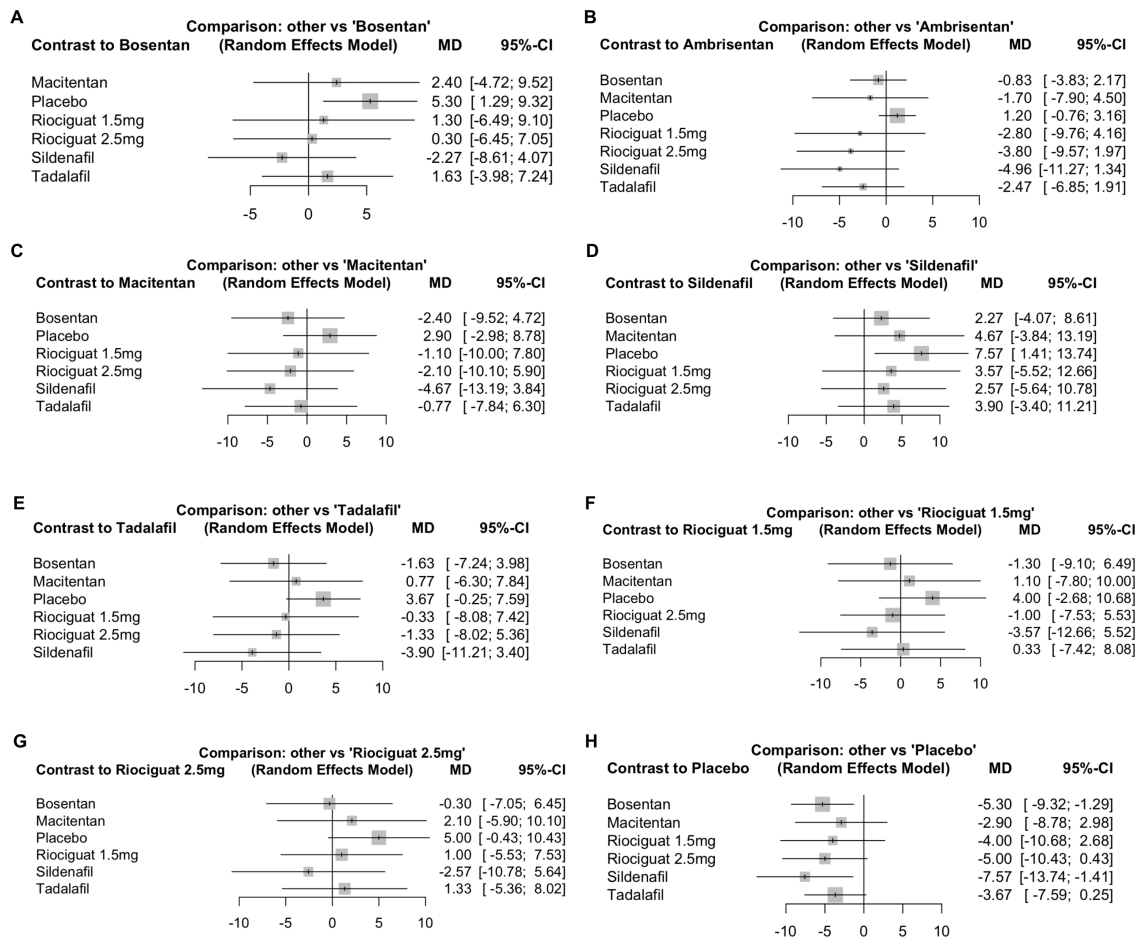
Supplementary Figure S7. Effect of pulmonary vasodilators on the primary efficacy outcome (PVR) of sensitivity analysis excluding Fontan patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus ambrisentan; (C) versus macitentan; (D) versus tadalafil; (E) versus riociguat 1.5 mg; (F) versus riociguat 2.5 mg; (G) versus bosentan+sildenafil; (H) versus placebo. CI, confidence interval; MD, mean difference; PVR, pulmonary vascular resistance.



Supplementary Figure S8. Effect of pulmonary vasodilators on the secondary efficacy outcome (mPAP) of sensitivity analysis excluding Fontan patients.

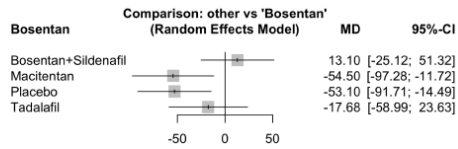
Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus ambrisentan; (C) versus macitentan; (D) versus sildenafil; (E) versus tadalafil; (F) versus riociguat 1.5 mg; (G) versus riociguat 2.5 mg; (H) versus placebo. CI, confidence interval; MD, mean difference; mPAP, mean pulmonary arterial pressure.



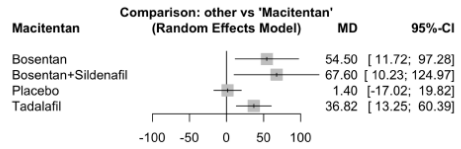
Supplementary Figure S9. Effect of pulmonary vasodilators on the primary efficacy outcome (6MWD) of subgroup analysis in ES patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus macitentan; (C) versus tadalafil; (D) versus bosentan+sildenafil; (E) versus placebo. 6MWD, 6-minute walk distance CI, confidence interval; MD, mean difference.

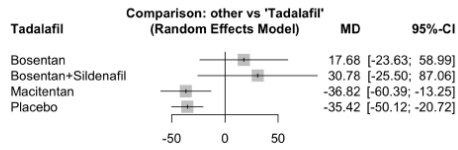
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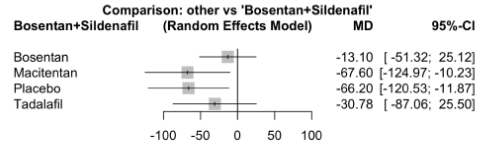
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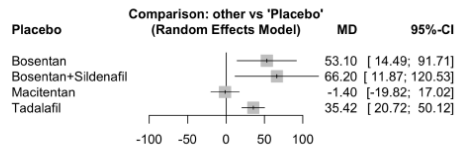
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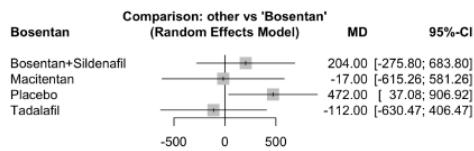
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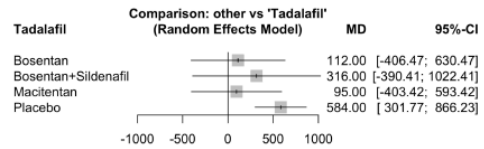
Supplementary Figure S10. Effect of pulmonary vasodilators on the secondary efficacy outcome (PVR) of subgroup analysis in ES patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus tadalafil; (C) versus macitentan; (D) versus bosentan+sildenafil; (E) versus placebo. CI, confidence interval; MD, mean difference; PVR, pulmonary vascular resistance.

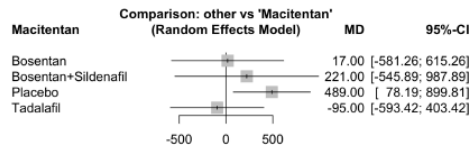
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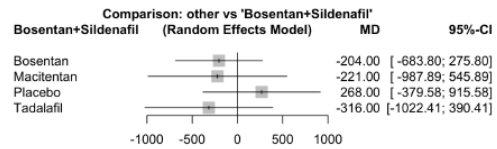
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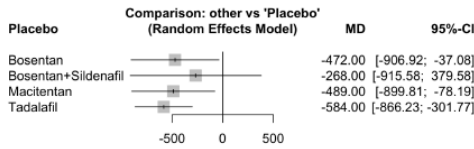
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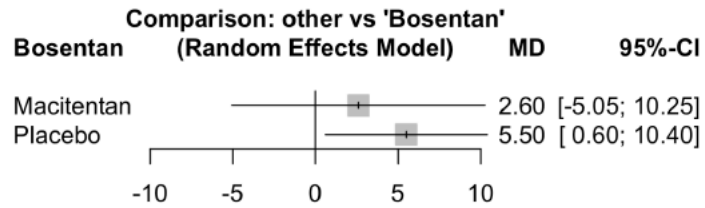
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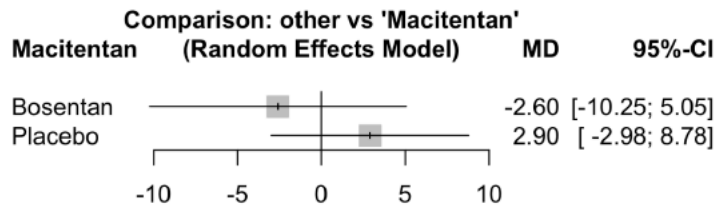
Supplementary Figure S11. Effect of pulmonary vasodilators on the secondary efficacy outcome (mPAP) of subgroup analysis in ES patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus macitentan; (C) versus placebo. CI, confidence interval; MD, mean difference; mPAP, mean pulmonary arterial pressure.

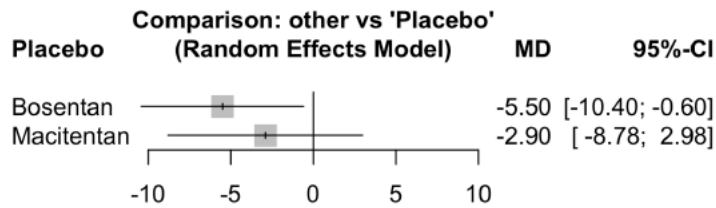
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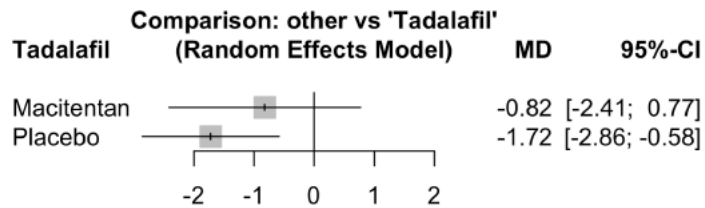
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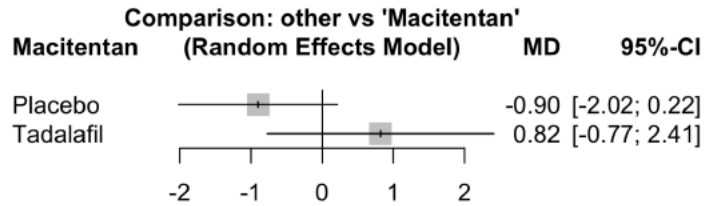
Supplementary Figure S12. Effect of pulmonary vasodilators on the secondary efficacy outcome (SpO₂) of subgroup analysis in ES patients.

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 bosentan+sildenafil; (F) versus placebo. CI, confidence interval; MD, mean difference; SpO₂, resting oxygen saturation.

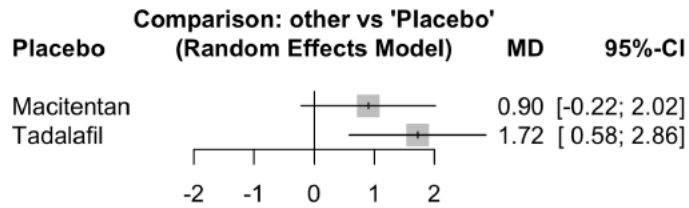
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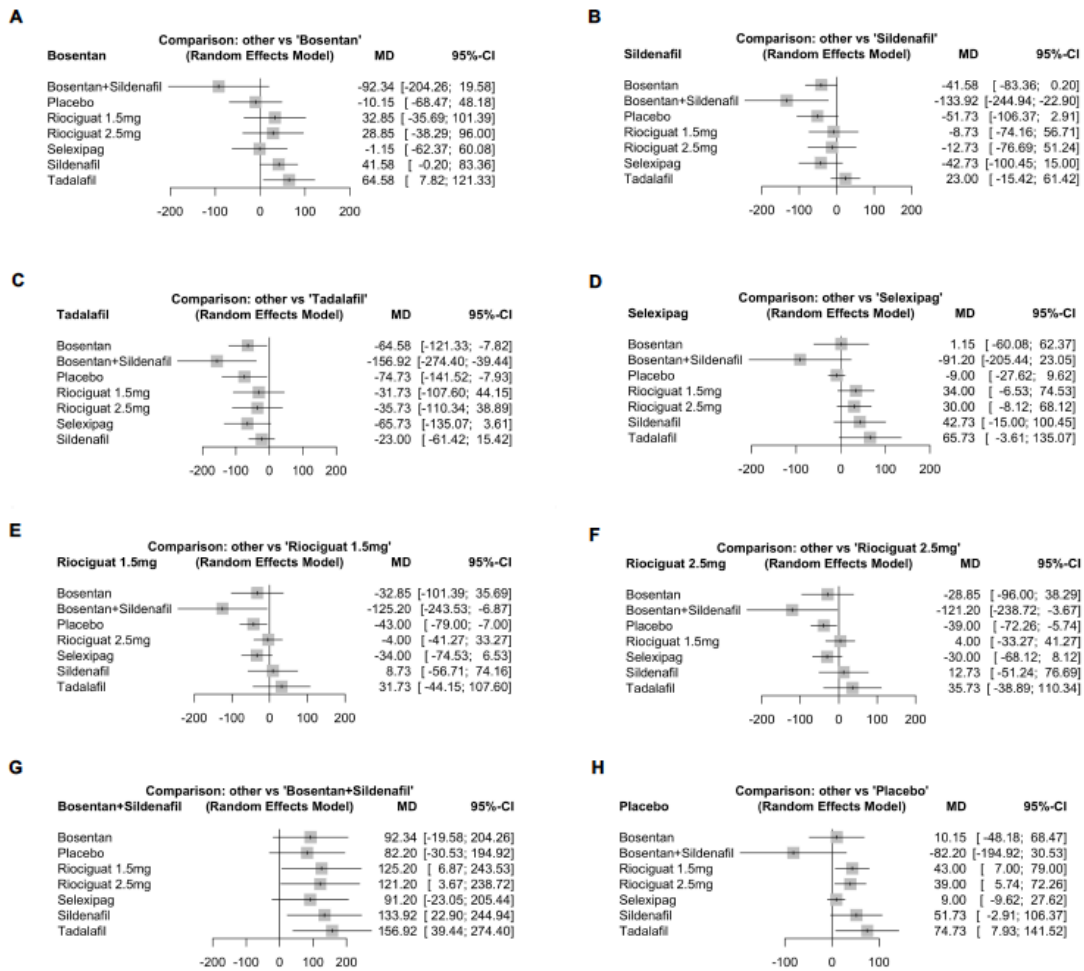


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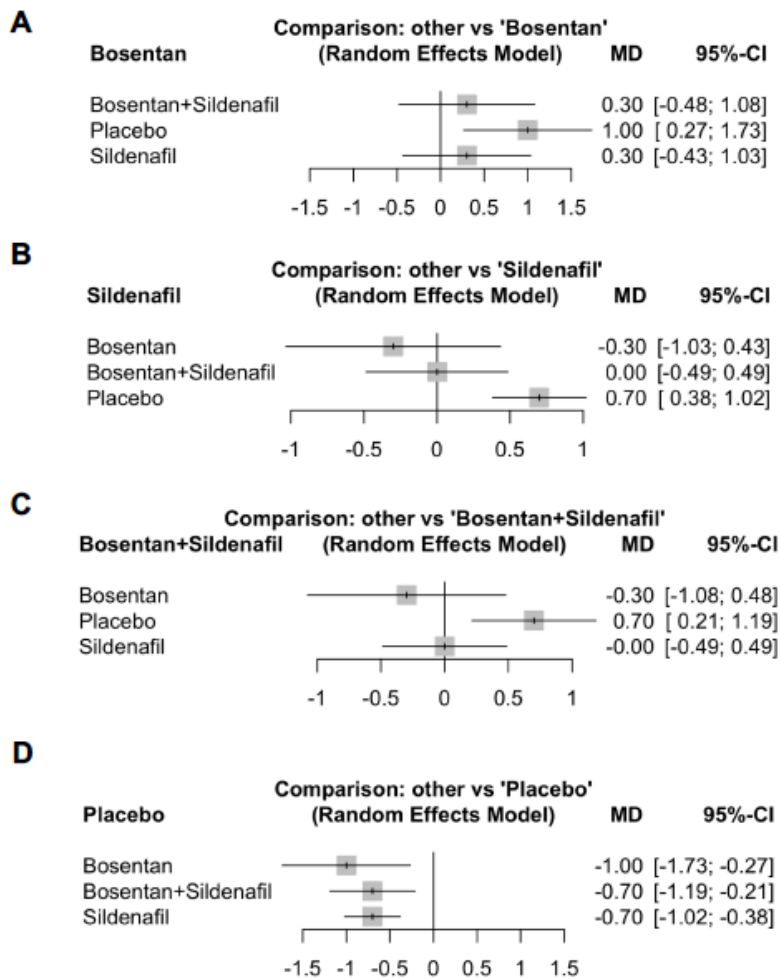
Supplementary Figure S13. Effect of pulmonary vasodilators on the primary efficacy outcome (6MWD) of subgroup analysis in CHD-PH patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus sildenafil; (C) versus tadalafil; (D) versus selexipag; (E) versus riociguat 1.5 mg; (F) versus riociguat 2.5 mg; (G) versus bosentan+sildenafil; (H) versus placebo. 6MWD, 6-minute walk distance; CI, confidence interval; MD, mean difference.



Supplementary Figure S14. Effect of pulmonary vasodilators on the primary efficacy outcome (NYHA functional class) of subgroup analysis in CHD-PH patients.

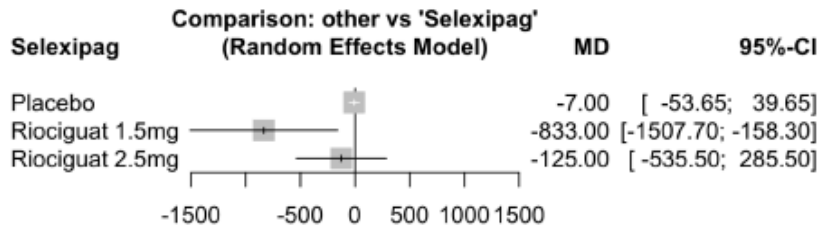
Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus sildenafil; (C) versus bosentan+sildenafil; (D) versus placebo. CI, confidence interval; MD, mean difference; NYHA, New York Heart Association.



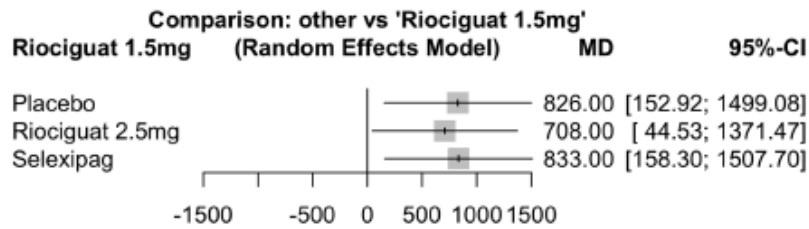
Supplementary Figure S15. Effect of pulmonary vasodilators on the primary efficacy outcome (NT-proBNP) of subgroup analysis in CHD-PH patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus selexipag; (B) versus riociguat 1.5mg; (C) versus riociguat 2.5mg; (D) versus placebo. CI, confidence interval; MD, mean difference; NT-proBNP, N-terminal pro brain natriuretic peptide.

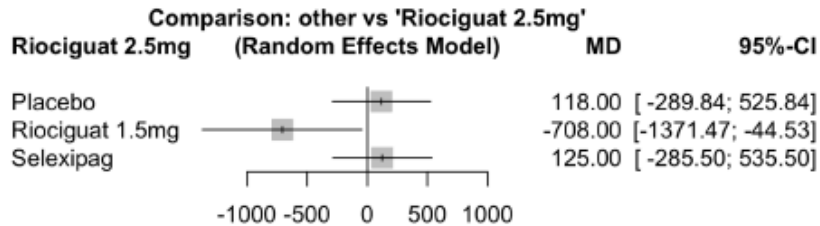
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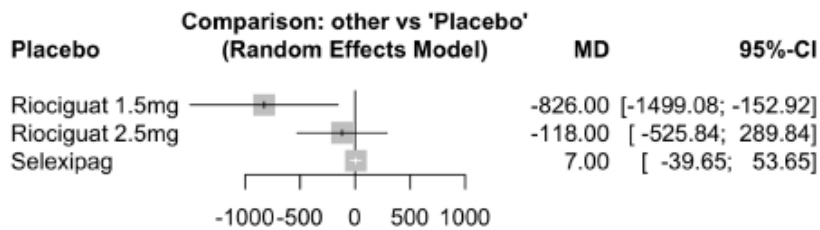
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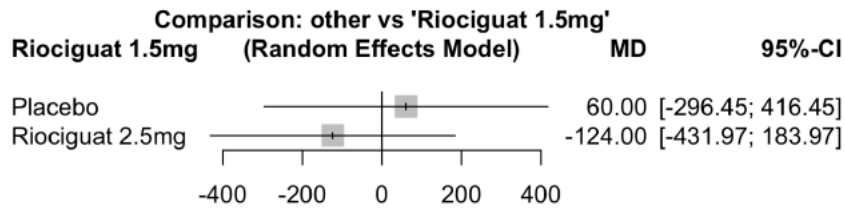
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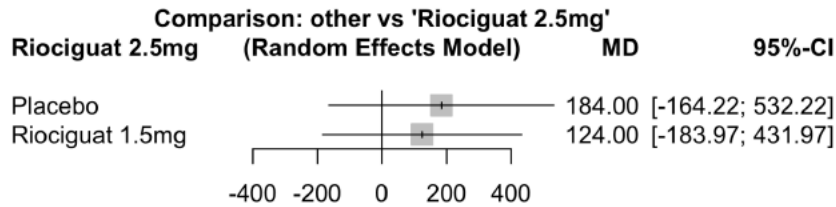
Supplementary Figure S16. Effect of pulmonary vasodilators on the secondary efficacy outcome (PVR) of subgroup analysis in CHD-PH patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus tadalafil; (C) versus macitentan; (D) versus bosentan+sildenafil; (E) versus placebo. CI, confidence interval; MD, mean difference; PVR, pulmonary vascular resistance.

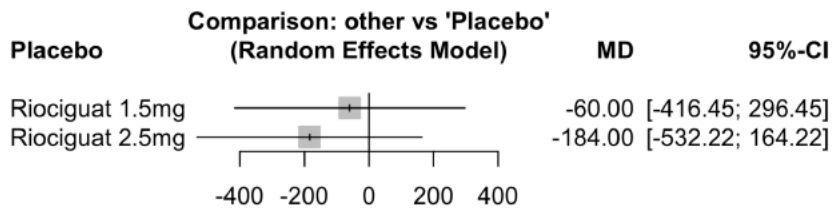
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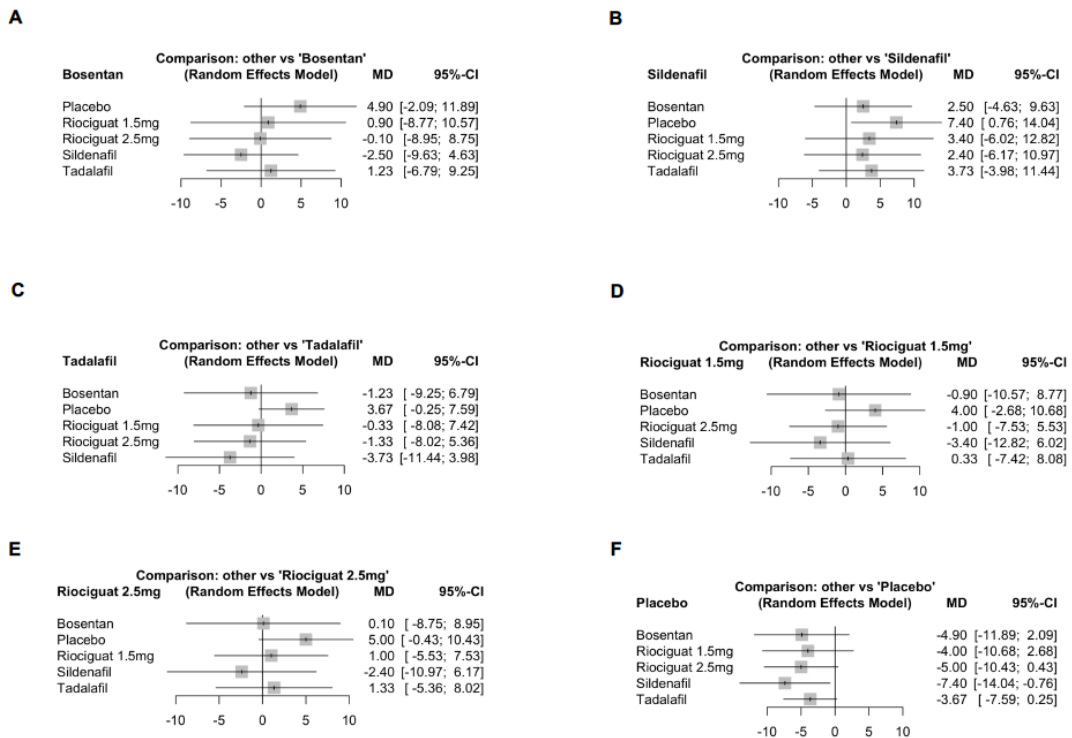


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Supplementary Figure S17. Effect of pulmonary vasodilators on the secondary efficacy outcome (mPAP) of subgroup analysis in CHD-PH patients.

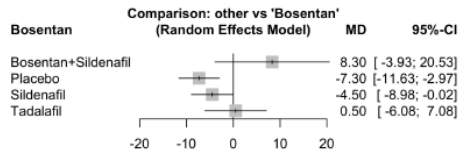
Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus sildenafil; (C) versus tadalafil; (D) versus riociguat 1.5mg; (E) versus riociguat 2.5mg; (F) versus placebo. CI, confidence interval; MD, mean difference; mPAP, mean pulmonary arterial pressure.



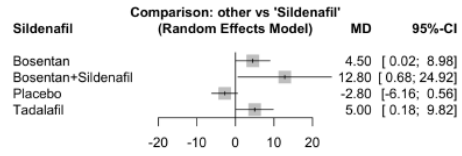
Supplementary Figure S18. Effect of pulmonary vasodilators on the secondary efficacy outcome (SpO₂) of subgroup analysis in CHD-PH patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus sildenafil; (C) versus tadalafil; (D) versus bosentan+sildenafil; (E) versus placebo. CI, confidence interval; MD, mean difference; SpO₂, resting oxygen saturation.

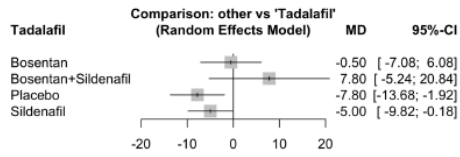
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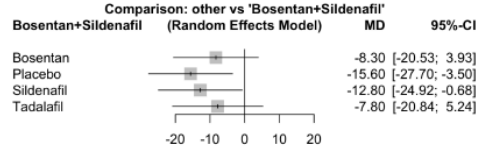
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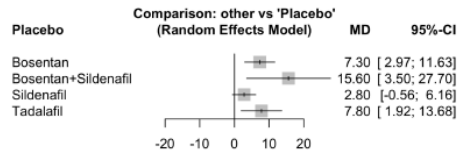
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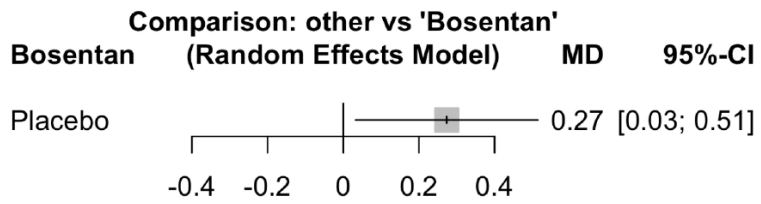
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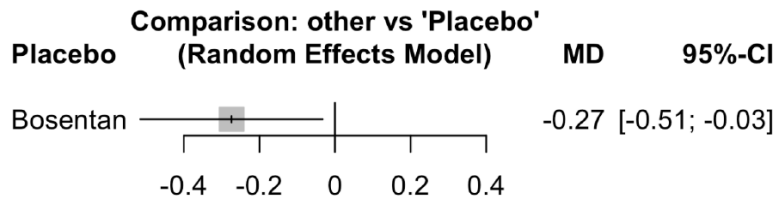
Supplementary Figure S19. Effect of pulmonary vasodilators on the primary efficacy outcome (NYHA functional class) of subgroup analysis in Fontan patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus placebo. CI, confidence interval; MD, mean difference; NYHA, New York Heart Association.

A



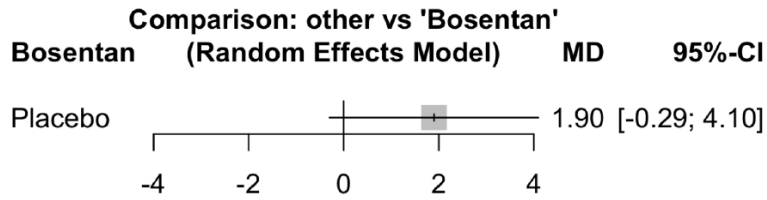
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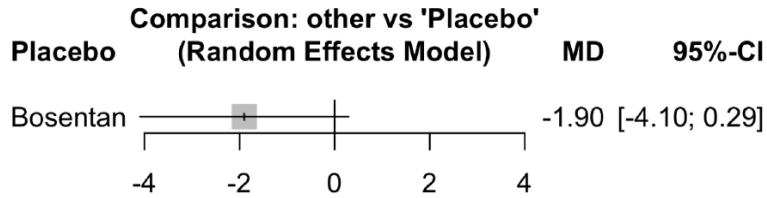
Supplementary Figure S20. Effect of pulmonary vasodilators on the primary efficacy outcome (NT-proBNP) of subgroup analysis in Fontan patients.

Forest plots for the comparisons among pulmonary vasodilators (random effects model): (A) versus bosentan; (B) versus placebo. CI, confidence interval; MD, mean difference; NT-proBNP, N-terminal pro brain natriuretic peptide.

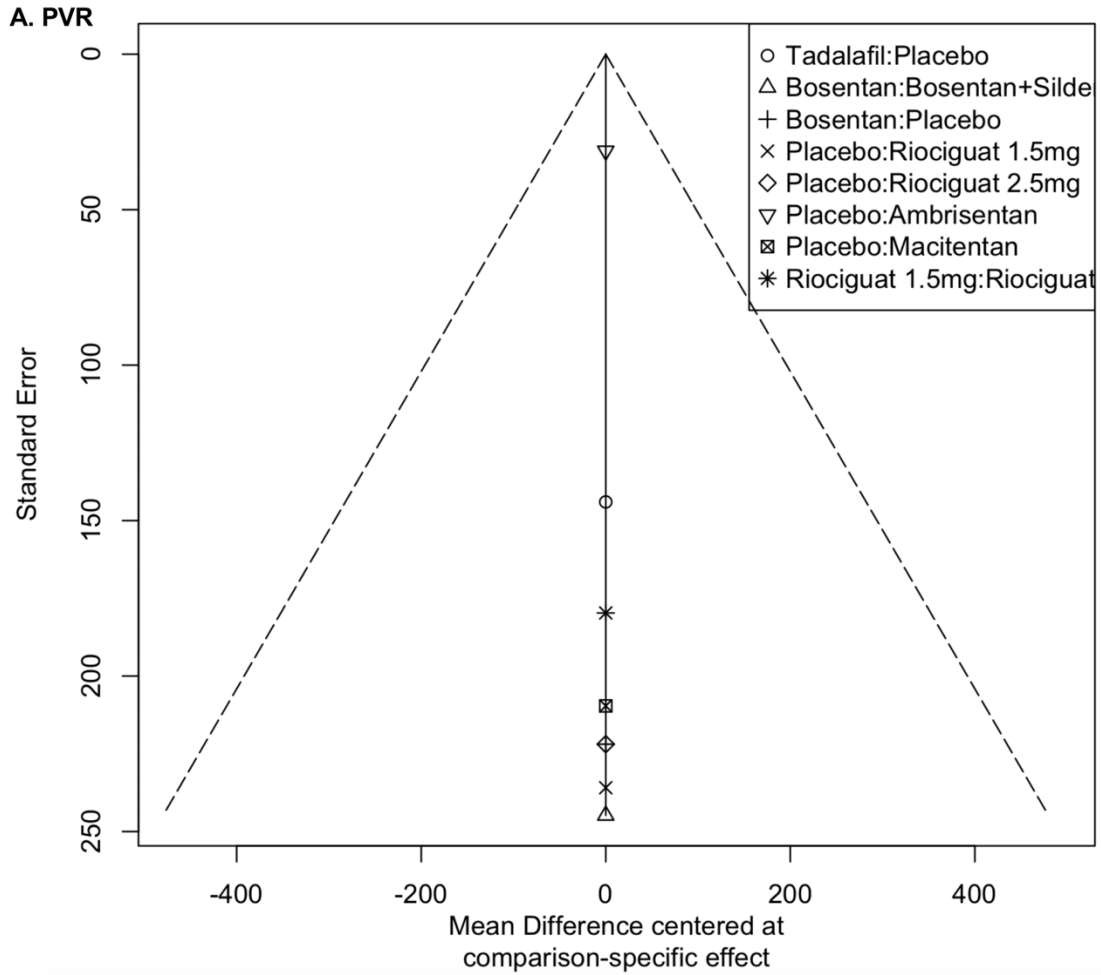
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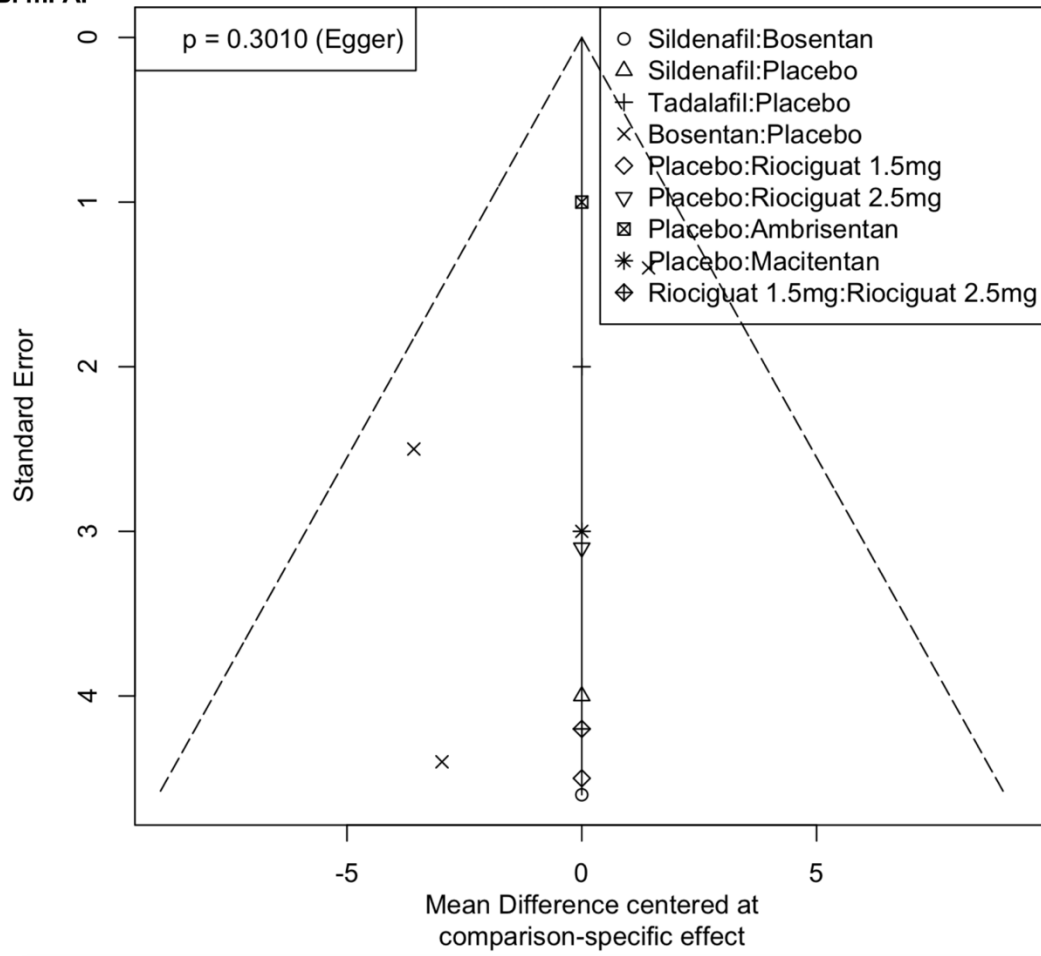
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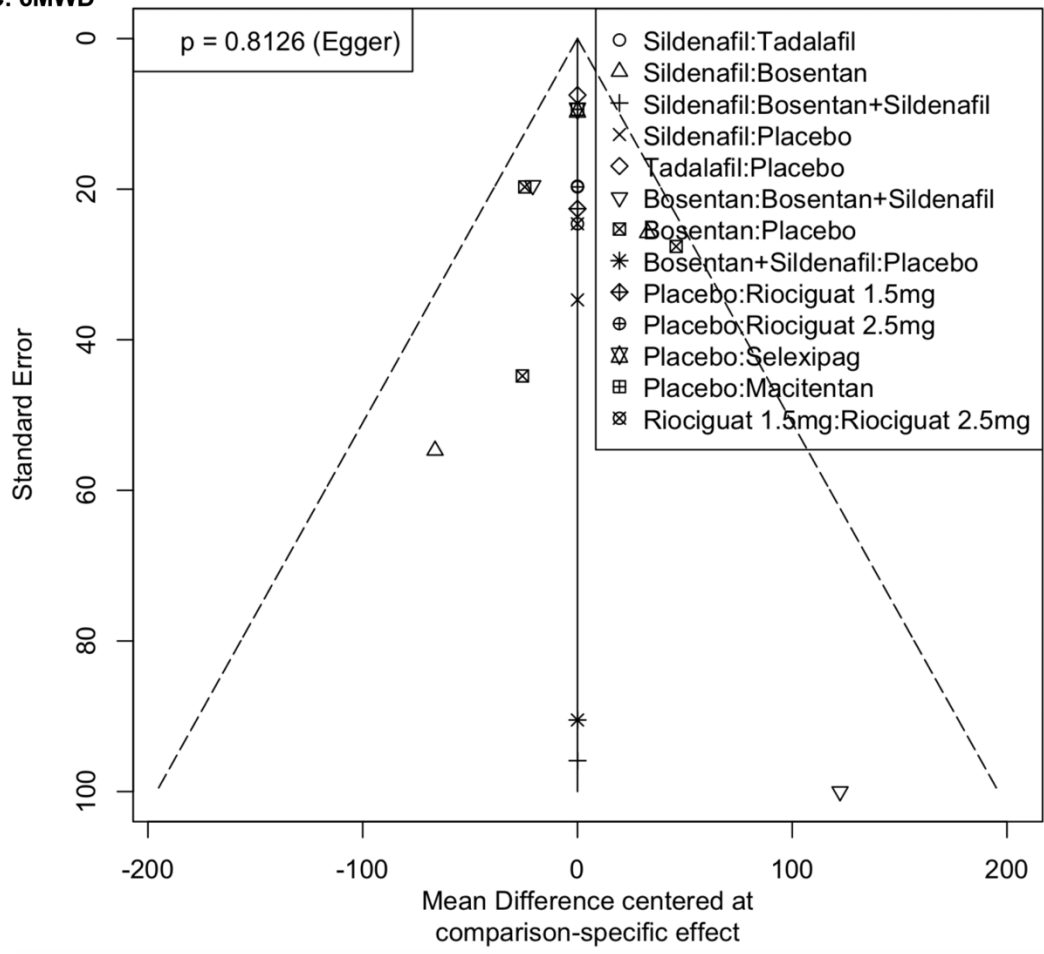
Supplementary Figure S21. Funnel plot for each analysis. (A) PVR; (B) mPAP; (C) 6MWD; (D) SpO₂; (E) NYHA; (F) NT-proBNP. 6MWD, 6-minute walk distance; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PVR, pulmonary vascular resistance; SpO₂, resting oxygen saturation.



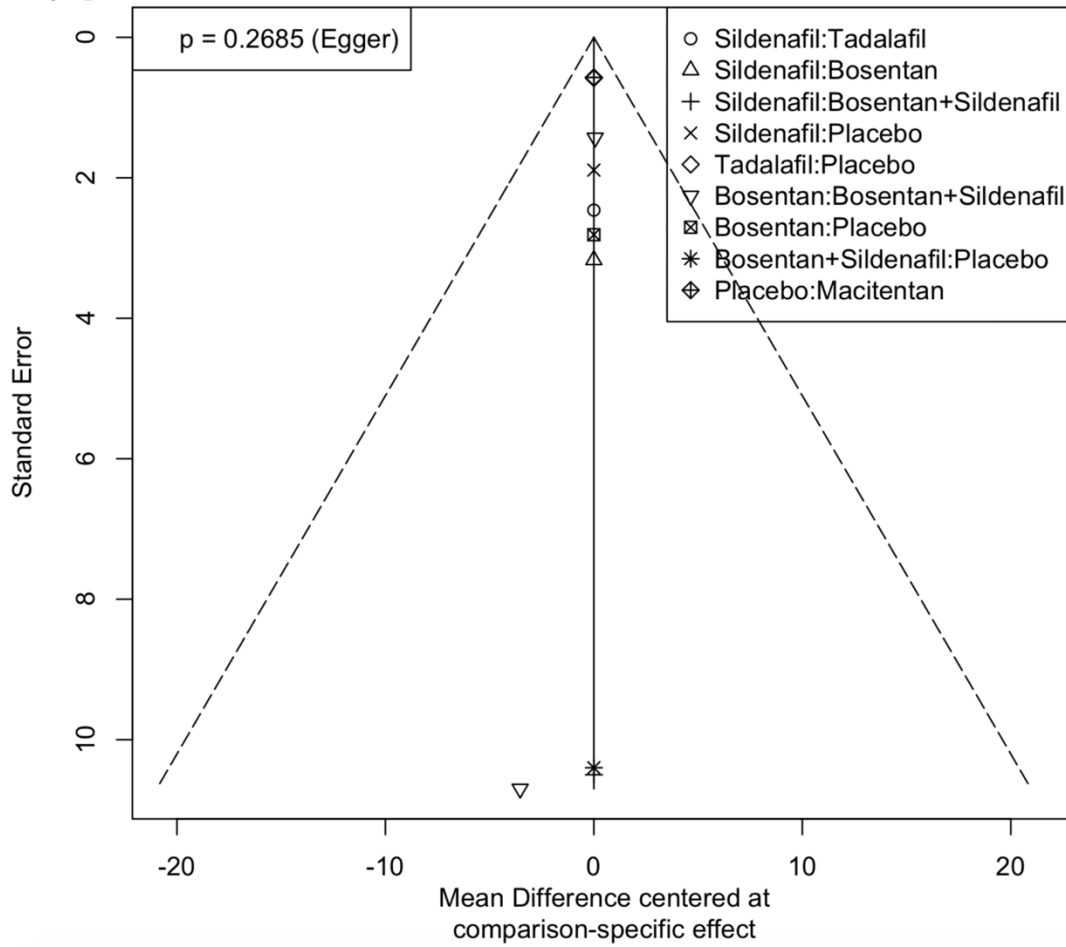
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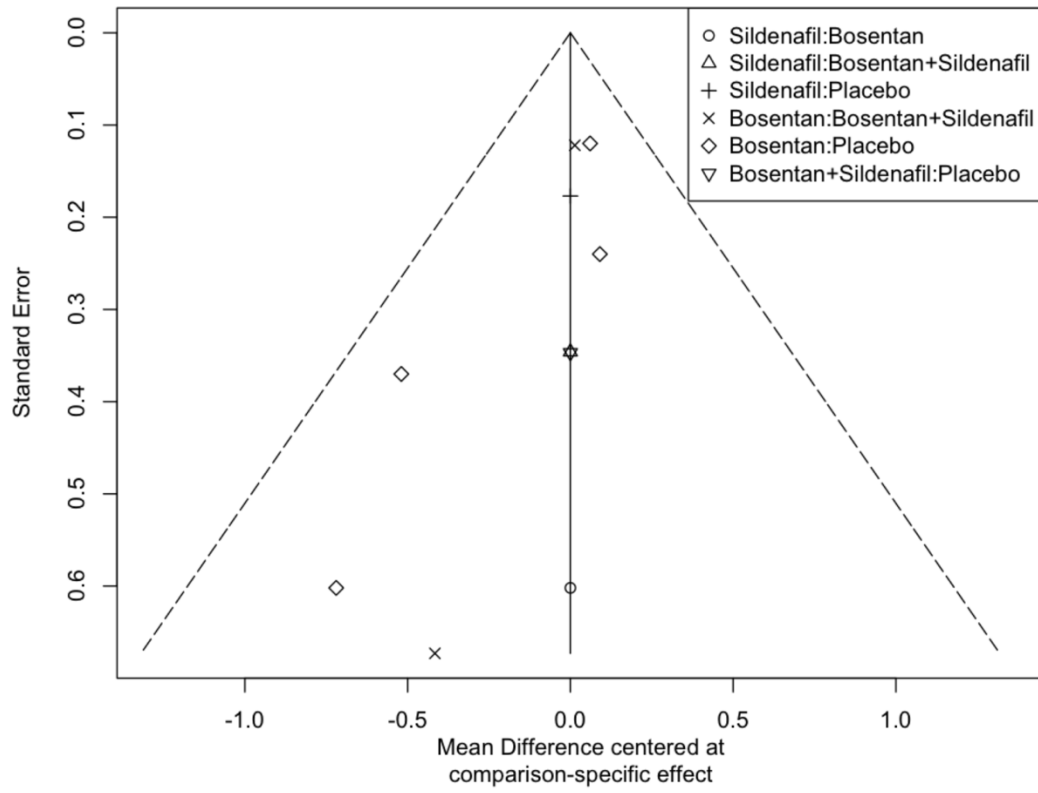
C. 6MWD



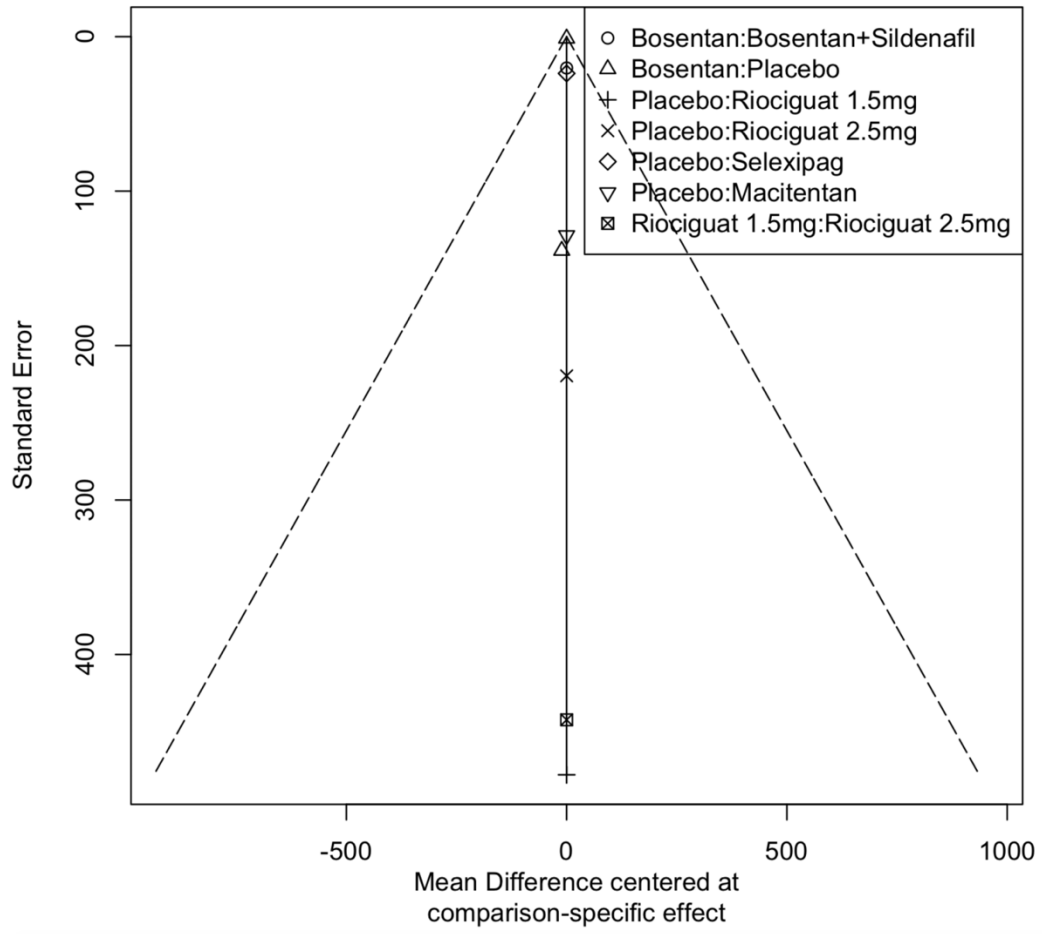
D. SpO₂



E. NYHA



F. NT-proBNP



Supplementary Table. Quality assessment of observational studies based on Newcastle-Ottawa

Scale (NOS) score (range, 1-9). NOS score ≥ 8 is low risk, 6-7 is moderate risk and ≤ 5 is high risk.

Study	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts	Outcome assessment	Length of follow-up	Adequacy of follow-up	NOS score
van Riel AC et al. [16]	1	0	1	1	2	1	1	1	8
Negoi et al. [17]	1	1	1	1	1	1	1	1	8
Clavé et al. [18]	1	0	1	1	2	1	1	1	8