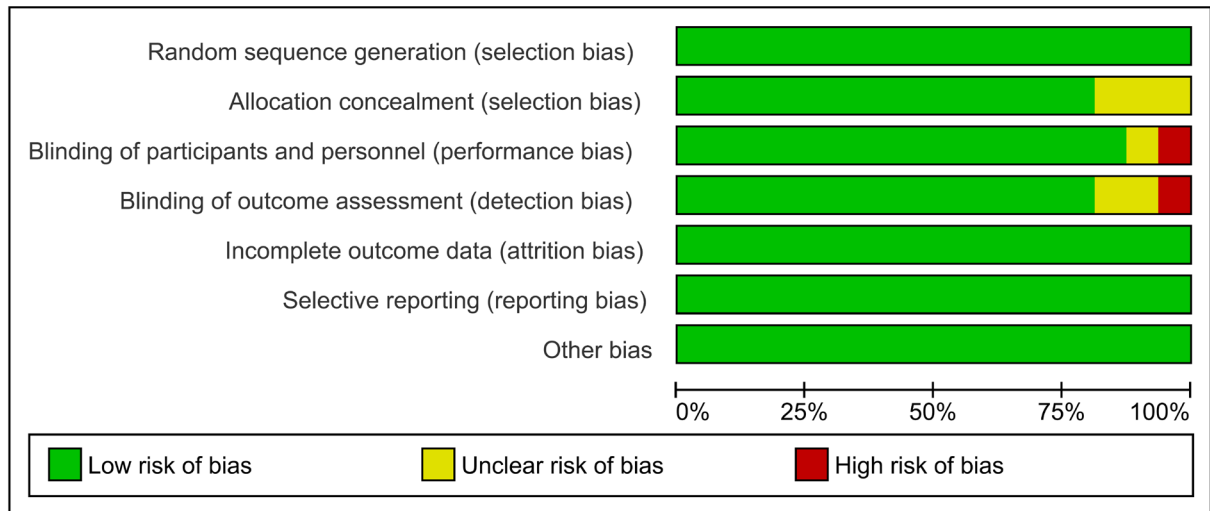


Supplementary Appendix 1. Risk of bias – summary for all studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Galie 2009 (PHIRST)	+	+	+	?	+	+	+
Galie 2015 (PATENT PLUS)	+	+	+	+	+	+	+
Ghofrani 2013 (PATENT 1)	+	+	+	+	+	+	+
Hoepfer 2006 (COMBI)	+	+	-	-	+	+	+
Humbert 2004	+	+	+	+	+	+	+
McLaughlin 2006 (STEP)	+	+	+	+	+	+	+
McLaughlin 2010 (TRIUMPH-1)	+	+	+	+	+	+	+
McLaughlin 2015 (COMPASS-2)	+	?	?	+	+	+	+
Pulido 2013 (SERAPHIN)	+	+	+	+	+	+	+
Simonneau 2008	+	+	+	+	+	+	+
Simonneau 2012	+	?	+	+	+	+	+
Sitbon 2015 (GRIPHON)	+	+	+	+	+	+	+
Tapson 2012 (FREEDOM-C)	+	+	+	+	+	+	+
Tapson 2013 (FREEDOM-C2)	+	+	+	+	+	+	+
Vizza 2017	+	+	+	+	+	+	+
Zhuang 2014	+	?	+	?	+	+	+

Supplementary Appendix 2. Risk of bias – overall.



Supplementary Appendix 3. Further results of NMA for outcomes 6MWD, all-cause mortality and discontinuation due to adverse events.

Supplementary Appendix 3a. Mutual comparison of mean differences in baseline change of 6-min walk distance (6MWD) in meters for PAH-specific drugs with 95% CrI in parenthesis (effect size), that is for background therapies as listed in first column. Numbers in bold represent statistically significant differences.

Background therapy (BT)	Add-on therapy	Effect size# [m] (95% CrI)	SD [m] (95% CrI)	DIC	D _{res}	N	Studies included
epoprostenol*	sildenafil*	28 (11, 46)	2.4 (0.2, 10)	33.3	3.8	4	Simonneau 2008 (PACES)
epoprostenol*	bosentan*	18 (-33, 70)					Humbert 2004 (BREATHE-2)
ERA or PDE5i or ERA&PDE5i or None (MIX 1)	selexipag	14 (3.4, 24)	2.5 (0.2, 8.9)	29.1	3.2	4	Sitbon 2015 (GRIPHON) Simonneau 2012
ERA&PDE5i	oral treprostinil	6.1 (-1.8, 14)	2.5 (0.2, 7.5)	24.8	3.2	4	Tapson 2012 (FREEDOM-C) Tapson 2013 (FREEDOM-C2)
PCA	riociguat	105 (62, 148)	<i>Fixed effect estimate in RevMan</i>				Ghofrani 2013 (PATENT-1)

#For BT+add-on therapy vs. BT.

* The same network meta-analysis model

CrI: credible interval, D_{res}: overall residual deviance, DIC: deviance information criterion, ERA: endothelin receptor antagonists, N: number of data points, PCA: non-intravenous formulations of prostacyclin analogue, PDE5i: phosphodiesterase type 5 inhibitor, PDE5i&ERA: PDE5i and ERA combined, SD: between-trial standard deviation (heterogeneity)

Supplementary Appendix 3b. Comparison of all-cause mortality expressed as median values of odds ratios with 95% CrI in parenthesis (effect size). The odds ratios below 1 favour the background+add-on therapy. There were no statistically significant differences.

Background therapy (BT)	Add-on therapy	BT r/n	Add-on r/n	Effect size# (95% CrI)	CV (95% CrI)	DIC	D _{res}	N	Studies included
ERA	sildenafil 20mg TID or tadalafil 40mg or riociguat 2.5mg TID or inhaled treprostinil	5/445	1/559	0.09 (0.002, 1.1)*	1.16 (0.5, 16)	27.4	11.4	10	Vizza 2017, Zhuang 2014, Galie 2009 (PHIRST), McLaughlin 2010 (TRIUMPH-1), Ghofrani 2013 (PATENT-1)
PDE5i	bosentan 125mg BID or macitentan 10mg	37/425	24/401	0.7 (0.1, 3.0)*	0.59 (0.5, 39)	25.2	3.7	4	McLaughlin 2015 (COMPASS-2), Pulido 2013, Jansa 2018 (SERAPHIN)
epoprostenol	sildenafil 80mg TID or bosentan 125mg BID	7/144	3/156	0.4 (0.02, 8.2)*	1.57 (0.5, 3.3)	16.5	6.4	4	Humbert 2004, Simonneau 2008
ERA or PDE5i or ERA&PDE5i (MIX 2)	oral treprostinil	7/329	9/331	1.3 (0.2, 7.9)	0.75 (0.5, 32)	19.8	3.6	4	Tapson 2012, Tapson 2013
ERA&PDE5i	selexipag	34/197	30/179	0.96 (0.56, 1.65)	<i>Fixed effect estimate in RevMan</i>				Sitbon 2015

#For BT+add-on therapy vs. BT

*This is a common effect size for all the medicines used as add-on therapy

r: sum of events in the study arm, n: sum of patients in the study arm, CrI: credible interval, CV: between-trial coefficient of variation (heterogeneity), DIC: deviance information criterion, D_{res}: overall residual deviance, N: number of data points,

ERA: endothelin receptor antagonists, PDE5i: phosphodiesterase type 5 inhibitors, BID: two times daily. TID: three times daily.

Supplementary Appendix 3c. Comparison of discontinuation due to adverse event expressed as median values of odds ratios with 95% CrI in parenthesis (effect size). The odds ratios below 1 favour the background+add-on therapy. There were no statistically significant differences.

Background therapy (BT)	Add-on therapy	BT r/N1	Add-on r/N2	Effect size [#] (95% CrI)	CV (95% CrI)	DIC	D _{res}	N	Studies included
ERA [§]	sildenafil 20mg TID or tadalafil 40mg or riociguat 2.5mg TID [§]	22/325	20/444	0.82 (0.3, 3.6)*	0.65 (0.5, 38)	62.9	15.5	14	Zhuang 2014, Galie 2009 (PHIRST), Vizza 2017, Ghofrani 2013 (PATENT-1)
ERA [§]	inhaled iloprost or inhaled treprostinil [§]	5/174	9/166	2.2 (0.4, 16)*					McLaughlin 2006 (STEP), Hoepfer 2006 (COMBI), McLaughlin 2010 (TRIUMPH-1)
PDE5i	bosentan 125mg BID or macitentan 10mg	53/425	65/401	1.38 (0.2, 2.1)*	0.96 (0.5, 6.5)	28.4	4.2	4	McLaughlin 2015 COMPASS-2), Pulido 2013 Jansa 2018 (SERAPHIN)
ERA or PDE5i or ERA&PDE5i or None (MIX 1)	selexipag	42/592	74/607	2.18 (0.3, 31)	0.94 (0.5, 23)	20.9	3.7	4	Sitbon 2015 (GRIPHON) Simonneau 2012
EPOP	sildenafil 80mg TID or bosentan 125mg BID	15/144	8/156	0.5 (0.0005, 416)*	2.38 (0.1, 13)	19.4	3.9	4	Humbert 2004 (BREATHE-2), Simonneau 2008 (PACES)
ERA or PDE5i or ERA&PDE5i (MIX 2)	oral treprostinil	13/329	43/331	3.8 (0.8, 19)	0.62 (0.5, 37)	24.1	3.6	4	Tapson 2012 (FREEDOM-C) Tapson 2013 (FREEDOM-C2)

[#]For BT+add-on therapy vs. BT.

*This is a common effect size for all the medicines used as add-on therapy.

[§]Single network meta-analysis model with 2 interventions consisted of oral and inhaled PAH medicines.

r: sum of events in the study arm, n: sum of patients in the study arm, CrI: credible interval, CV: between-trial coefficient of variation (heterogeneity), DIC: deviance information criterion,

D_{res}: overall residual deviance, N: number of data points,

ERA: endothelin receptor antagonists, PDE5i: phosphodiesterase type 5 inhibitors, BID: two times daily. TID: three times daily.