TL # 102: **Indacaterol for chronic obstructive pulmonary disease**

Risk of bias

Risk of bias was assessed for each of the included RCTs using the Cochrane risk of bias tool.

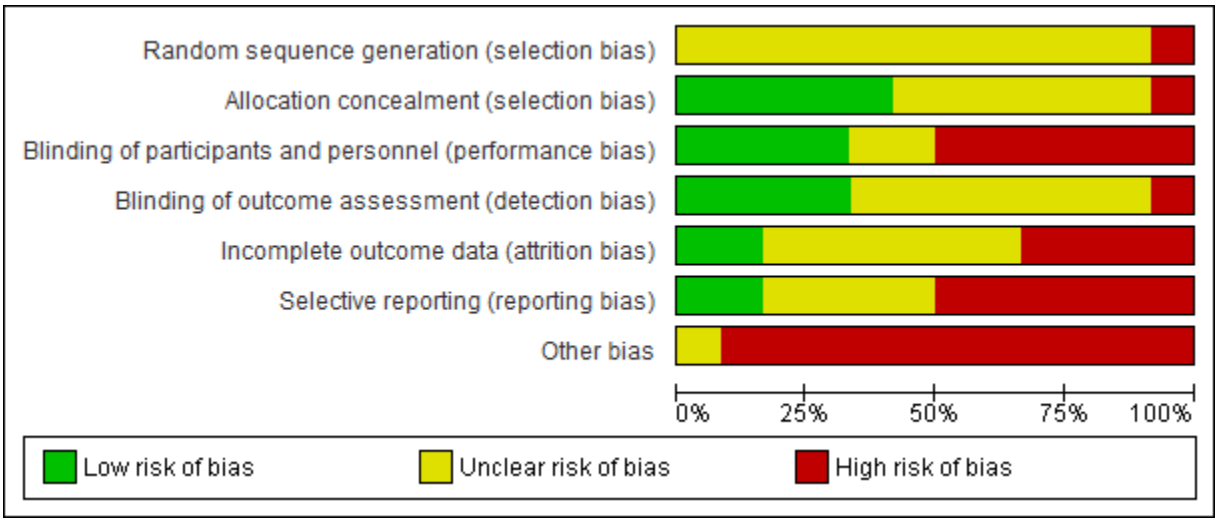


Figure 1: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

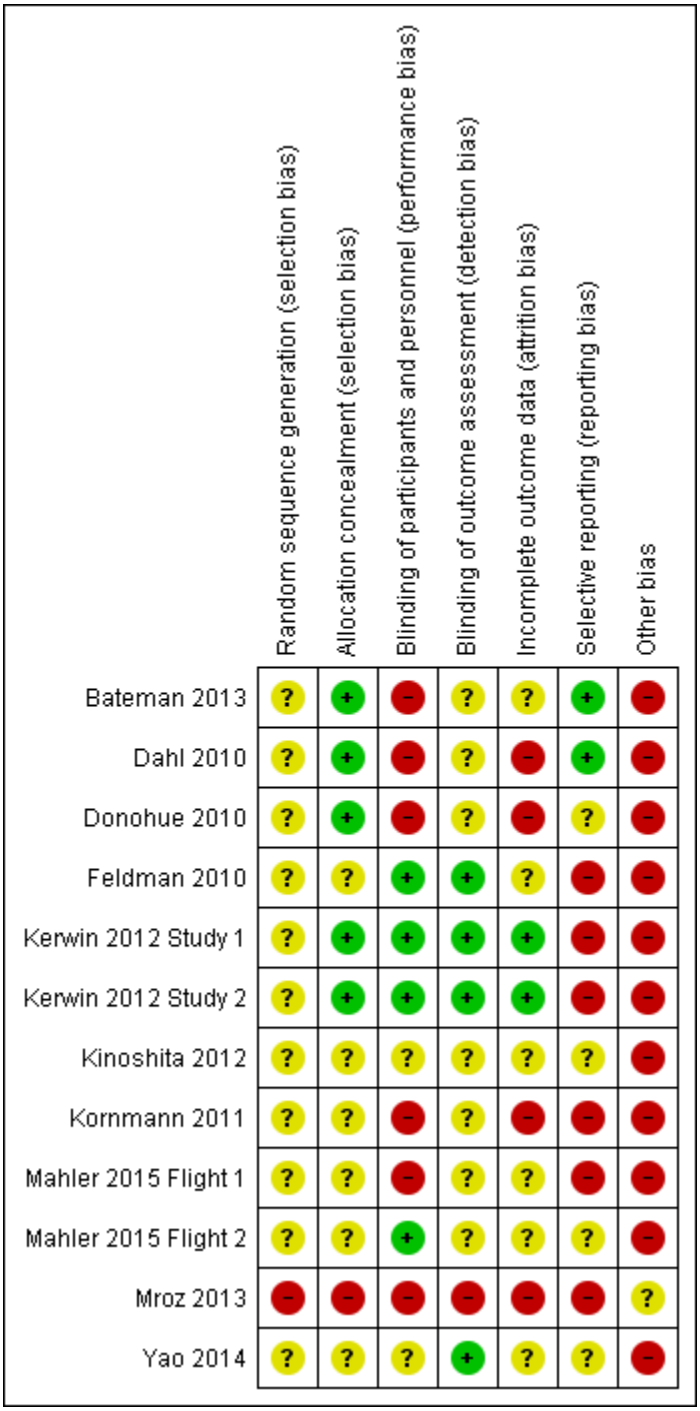
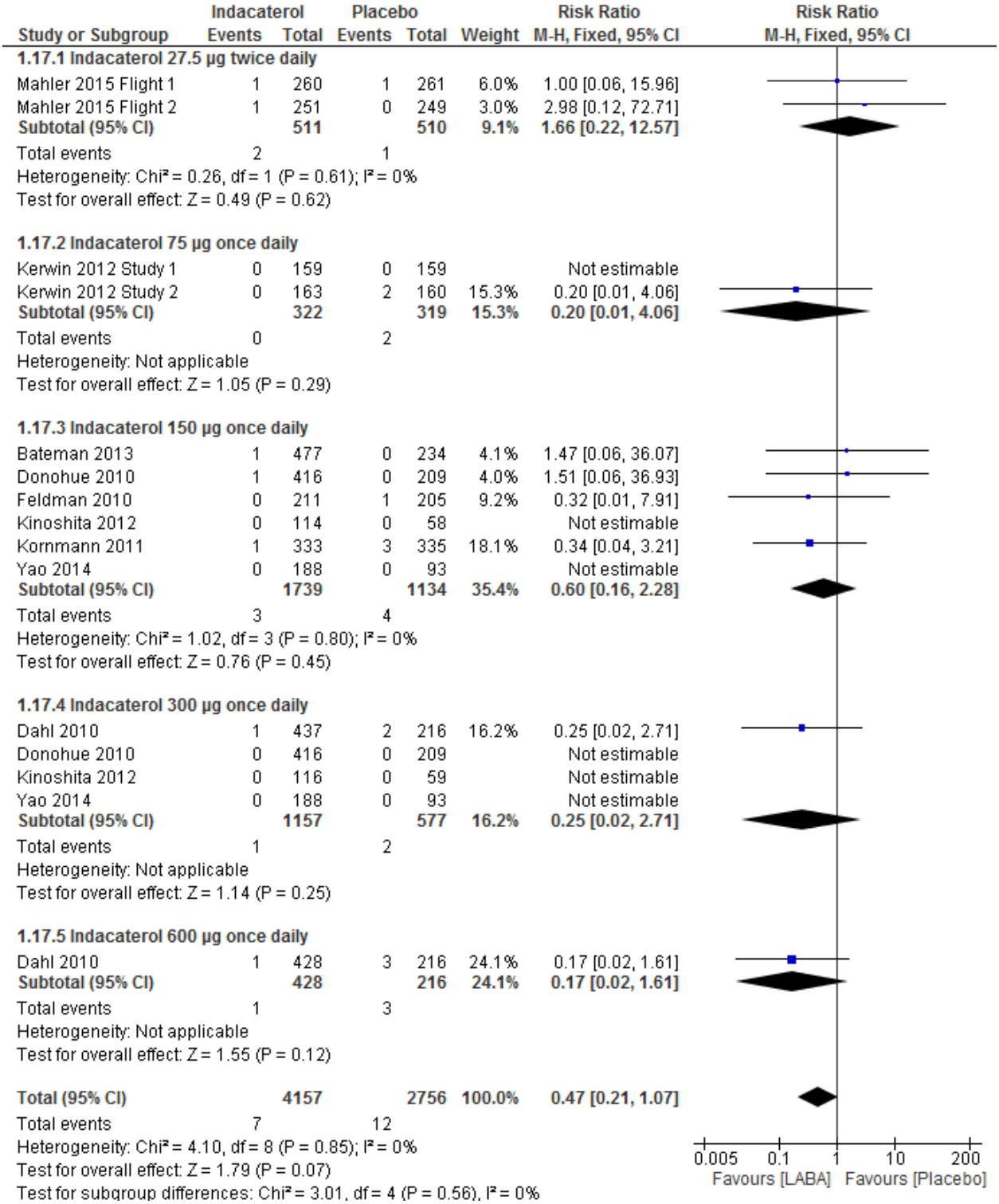


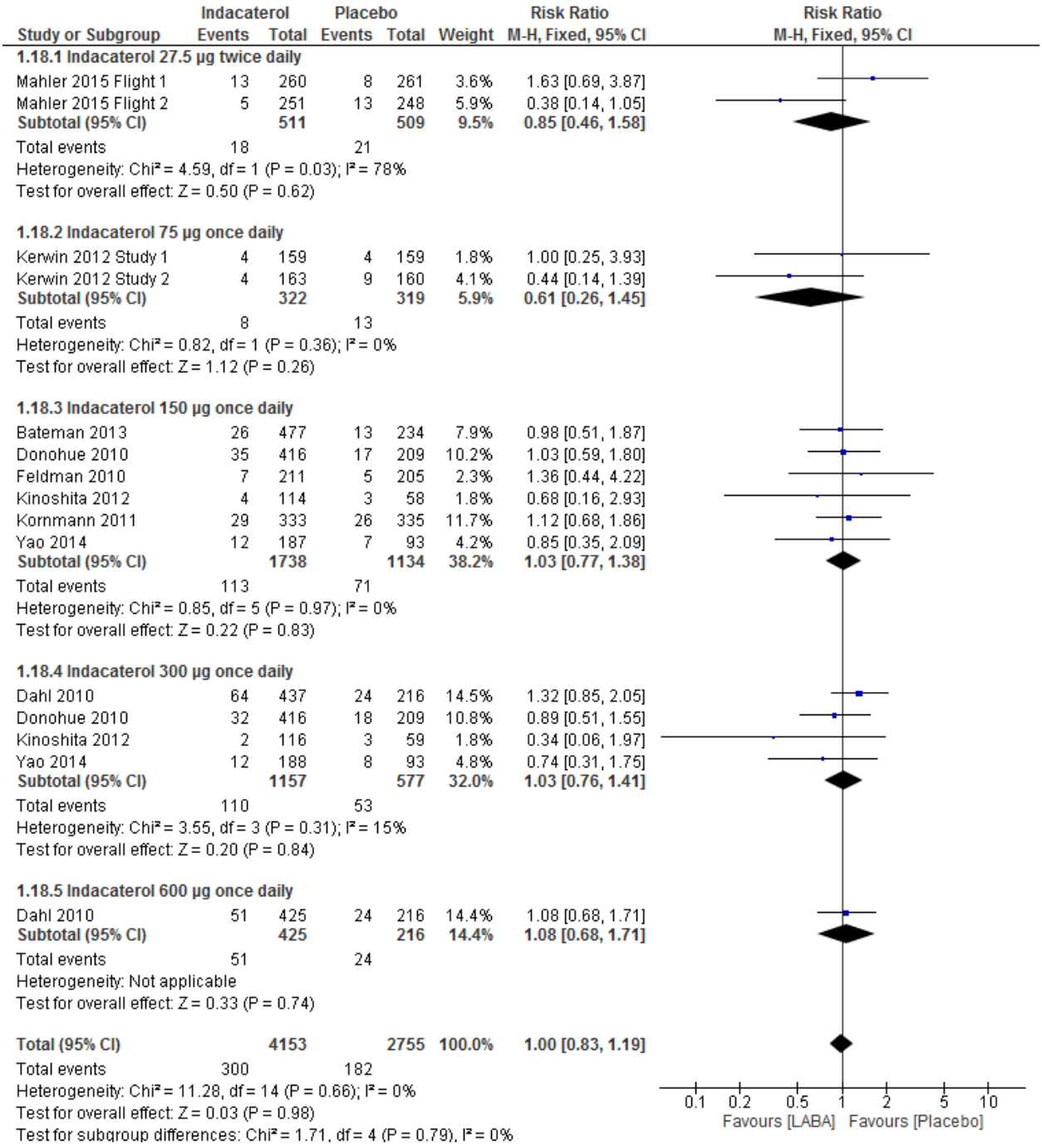
Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Comparison 1: Indacaterol vs placebo (dose ranging efficacy)

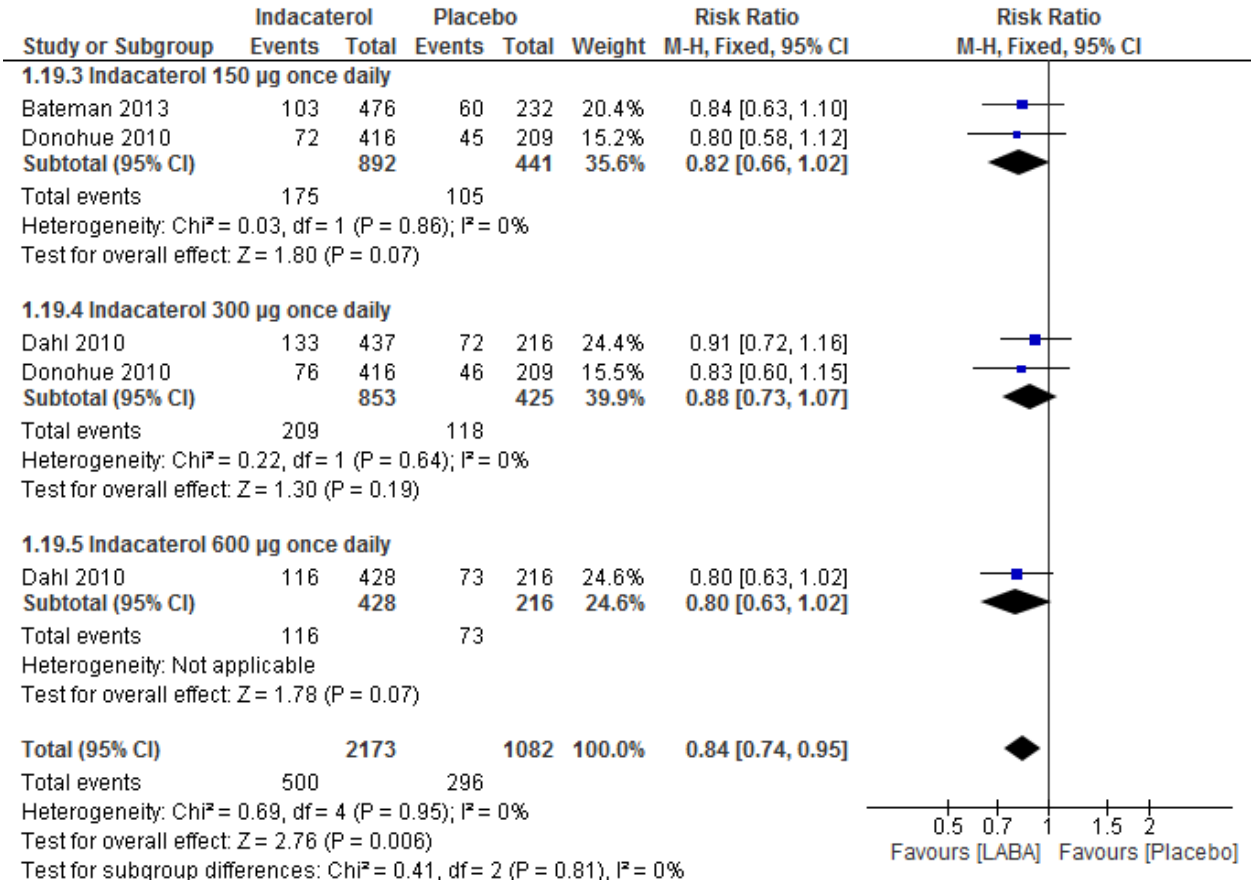
Outcome 1: All-cause mortality



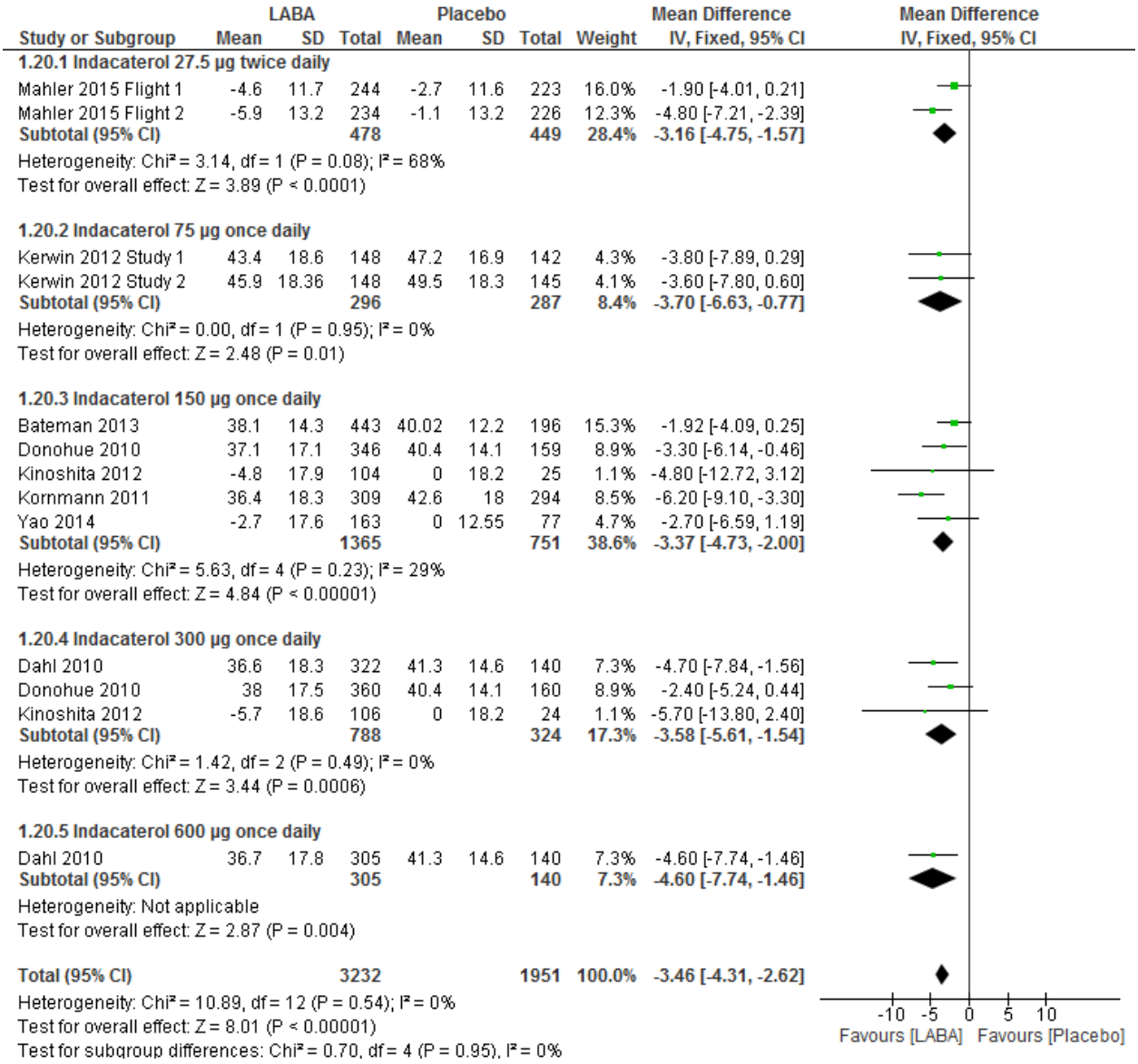
Outcome 2: One or more total Serious Adverse Events



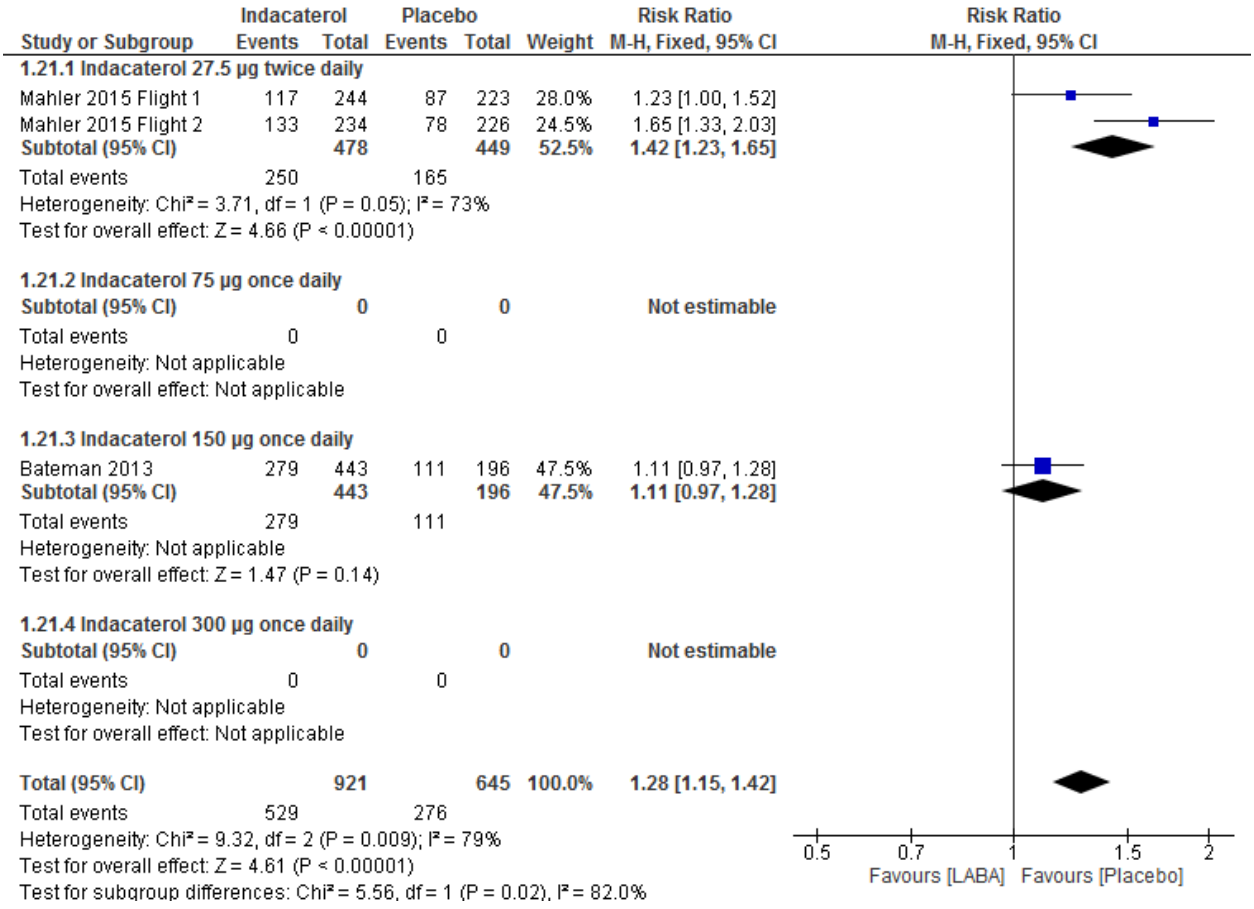
Outcome 3: Number of patients with 1 or more acute exacerbation of any severity



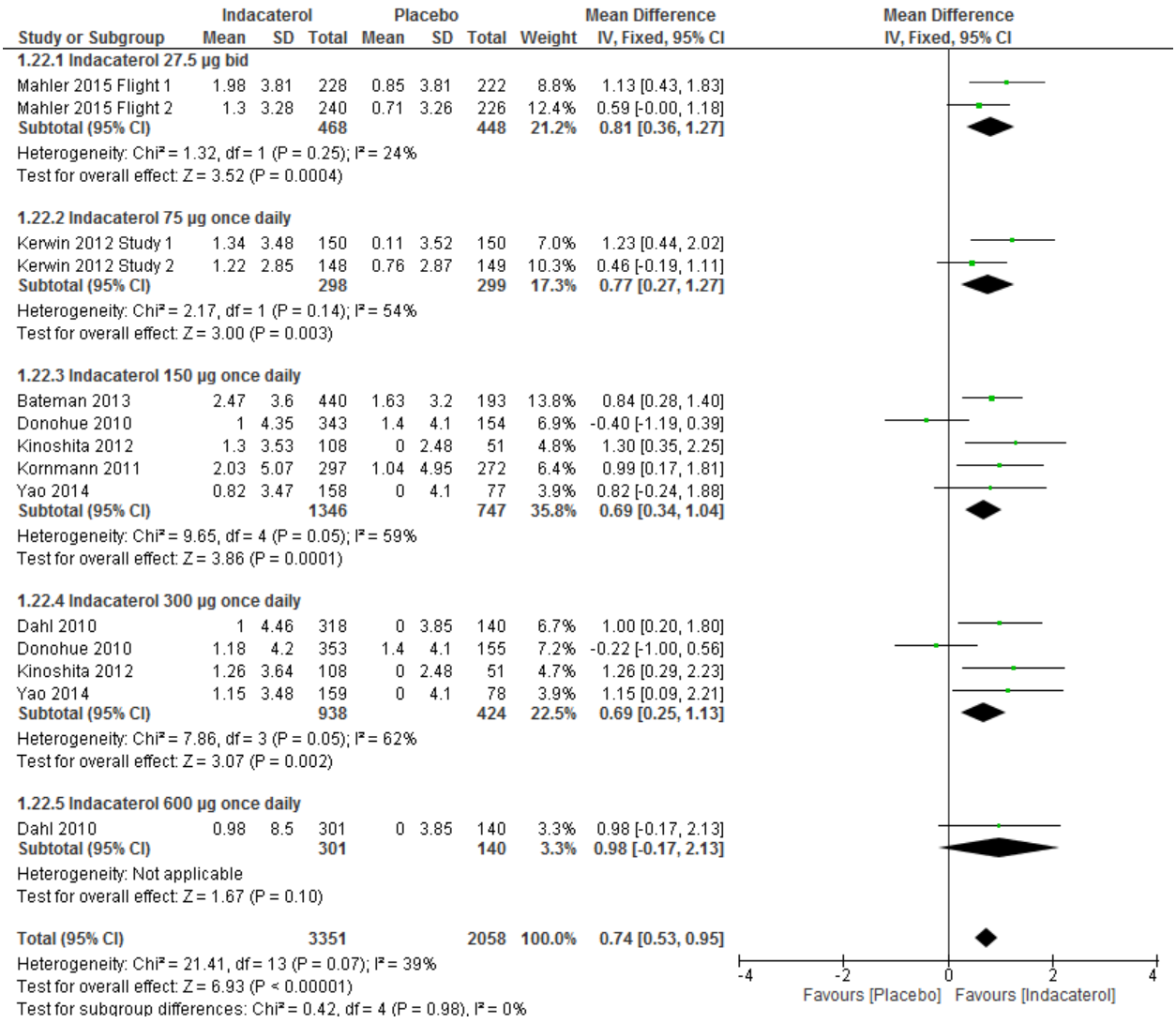
Outcome 4: Mean difference in total SGRQ score (possible range of score is 0-100)



Outcome 5: Minimal Clinical Important Difference (MCID) in Total SGRQ score

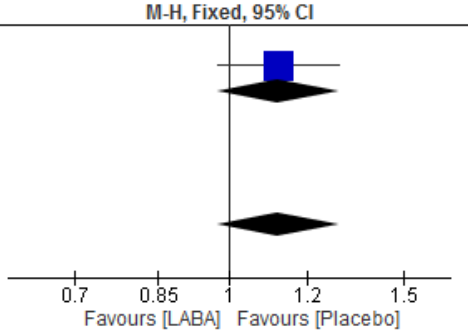


Outcome 6: Mean difference in Transient Dyspnea Index (range of score from + 3 to -3)



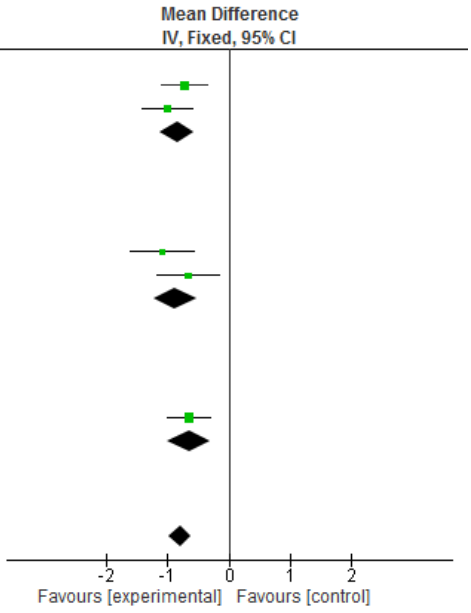
Outcome 7: Minimal Clinical Important difference in TDI score by 1 point or more

Study or Subgroup	Indacaterol Events	Indacaterol Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.3 Indacaterol 150 µg once daily						
Bateman 2013	284	440	111	193	100.0%	1.12 [0.98, 1.29]
Subtotal (95% CI)		**440**		**193**	**100.0%**	**1.12 [0.98, 1.29]**
Total events	284		111			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.11)						
Total (95% CI)		**440**		**193**	**100.0%**	**1.12 [0.98, 1.29]**
Total events	284		111			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.62 (P = 0.11)						
Test for subgroup differences: Not applicable						

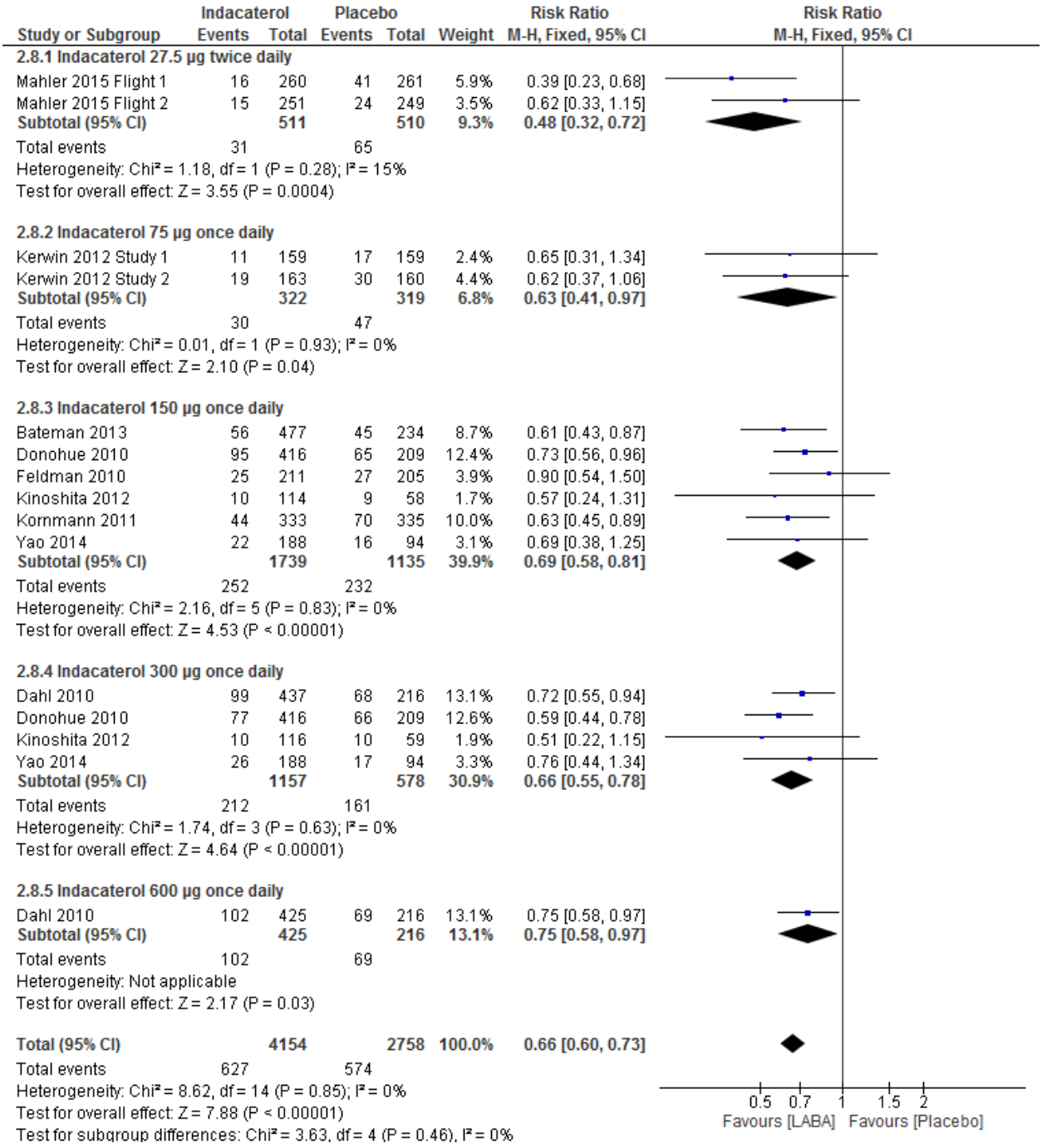


Outcome 8: Decrease from baseline in the number of rescue medications used

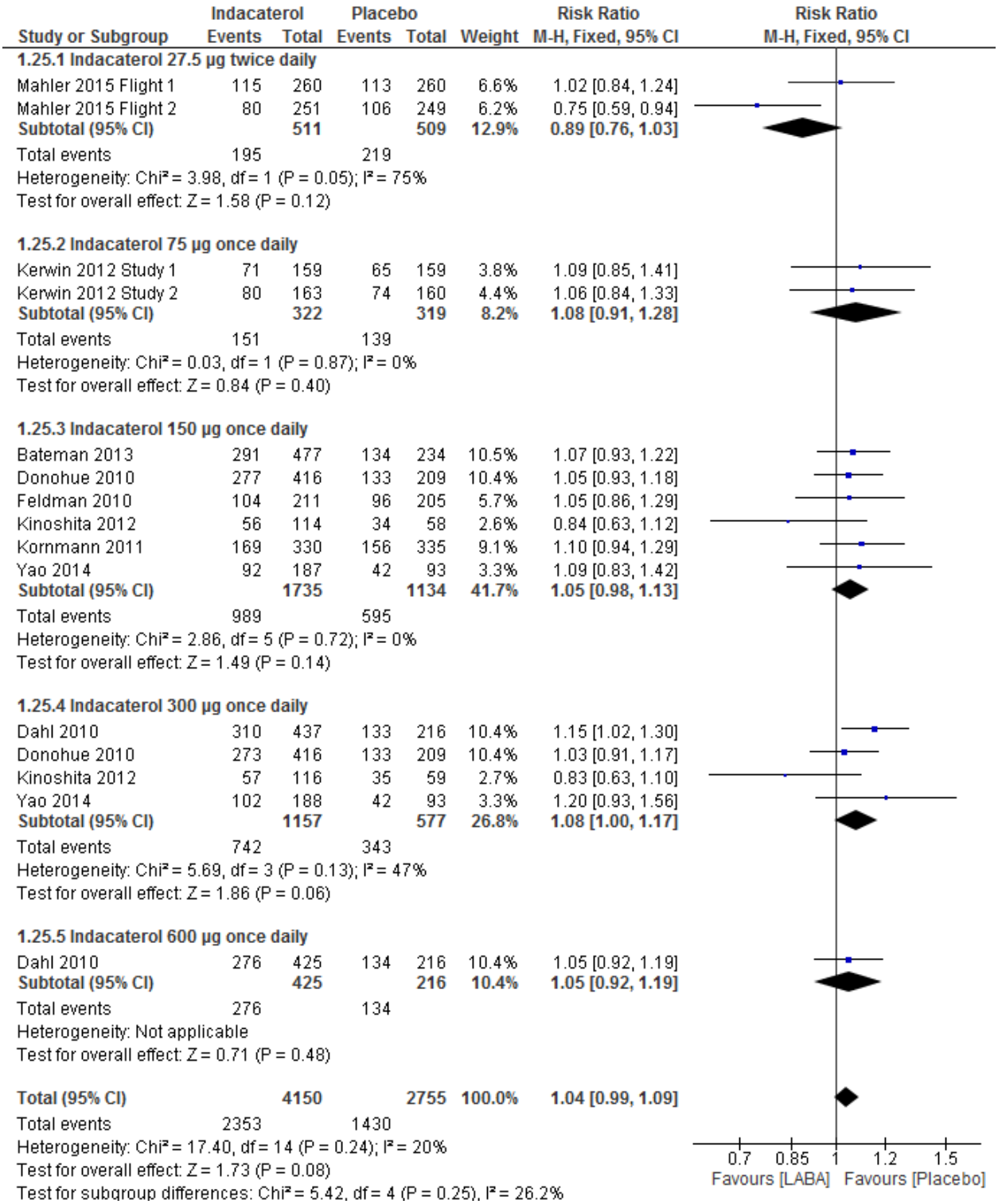
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
1.27.1 Indacaterol 27.5 µg twice daily								
Mahler 2015 Flight 1	-1.72	2.13	250	-1	2.12	240	25.0%	-0.72 [-1.10, -0.34]
Mahler 2015 Flight 2	-2.05	2.33	242	-1.04	2.35	235	20.1%	-1.01 [-1.43, -0.59]
Subtotal (95% CI)			**492**			**475**	**45.0%**	**-0.85 [-1.13, -0.57]**
Heterogeneity: $Chi^2 = 1.02$, df = 1 (P = 0.31); $I^2 = 2\%$								
Test for overall effect: Z = 5.94 (P < 0.00001)								
1.27.2 Indacaterol 75 µg once daily								
Kerwin 2012 Study 1	-1.58	2.3	153	-0.49	2.29	153	13.4%	-1.09 [-1.60, -0.58]
Kerwin 2012 Study 2	-1.15	2.28	150	-0.49	2.28	154	13.5%	-0.66 [-1.17, -0.15]
Subtotal (95% CI)			**303**			**307**	**26.8%**	**-0.87 [-1.24, -0.51]**
Heterogeneity: $Chi^2 = 1.35$, df = 1 (P = 0.25); $I^2 = 26\%$								
Test for overall effect: Z = 4.72 (P < 0.00001)								
1.27.3 Indacaterol 150 µg once daily								
Bateman 2013	-1.57	2.16	416	-0.92	2.07	199	28.1%	-0.65 [-1.00, -0.30]
Subtotal (95% CI)			**416**			**199**	**28.1%**	**-0.65 [-1.00, -0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.59 (P = 0.0003)								
Total (95% CI)			**1211**			**981**	**100.0%**	**-0.80 [-0.99, -0.61]**
Heterogeneity: $Chi^2 = 3.33$, df = 4 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 8.33 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 0.97$, df = 2 (P = 0.62), $I^2 = 0\%$								



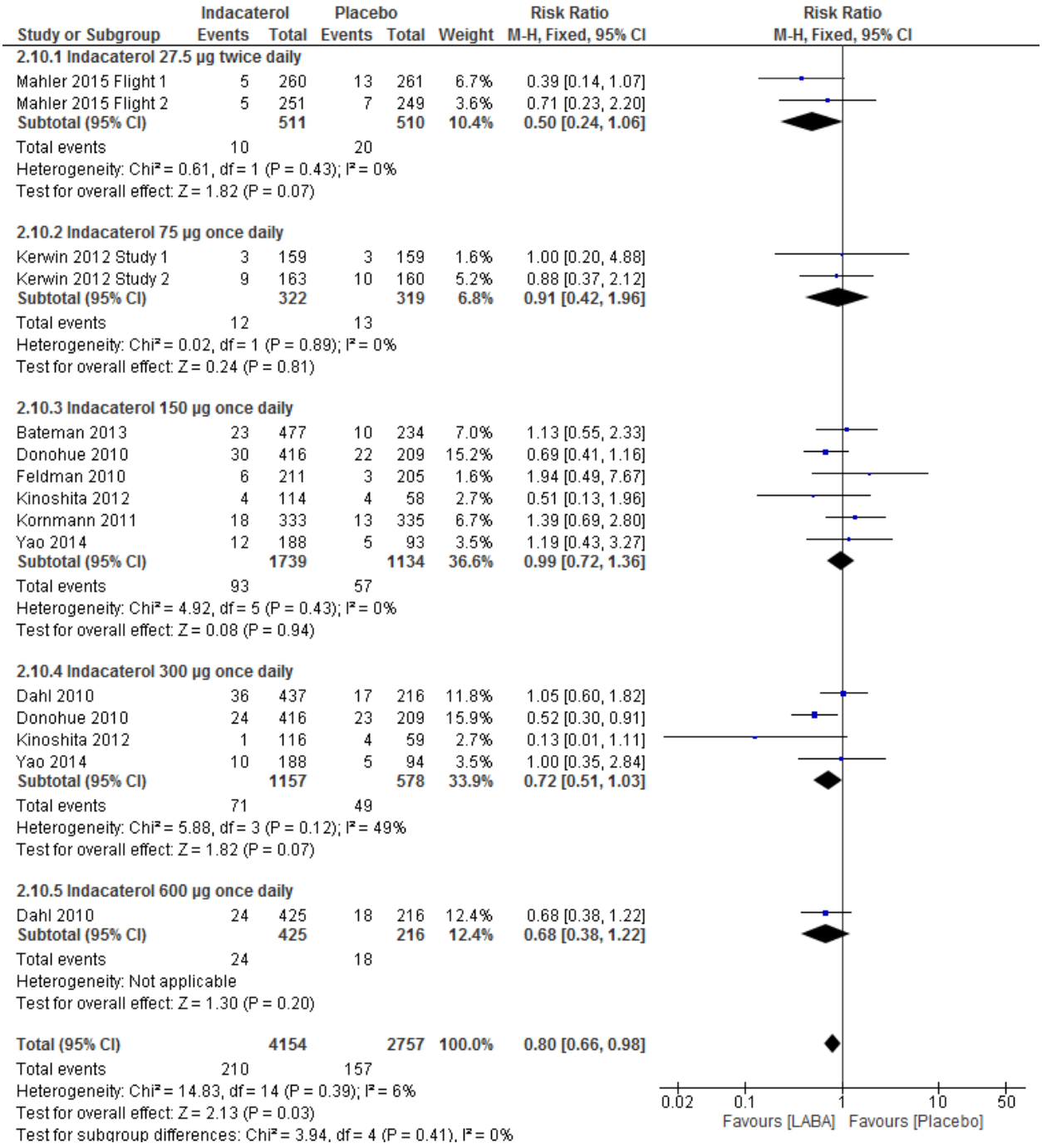
Outcome 9: Total withdrawals



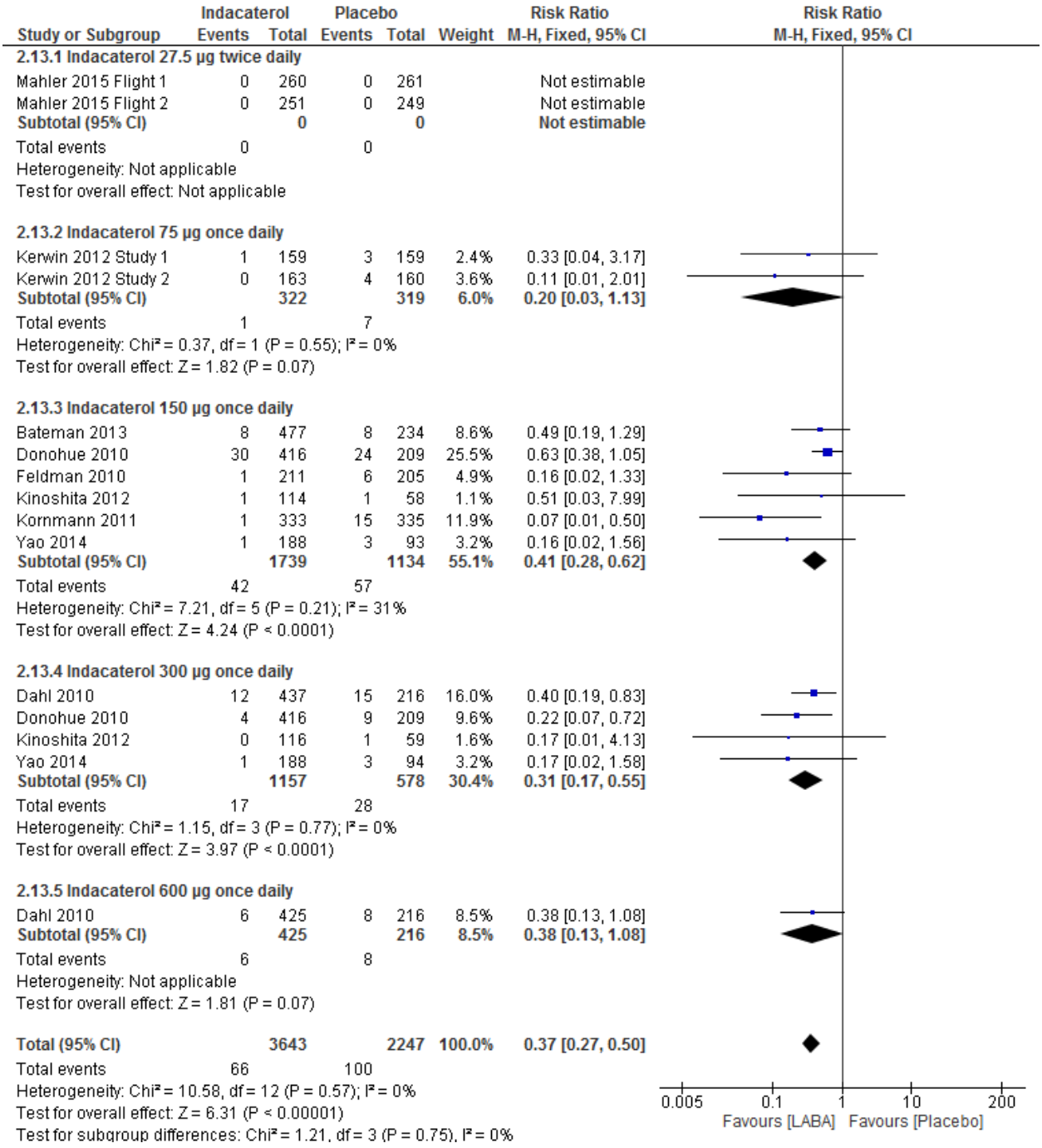
Outcome 10: Total Adverse events



Outcome 11: Withdrawal Due to Adverse Events



Outcome 12: Withdrawal due to lack of therapeutic effect

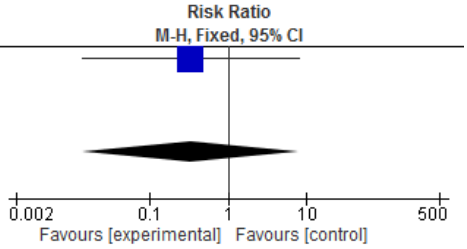


Comparison 2: Indacaterol 300 µg/d vs 150µg/d within same study

Outcome 1: All-Cause mortality

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	0	416	1	416	100.0%	0.33 [0.01, 8.16]
Kinoshita 2012	0	116	0	114		Not estimable
Yao 2014	0	188	0	188		Not estimable
Total (95% CI)		**720**		**718**	**100.0%**	**0.33 [0.01, 8.16]**
Total events	0		1			

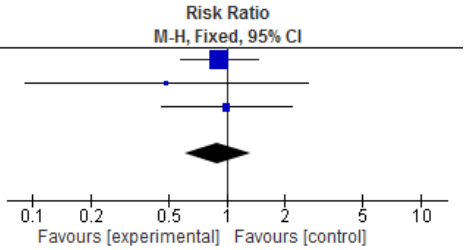
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



Outcome 2: Total Serious Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	32	416	35	416	68.5%	0.91 [0.58, 1.45]
Kinoshita 2012	2	116	4	114	7.9%	0.49 [0.09, 2.63]
Yao 2014	12	188	12	187	23.6%	0.99 [0.46, 2.16]
Total (95% CI)		**720**		**717**	**100.0%**	**0.90 [0.61, 1.32]**
Total events	46		51			

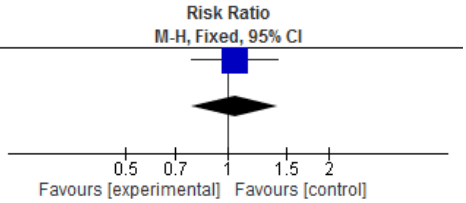
Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



Outcome 3: Number of patients with 1 or more acute exacerbation of any severity

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	76	416	72	416	100.0%	1.06 [0.79, 1.41]
Total (95% CI)		**416**		**416**	**100.0%**	**1.06 [0.79, 1.41]**
Total events	76		72			

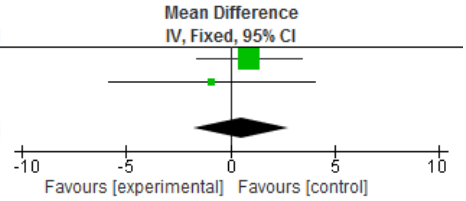
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



Outcome 4: Mean difference in SRGQ total score

Study or Subgroup	Indacaterol 300µg Mean	SD	Total	Indacaterol 150µg Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Donohue 2010	38	17.5	360	37.1	17.1	346	78.9%	0.90 [-1.65, 3.45]
Kinoshita 2012	-5.7	18.6	106	-4.8	17.9	104	21.1%	-0.90 [-5.84, 4.04]
Total (95% CI)			**466**			**450**	**100.0%**	**0.52 [-1.75, 2.79]**

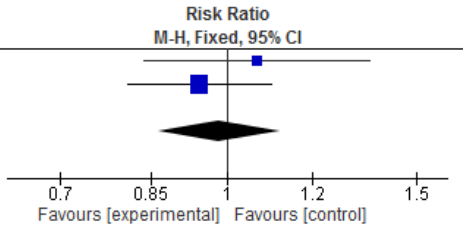
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)



Outcome 5: Patients with MCID in total SGRQ score (≥ 4 point difference)

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kinoshita 2012	64	116	59	114	32.6%	1.07 [0.84, 1.36]
Yao 2014	116	188	123	188	67.4%	0.94 [0.81, 1.10]
Total (95% CI)		**304**		**302**	**100.0%**	**0.98 [0.86, 1.12]**
Total events	180		182			

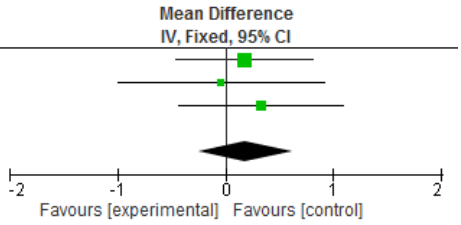
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)



Outcome 6: Mean difference in Transient Dyspnea Index total score

Study or Subgroup	Indacaterol 300µg Mean	SD	Total	Indacaterol 150µg Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Donohue 2010	1.18	4.2	353	1	4.35	343	46.9%	0.18 [-0.46, 0.82]
Kinoshita 2012	1.26	3.64	108	1.3	3.53	108	20.7%	-0.04 [-1.00, 0.92]
Yao 2014	1.15	3.48	159	0.82	3.47	158	32.4%	0.33 [-0.44, 1.10]
Total (95% CI)			**620**			**609**	**100.0%**	**0.18 [-0.25, 0.62]**

Heterogeneity: Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)

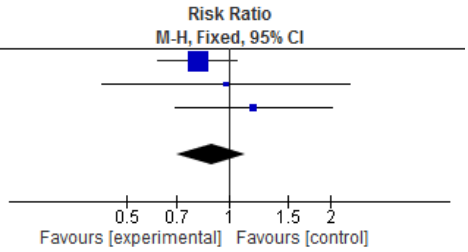


Outcome 7: Patients with MCID in TDI total score of 1 point or more is not reported.

Outcome 8: Total withdrawals

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	77	416	95	416	74.8%	0.81 [0.62, 1.06]
Kinoshita 2012	10	116	10	114	7.9%	0.98 [0.43, 2.27]
Yao 2014	26	188	22	188	17.3%	1.18 [0.70, 2.01]
Total (95% CI)		**720**		**718**	**100.0%**	**0.89 [0.71, 1.12]**
Total events	113		127			

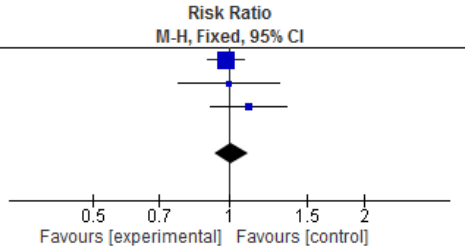
Heterogeneity: Chi² = 1.62, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



Outcome 9: Total Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	273	416	277	416	65.1%	0.99 [0.89, 1.09]
Kinoshita 2012	57	116	56	114	13.3%	1.00 [0.77, 1.30]
Yao 2014	102	188	92	188	21.6%	1.11 [0.91, 1.35]
Total (95% CI)		**720**		**718**	**100.0%**	**1.01 [0.93, 1.10]**
Total events	432		425			

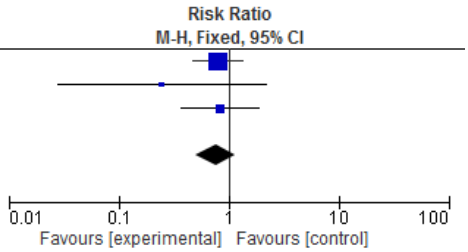
Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)



Outcome 10: Withdrawal due to Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Donohue 2010	24	416	30	416	65.2%	0.80 [0.48, 1.34]
Kinoshita 2012	1	116	4	114	8.8%	0.25 [0.03, 2.16]
Yao 2014	10	188	12	188	26.1%	0.83 [0.37, 1.88]
Total (95% CI)		**720**		**718**	**100.0%**	**0.76 [0.50, 1.16]**
Total events	35		46			

Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

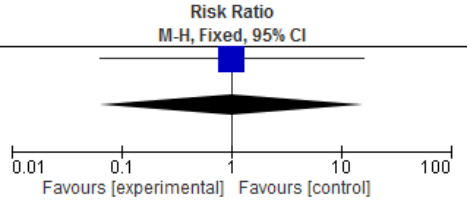


Comparison 3: Indacaterol 600 µg/d vs 300µg/d within same study

Outcome 1: Total mortality

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	1	428	1	437	100.0%	1.02 [0.06, 16.27]
Total (95% CI)		**428**		**437**	**100.0%**	**1.02 [0.06, 16.27]**
Total events	1		1			

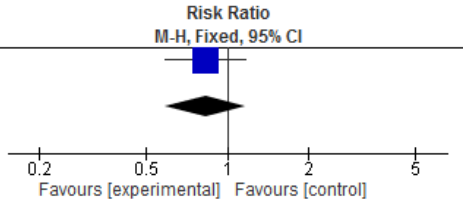
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



Outcome 2: Total Serious Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	51	425	63	437	100.0%	0.83 [0.59, 1.17]
Total (95% CI)		**425**		**437**	**100.0%**	**0.83 [0.59, 1.17]**
Total events	51		63			

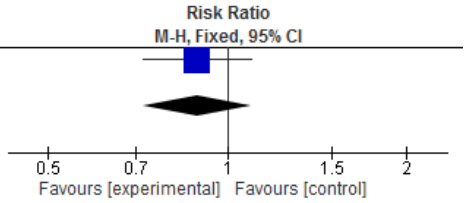
Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



Outcome 3: Number of patients with 1 or more acute exacerbation of COPD of any severity

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	116	428	133	437	100.0%	0.89 [0.72, 1.10]
Total (95% CI)		**428**		**437**	**100.0%**	**0.89 [0.72, 1.10]**
Total events	116		133			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



Outcome 4: Mean difference in SRGQ total score is not reported

Outcome 5: Patients with MCID (4 point difference) in SGRQ score is not reported

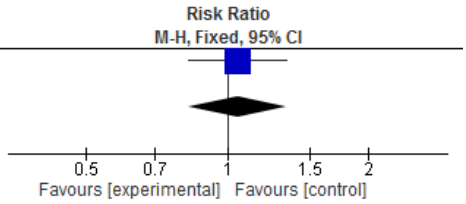
Outcome 6: Mean difference in TDI score is not reported

Outcome 7: Patients with MCID in TDI score of 1 point or more is not reported.

Outcome 8: Total withdrawals

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	102	428	99	437	100.0%	1.05 [0.83, 1.34]
Total (95% CI)		**428**		**437**	**100.0%**	**1.05 [0.83, 1.34]**
Total events	102		99			

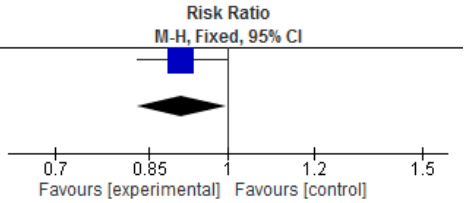
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)



Outcome 9: Total Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	276	428	310	437	100.0%	0.91 [0.83, 1.00]
Total (95% CI)		**428**		**437**	**100.0%**	**0.91 [0.83, 1.00]**
Total events	276		310			

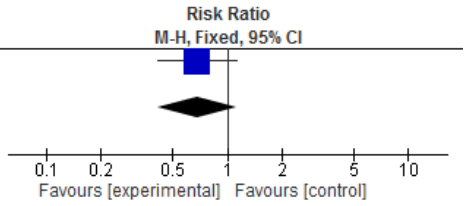
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04)



Outcome 10: Withdrawal due to Adverse Events

Study or Subgroup	Indacaterol 300µg Events	Total	Indacaterol 150µg Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahl 2010	24	428	36	437	100.0%	0.68 [0.41, 1.12]
Total (95% CI)		**428**		**437**	**100.0%**	**0.68 [0.41, 1.12]**
Total events	24		36			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.51 (P = 0.13)



Summary of findings:

INDACATEROL compared to Placebo in adult patients with chronic obstructive pulmonary disease

Patient or population: adult patients with chronic obstructive pulmonary disease
Setting: Outpatient
Intervention: Indacaterol (55 µg/d to 600 µg/d)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with INDACATEROL**				
All-cause mortality	4 per 1,000	**2 per 1,000** (1 to 5)	**RR 0.47** (0.21 to 1.07)	6913 (11 RCTs)	⊕⊕⊕⊕ HIGH	
Total SAE	66 per 1,000	**66 per 1,000** (55 to 79)	**RR 1.00** (0.83 to 1.19)	6908 (11 RCTs)	⊕⊕◯◯ LOW [a,b]	
Number of patients with one or more exacerbation	274 per 1,000	**230 per 1,000** (202 to 260)	**RR 0.84** (0.74 to 0.95)	3255 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	
Mean difference in total SGRQ score	The mean difference in Total SGRQ score was **0**	The mean difference in Total SGRQ score in the intervention group was 3.46 lower (4.31 lower to 2.62 lower)	-	5183 (10 RCTs)	⊕⊕◯◯ LOW [a,b,e]	
Patients with SGRQ total score improved by 4 points	428 per 1,000	**548 per 1,000** (492 to 608)	**RR 1.28** (1.15 to 1.42)	1566 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	

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	Risk with Placebo	**Risk with INDACATEROL**				
Mean difference in TDI score	The mean difference in TDI score was **0**	The mean difference in TDI score in the intervention group was 0.74 higher (0.53 higher to 0.95 higher)	-	5409 (10 RCTs)	⊕⊕◯◯ LOW [a,b,c,f]	
Patients with TDI score improvement of 1 point or more	575 per 1,000	**644 per 1,000** (564 to 742)	**RR 1.12** (0.98 to 1.29)	633 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,g]	
Total withdrawal	208 per 1,000	**137 per 1,000** (125 to 152)	**RR 0.66** (0.60 to 0.73)	6912 (11 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	
Total Adverse events	519 per 1,000	**540 per 1,000** (514 to 566)	**RR 1.04** (0.99 to 1.09)	6905 (11 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	
Withdrawal due to adverse events	59 per 1,000	**46 per 1,000** (38 to 56)	**RR 0.78** (0.64 to 0.95)	6911 (11 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	

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Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with INDACATEROL**				
Decreased need for rescue medication compared to baseline (mean number of puffs)	The mean decreased need for rescue medication compared to baseline was **0**	The mean decreased need for rescue medication compared to baseline in the intervention group was 0.8 lower (0.99 lower to 0.61 lower)	-	2192 (5 RCTs)	⊕⊕⊕◯ MODERATE [a,b,h]	
Withdrawal due to lack of therapeutic effect	45 per 1,000	**16 per 1,000** (12 to 22)	**RR 0.37** (0.27 to 0.50)	5890 (9 RCTs)	⊕⊕⊕◯ MODERATE [a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Unclear/high risk of selection, performance, detection and selective reporting bias.

b. All studies were funded by the manufacturer and employees were directly involved in preparation and review of the manuscript.

c. The 2 studies at 75 µg/d dose do not report this important clinical outcome measure.

d. 3/12 studies report this outcome in 23% of total randomized patients.

e. This outcome is reported in 75% of total randomized patients.

f. This outcome in 78% of total randomized patients.

g. Reported in 1/12 studies in 9% of randomized patients.

h. Reported in 5/12 studies in 32% of total randomized patients.