

TL # 102: Indacaterol for chronic obstructive pulmonary disease

Table of content	Page number
1. Risk of Bias figures	2-3
2. Forest plots	
a. Indacaterol (various doses) vs. Placebo comparisons	4-14
b. Indacaterol active dose comparisons	15-18
3. Summary of Findings Table (Overall grading of Evidence)	19-22

Risk of bias

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

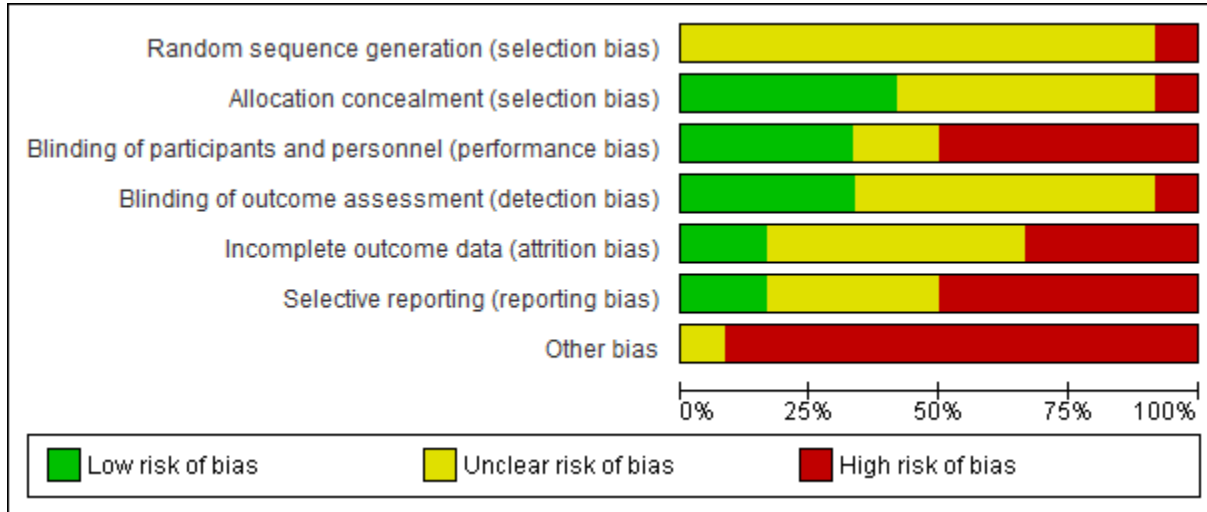


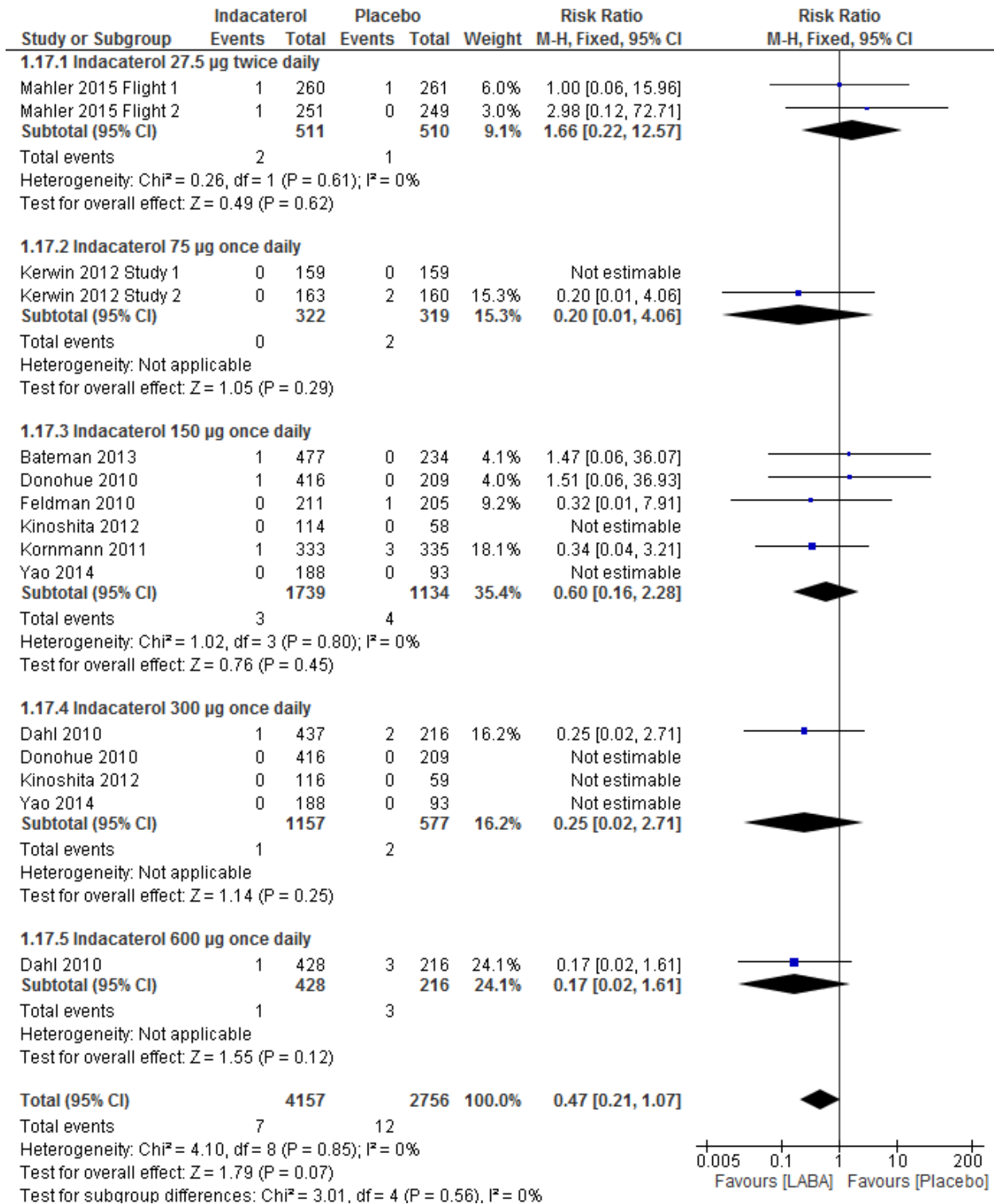
Figure 1: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

	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
Bateman 2013	?	+	-	?	?	+	-
Dahl 2010	?	+	-	?	-	+	-
Donohue 2010	?	+	-	?	-	?	-
Feldman 2010	?	?	+	+	?	-	-
Kerwin 2012 Study 1	?	+	+	+	+	-	-
Kerwin 2012 Study 2	?	+	+	+	+	-	-
Kinoshita 2012	?	?	?	?	?	?	-
Kornmann 2011	?	?	-	?	-	-	-
Mahler 2015 Flight 1	?	?	-	?	?	-	-
Mahler 2015 Flight 2	?	?	+	?	?	?	-
Mroz 2013	-	-	-	-	-	-	?
Yao 2014	?	?	?	+	?	?	-

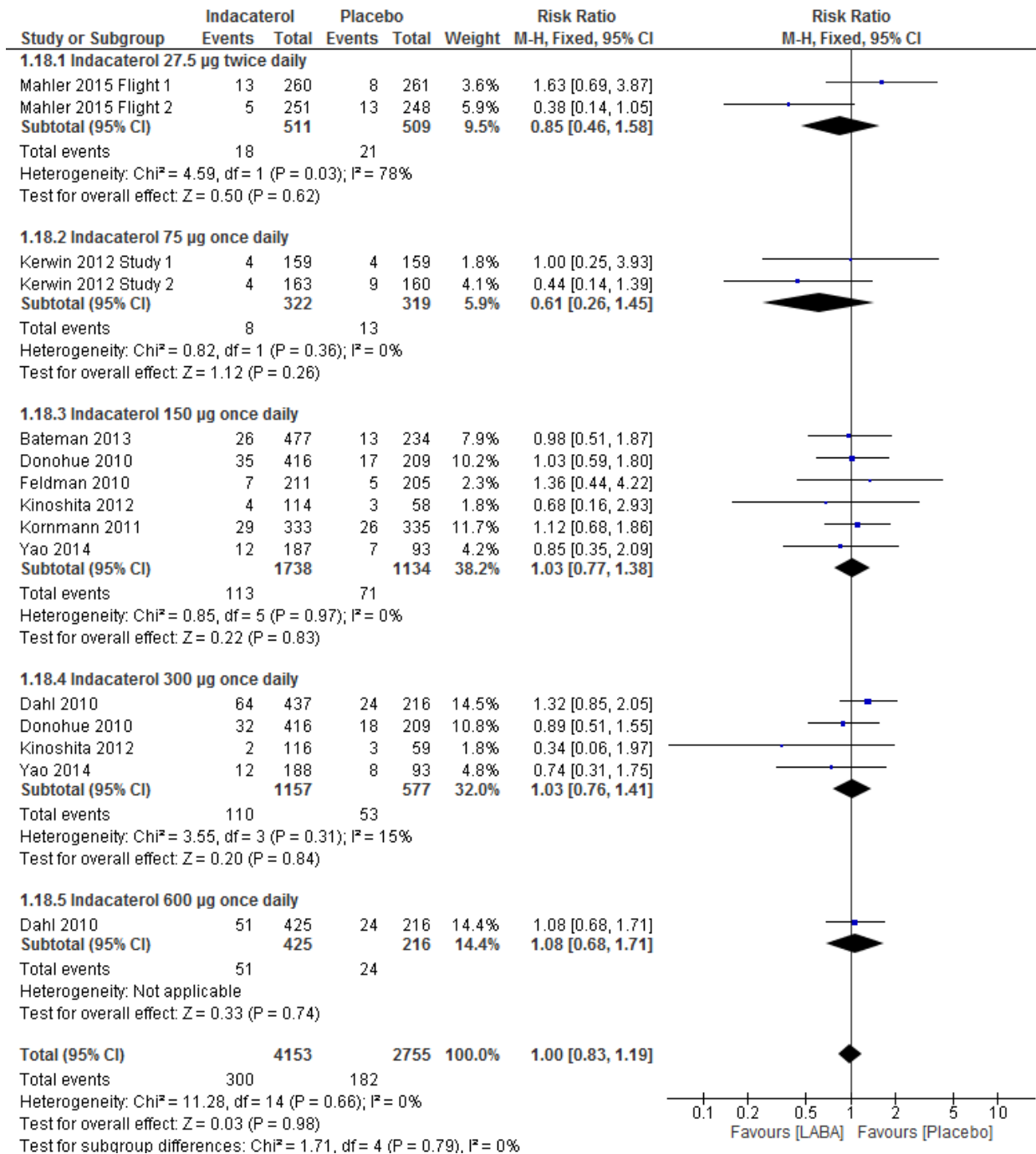
Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Comparison 1: Indacaterol vs placebo (dose ranging efficacy)

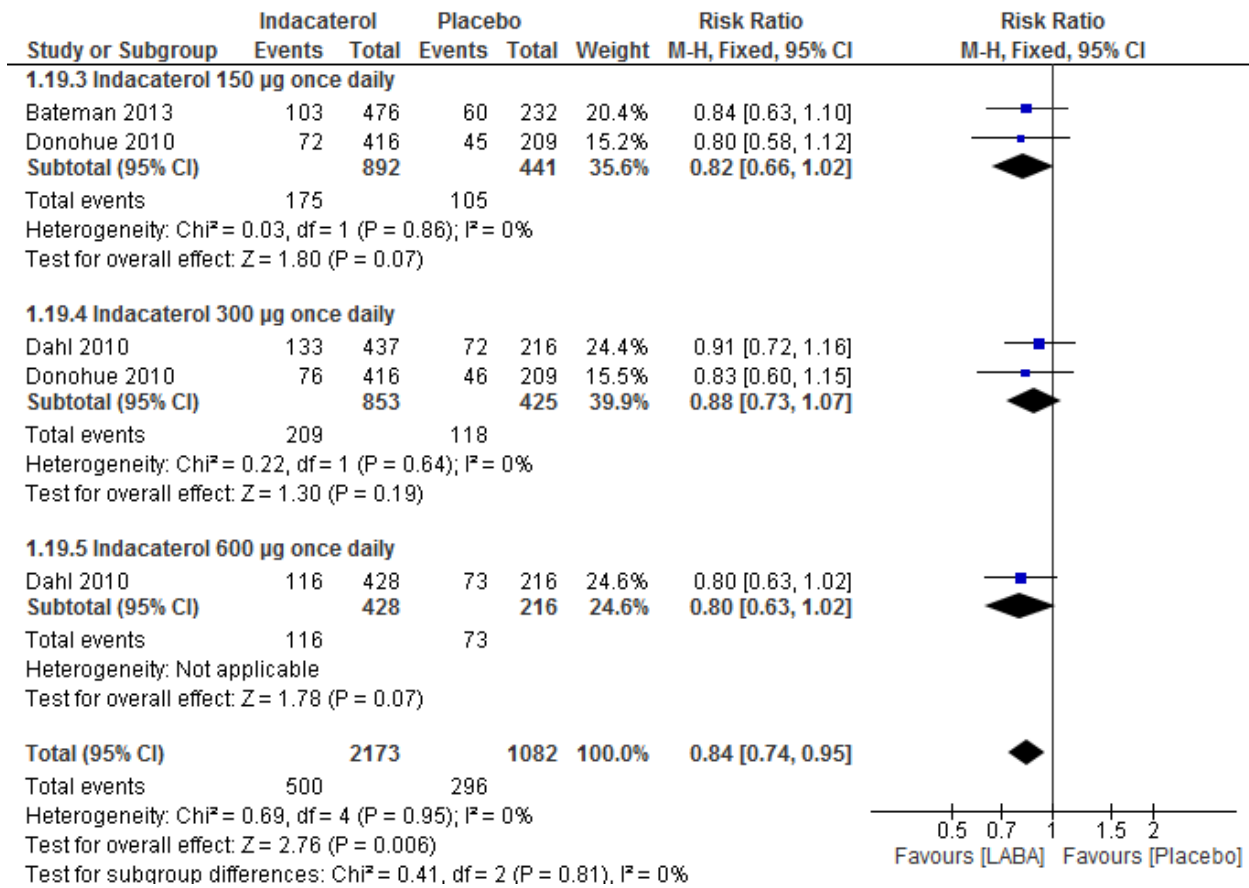
Outcome 1: All-cause mortality



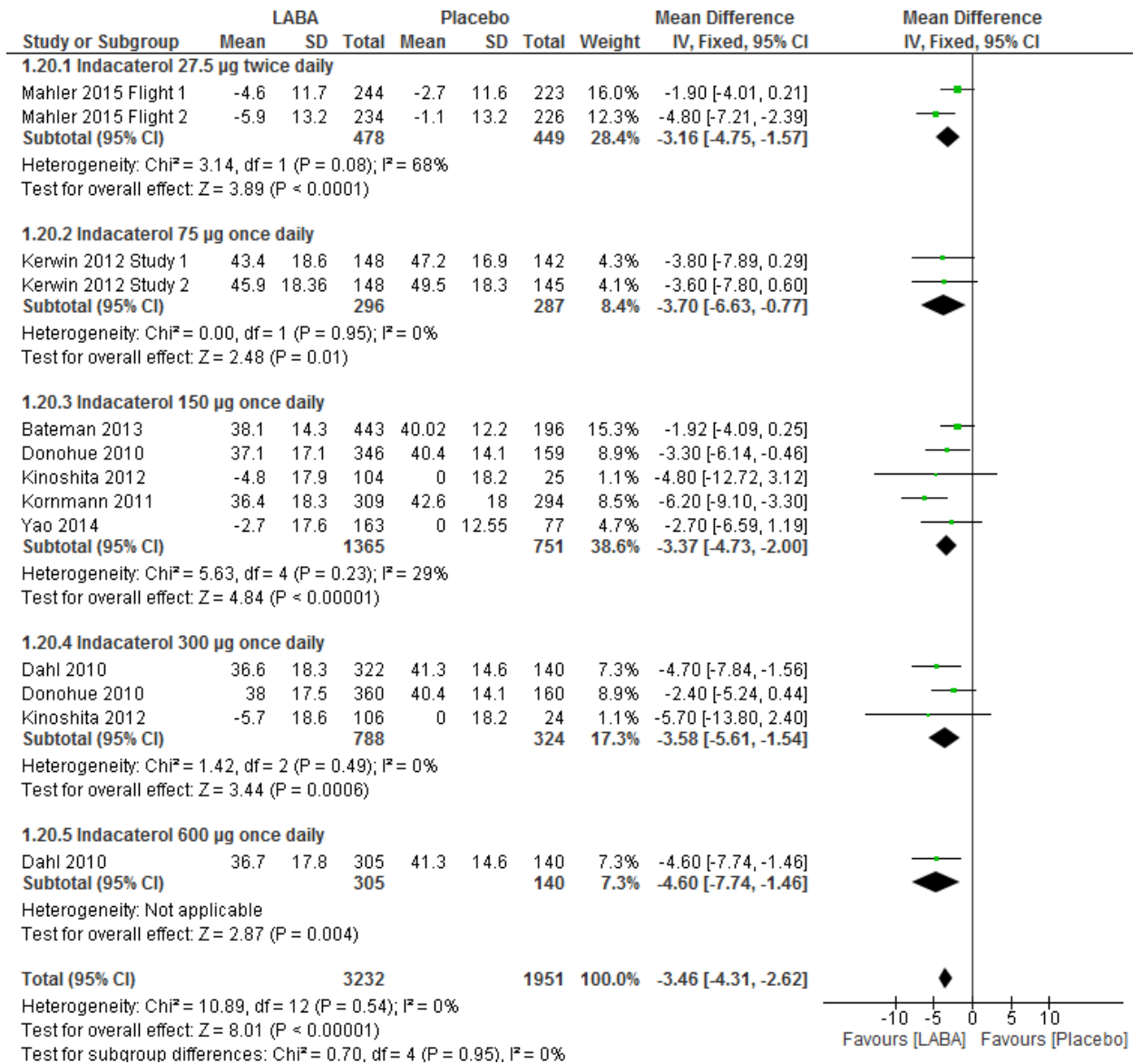
Outcome 2: One or more total Serious Adverse Events



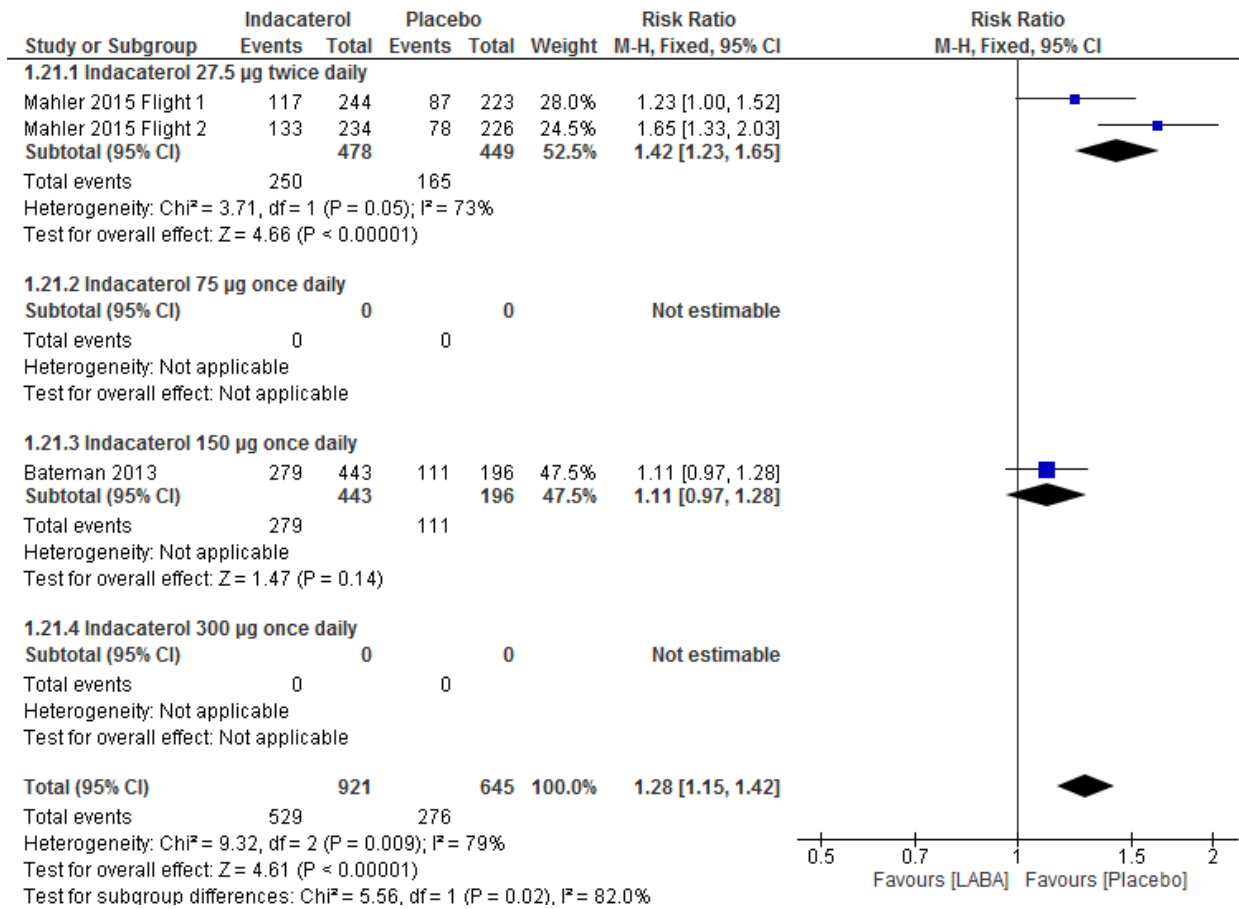
Outcome 3: Number of patients with 1 or more acute exacerbation of any severity



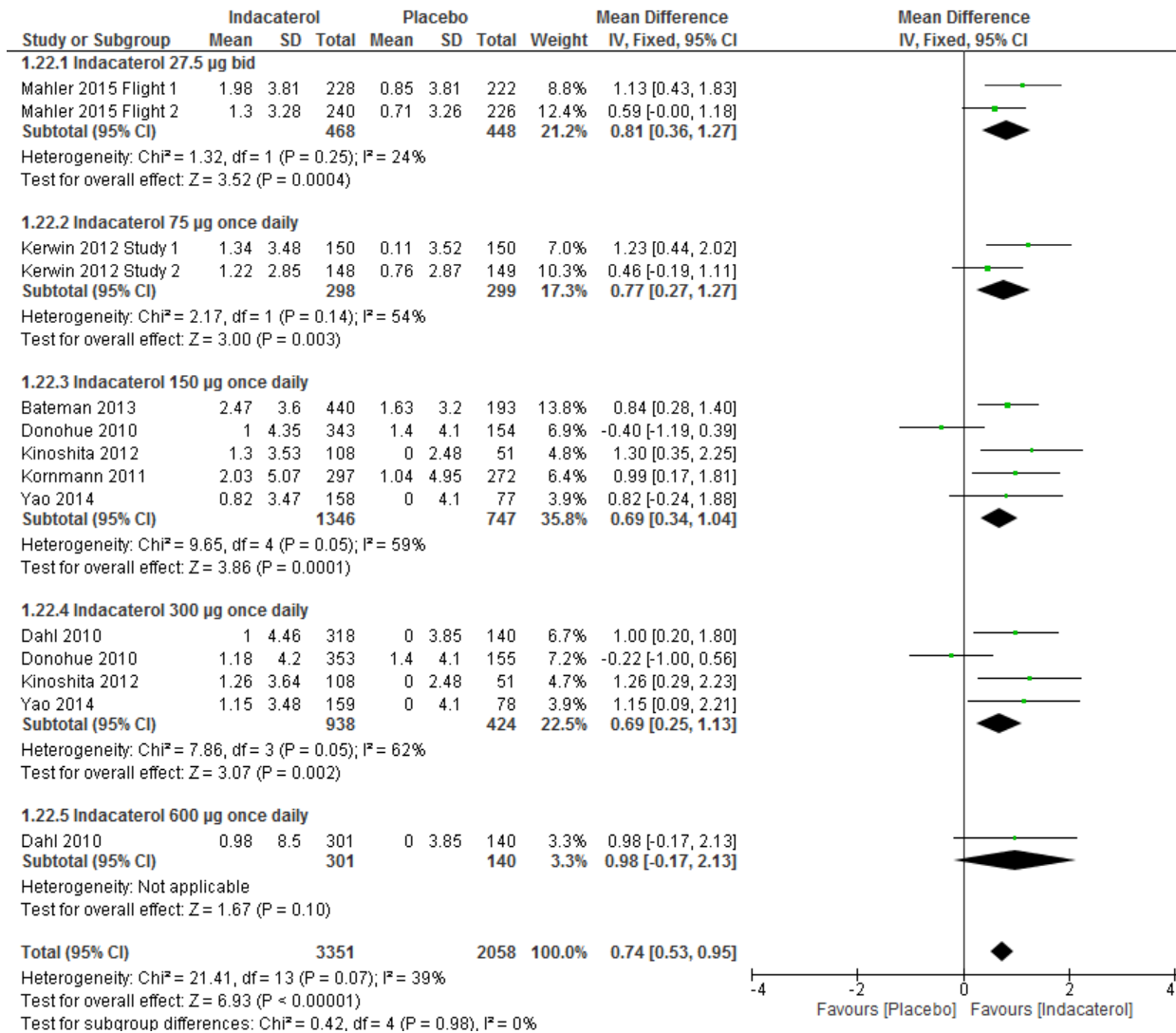
Outcome 4: Mean difference in total SGRQ score (possible range of score is 0-100)



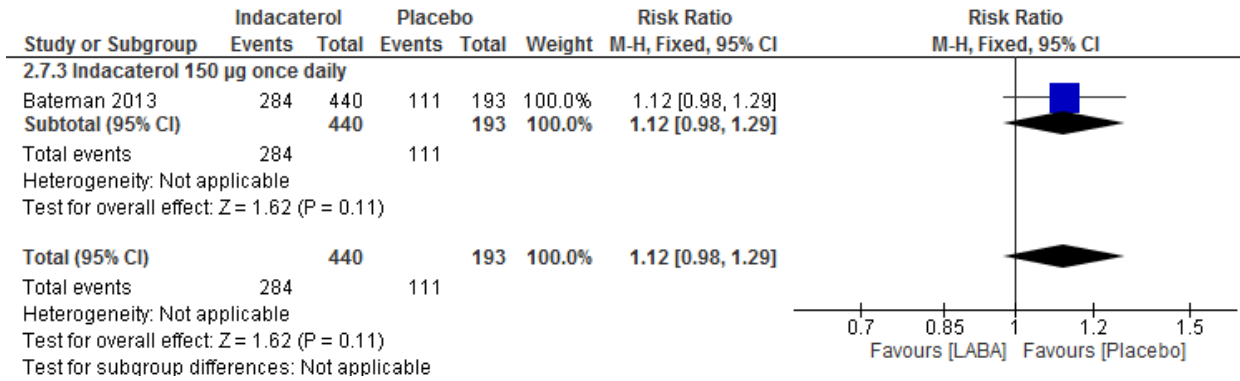
Outcome 5: Minimal Clinical Important Difference (MCID) in Total SGRQ score



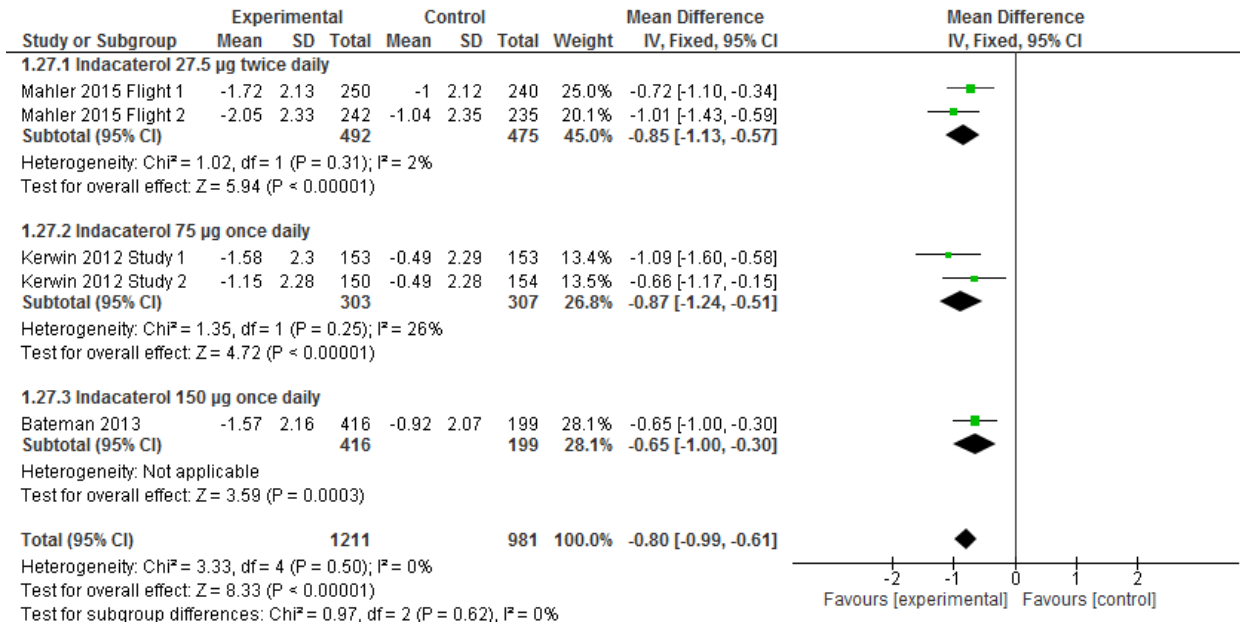
Outcome 6: Mean difference in Transient Dyspnea Index (range of score from + 3 to -3)



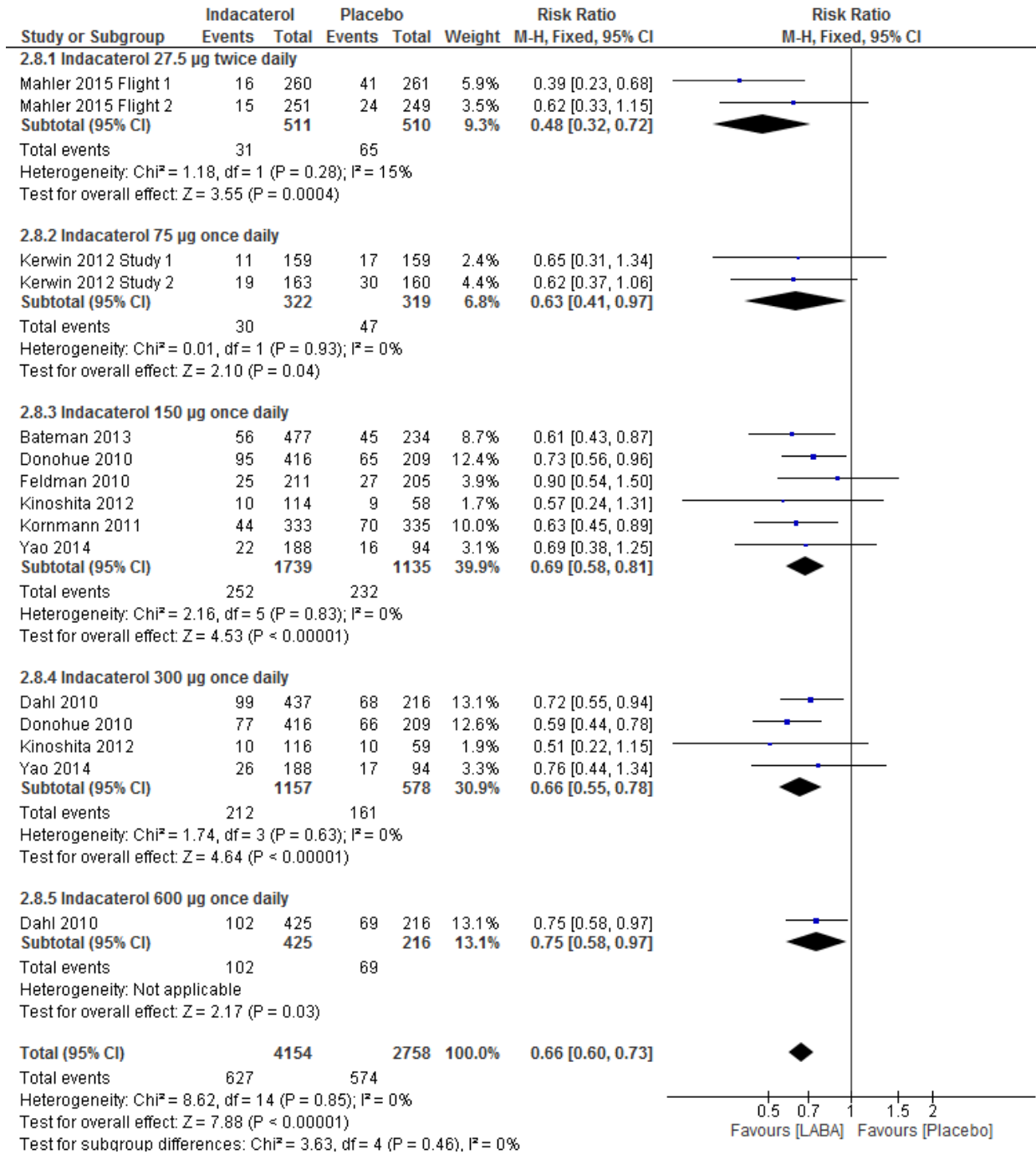
Outcome 7: Minimal Clinical Important difference in TDI score by 1 point or more



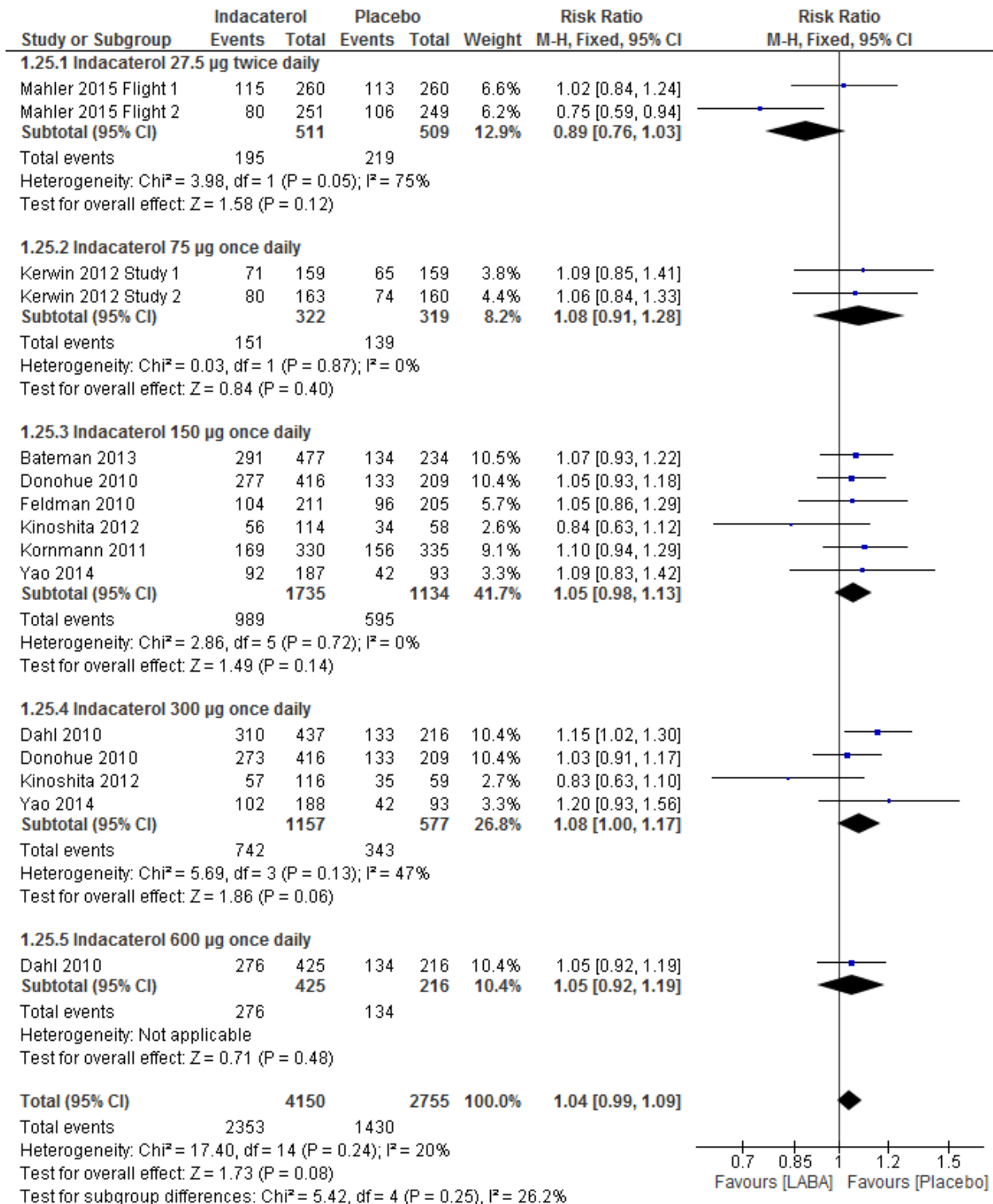
Outcome 8: Decrease from baseline in the number of rescue medications used



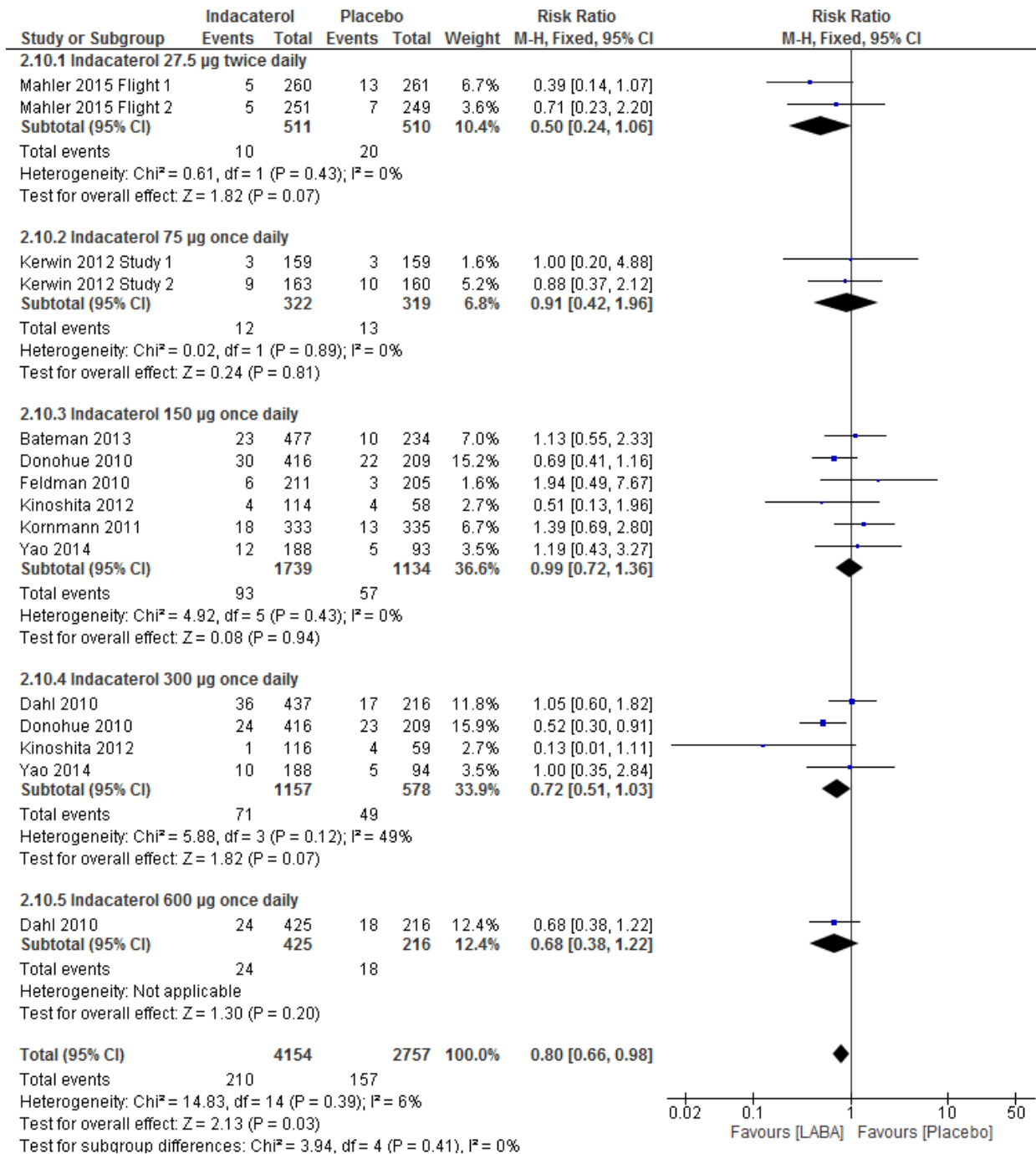
Outcome 9: Total withdrawals



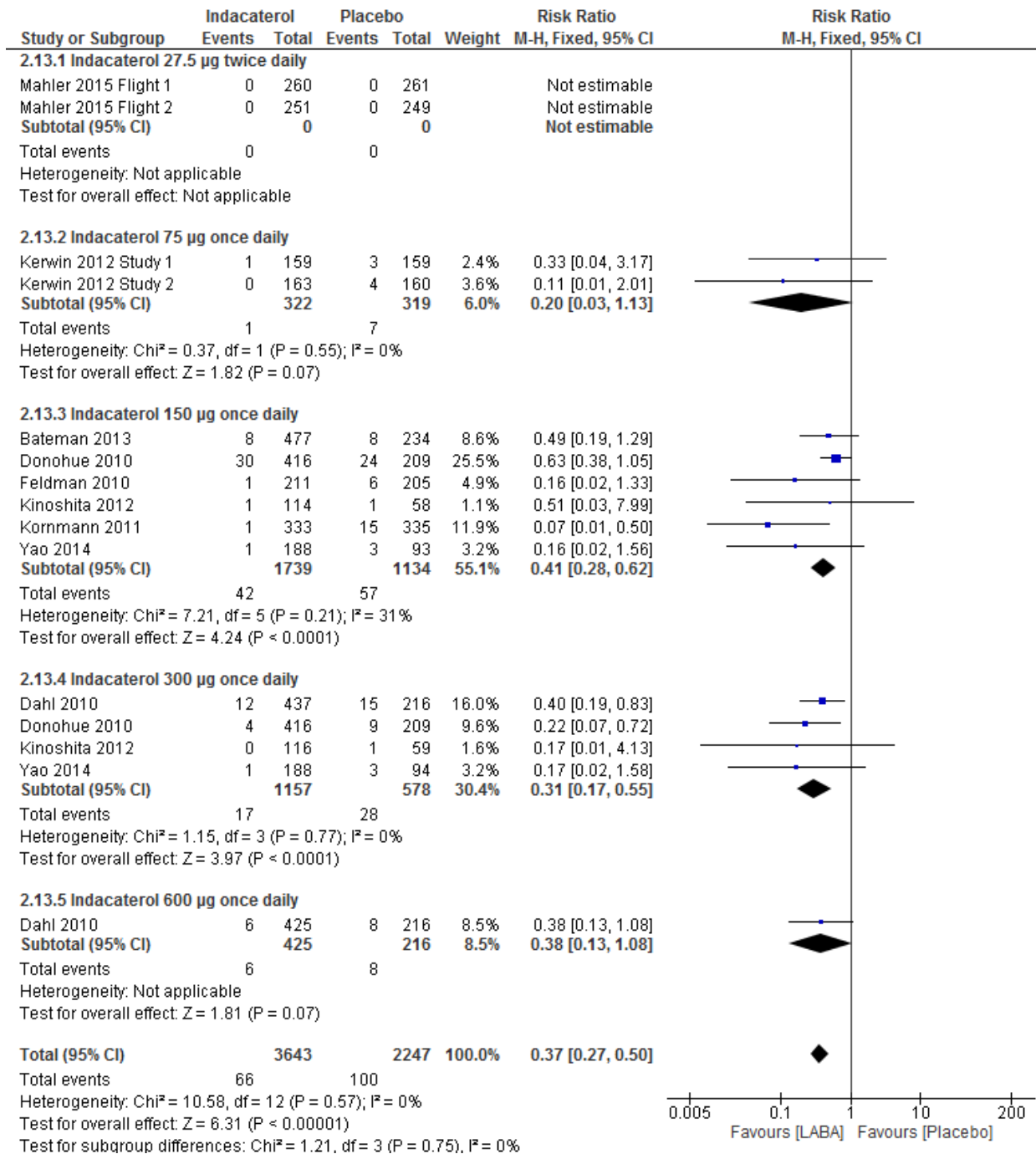
Outcome 10: Total Adverse events



Outcome 11: Withdrawal Due to Adverse Events

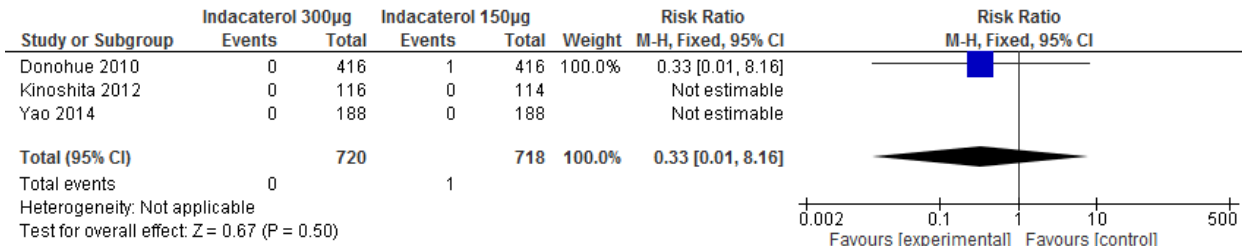


Outcome 12: Withdrawal due to lack of therapeutic effect

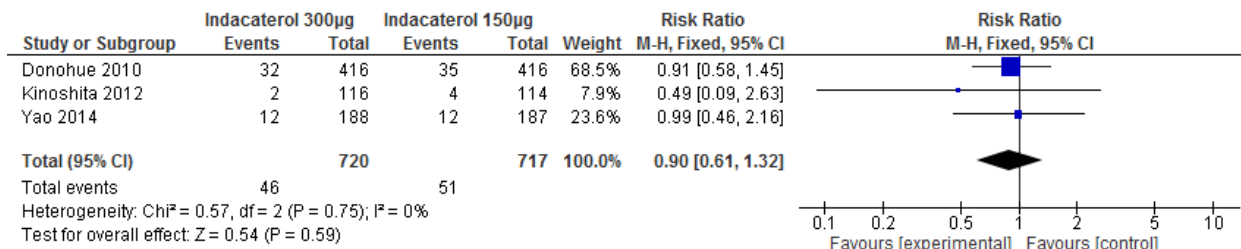


Comparison 2: Indacaterol 300 µg/d vs 150µg/d within same study

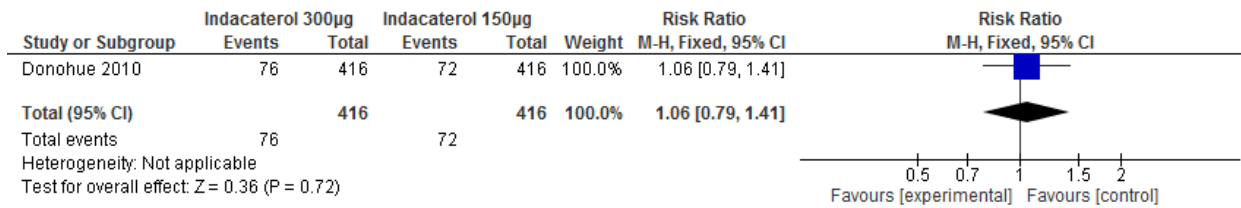
Outcome 1: All-Cause mortality



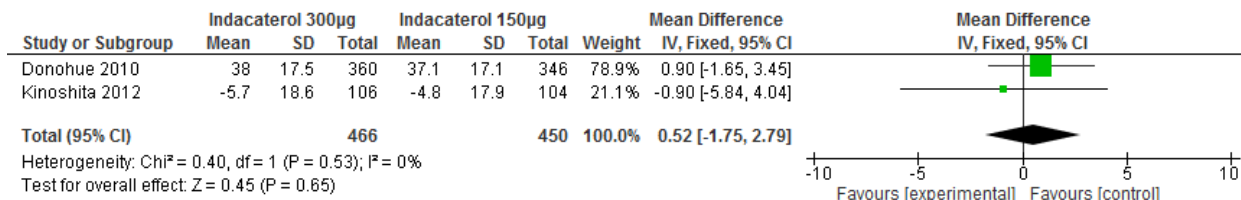
Outcome 2: Total Serious Adverse Events



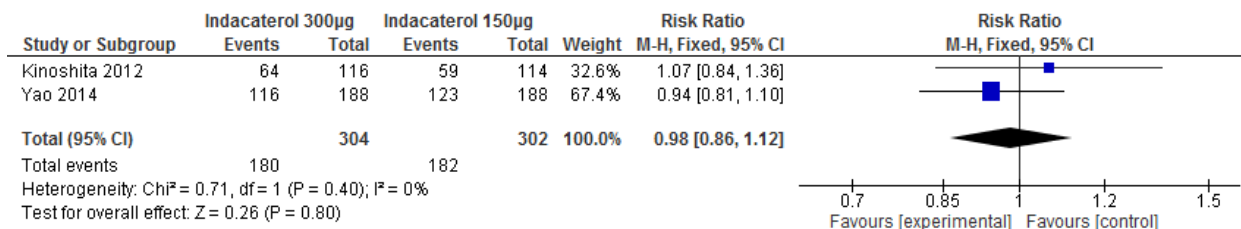
Outcome 3: Number of patients with 1 or more acute exacerbation of any severity



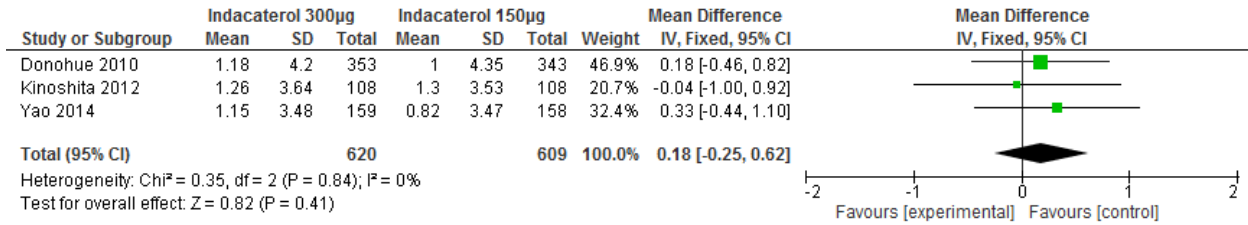
Outcome 4: Mean difference in SRGQ total score



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

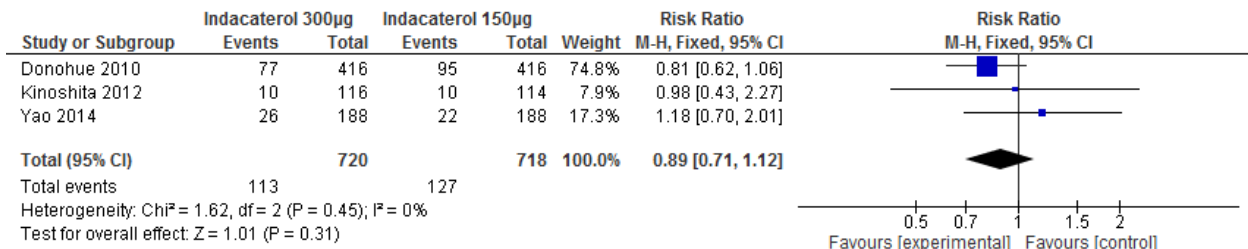


Outcome 6: Mean difference in Transient Dyspnea Index total score

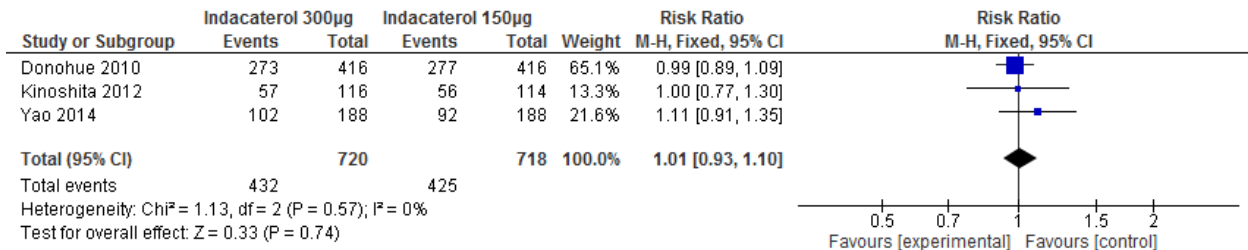


Outcome 7: Patients with MCID in TDI total score of 1 point or more is not reported.

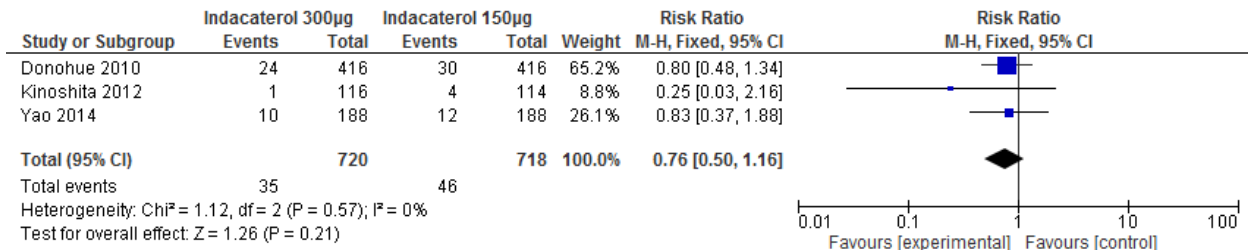
Outcome 8: Total withdrawals



Outcome 9: Total Adverse Events

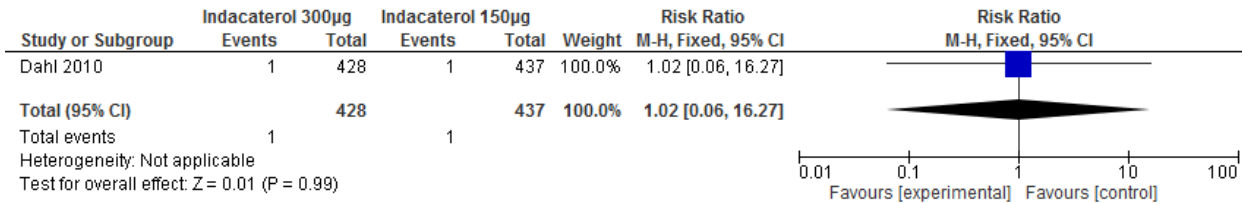


Outcome 10: Withdrawal due to Adverse Events

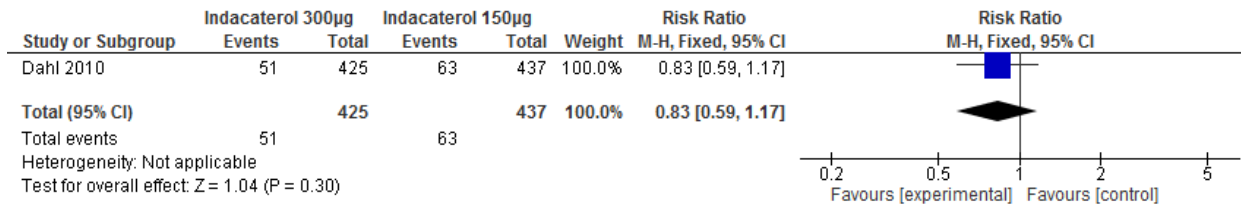


Comparison 3: Indacaterol 600 µg/d vs 300µg/d within same study

Outcome 1: Total mortality



Outcome 2: Total Serious Adverse Events



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



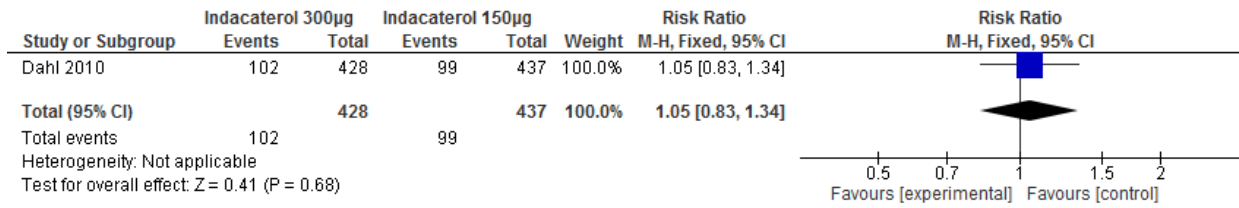
Outcome 4: Mean difference in SRGQ total score is not reported

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

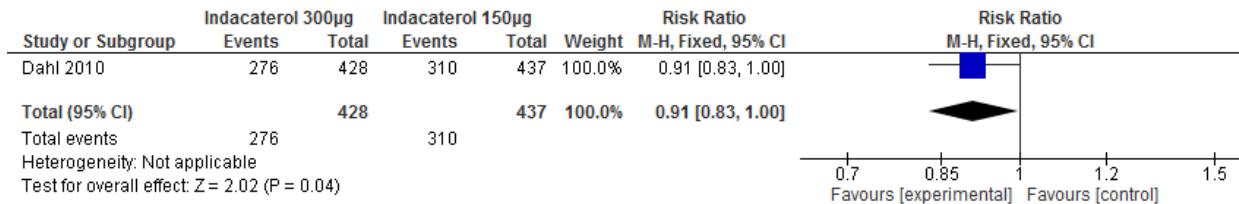
Outcome 6: Mean difference in TDI score is not reported

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

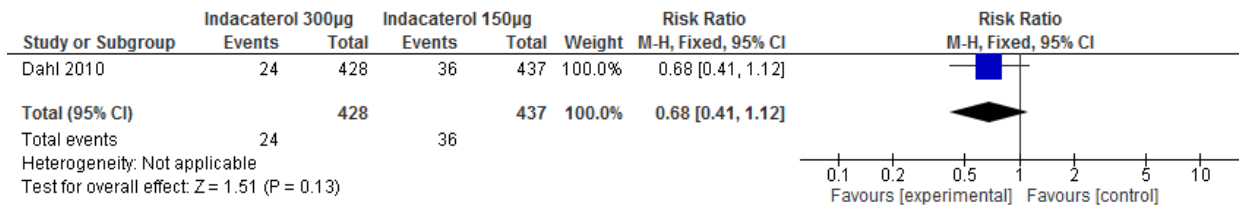
Outcome 8: Total withdrawals



Outcome 9: Total Adverse Events



Outcome 10: Withdrawal due to Adverse Events



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)	No 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}	

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)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	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}	

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)	No 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.