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Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis (Review)

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[Intervention Review]

Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis

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ABSTRACT

Background

Current guidelines recommend a higher-dose inhaled corticosteroids (ICS) or adding a long-acting muscarinic antagonist (LAMA) when asthma is not controlled with medium-dose (MD) ICS/long-acting beta2-agonist (LABA) combination therapy.

Objectives

To assess the effectiveness and safety of dual (ICS/LABA) and triple therapies (ICS/LABA/LAMA) compared with each other and with varying doses of ICS in adolescents and adults with uncontrolled asthma.

Search methods

We searched multiple databases for pre-registered randomised controlled trials (RCTs) of at least 12 weeks of study duration from 2008 to 18 February 2022.

Selection criteria

We searched studies, including adolescents and adults with uncontrolled asthma who had been treated with, or were eligible for, MD-ICS/LABA, comparing dual and triple therapies. We excluded cluster- and cross-over RCTs.

Data collection and analysis

We conducted a systematic review and network meta-analysis according to the previously published protocol. We used Cochrane's Screen4ME workflow to assess search results and Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of evidence. The primary outcome was steroid-requiring asthma exacerbations and asthma-related hospitalisations (moderate to severe and severe exacerbations).

Main results

We included 17,161 patients with uncontrolled asthma from 17 studies (median duration 26 weeks; mean age 49.1 years; male 40%; white 81%; mean forced expiratory volume in 1 second (MEF 1)1.9 litres and 61% predicted). The quality of included studies was generally good except for some outcomes in a few studies due to high attrition rates.

Medium-dose (MD) and high-dose (HD) triple therapies reduce steroid-requiring asthma exacerbations (hazard ratio (HR) 0.84 [95% credible interval (CrI) 0.71 to 0.99] and 0.69 [0.58 to 0.82], respectively) (high-certainty evidence), but not asthma-related hospitalisations, compared to MD-ICS/LABA.

High-dose triple therapy likely reduces steroid-requiring asthma exacerbations compared to MD triple therapy (HR 0.83 [95% CrI 0.69 to 0.996], [moderate certainty]). Subgroup analyses suggest the reduction in steroid-requiring exacerbations associated with triple therapies may be only for those with a history of asthma exacerbations in the previous year but not for those without.

High-dose triple therapy, but not MD triple, results in a reduction in all-cause adverse events (AEs) and likely reduces dropouts due to AEs compared to MD-ICS/LABA (odds ratio (OR) 0.79 [95% CrI 0.69 to 0.90], [high certainty] and 0.50 [95% CrI 0.30 to 0.84], [moderate certainty], respectively). Triple therapy results in little to no difference in all-cause or asthma-related serious adverse events (SAEs) compared to dual therapy (high certainty).

The evidence suggests triple therapy results in little or no clinically important difference in symptoms or quality of life compared to dual therapy considering the minimal clinically important differences (MCIDs) and HD-ICS/LABA is unlikely to result in any significant benefit or harm compared to MD-ICS/LABA.

Authors' conclusions

Medium-dose and HD triple therapies reduce steroid-requiring asthma exacerbations, but not asthma-related hospitalisations, compared to MD-ICS/LABA especially in those with a history of asthma exacerbations in the previous year. High-dose triple therapy is likely superior to MD triple therapy in reducing steroid-requiring asthma exacerbations.

Triple therapy is unlikely to result in clinically meaningful improvement in symptoms or quality of life compared to dual therapy considering the MCIDs.

High-dose triple therapy, but not MD triple, results in a reduction in all-cause AEs and likely reduces dropouts due to AEs compared to MD-ICS/LABA. Triple therapy results in little to no difference in all-cause or asthma-related SAEs compared to dual therapy.

HD-ICS/LABA is unlikely to result in any significant benefit or harm compared to MD-ICS/LABA, although long-term safety of higher rather than MD-

ICS remains to be demonstrated given the median duration of included studies was six months.

The above findings may assist deciding on a treatment option when asthma is not controlled with MD-ICS/LABA.

PLAIN LANGUAGE SUMMARY

What is triple inhaled therapy, when is it used, and what does it do in asthma?

How are inhalers used for the management of asthma?

Management of asthma involves a series of stepwise therapies depending on the severity of the disease. Initial therapy typically starts with as needed short-acting inhaler therapy (step 1), and a daily low- to medium-dose inhaled steroids is added for better asthma control when needed (step 2). Subsequently, a bronchodilator known as long-acting beta$_2$-agonist (LABA), which causes the passages of the airways to expand and relax so that breathing difficulty is reduced, is typically added to inhaled steroids if needed (steps 3 and 4).

What are the options when asthma is not controlled with a combination of inhaled steroids and LABA?

Current guidelines recommend a higher-dose of inhaled steroids or adding another bronchodilator known as long-acting muscarinic antagonist (LAMA), (i.e. triple inhaled therapy) (step 5), when asthma is not controlled with medium-dose inhaled steroids and LABA dual inhaled therapy.

How did we answer the question?

We collected and analysed data from 17 studies, including a total of 17,161 adolescents and adults with uncontrolled asthma, using a special method called a network meta-analysis, which enabled us to simultaneously compare multiple inhaler groups.

What did we find?

Triple inhaled therapy (i.e, inhaled steroids + LABA + LAMA) reduces asthma flare-ups, but not asthma-related hospitalisations. High-dose triple therapy, not medium-dose triple, is likely to be better tolerated due to less side effects compared to dual inhaled therapy (i.e. inhaled steroids + LABA).

Triple therapy may improve symptom and quality of life scores compared to dual therapy but not enough to be perceived by those being on it.

Higher than medium-dose inhaled steroids in dual inhaled therapy are unlikely to result in any additional benefit or harm.

Conclusions

Triple inhaled therapy, especially high-dose formulations, reduces asthma flare-ups and is likely to be better tolerated due to less side effects compared to dual therapy.

Triple inhaled therapy may or may not to improve symptoms or quality of life compared to dual therapy.

Increasing the strength of inhaled steroids from medium to high dose is likely beneficial in triple inhaled therapy but probably not in dual therapy.

Immuno modulators, which are injectable medications, or other options may be considered if asthma symptoms are not well controlled or for those requiring asthma-related hospitalisations despite being on medium-dose dual inhaled therapy.

SUMMARY OF FINDINGS

Summary of findings 1. NMA Summary of Findings for severe exacerbations (asthma-related hospitalisations)

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Severe exacerbations

Setting(s): Outpatient

Geometry of the Network in Figure 1*

Total studies: 8 RCTs **Total Participants**: 9983	**Hazard ratio**** **(95% CrI)**	**Anticipated absolute effect at the end of 1 year***(95% CrI)		**Certainty of the evidence**	**Ranking****** **(95% CrI)**	**Interpretation of Findings**
		With intervention ***(With MD-ICS/LABA)***	**Difference**			
HD-ICS/LABA (Direct evidence; 7 RCTs; 7023 participants)	**1.43** (0.76 to 2.77)	15 per 1000	5 per 1000 more (from 2 fewer to 18 more)	⊕⊕⊕◯ **Moderate** Due to substantial heterogeneity[1]	**3.0** (1.0 to 4.0)	Probably little or no difference
MD-TRIPLE (Direct evidence; 2 RCTs; 1023 participants)	**1.73** (0.90 to 3.32)	18 per 1000	8 per 1000 more (from 1 fewer to 24 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**4.0** (1.0 to 4.0)	Suggest little or no difference
HD-TRIPLE (Direct evidence; 2 RCTs; 1024 participants)	**1.14** (0.54 to 2.41)	12 per 1000	2 per 1000 more (from 4 fewer to 15 more)	⊕⊕◯◯ **Low** Due to imprecision[2]	**2.0** (1.0 to 4.0)	Suggest little or no difference
MD-ICS/LABA	Reference Comparator	(10 per 1000)[3]	Reference Comparator	Reference Comparator	**1.0** (1.0 to 3.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted.

** Network Meta-Analysis estimates are reported as hazard ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect (exacerbation rate at 1 year). Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the 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

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Explanatory Footnotes

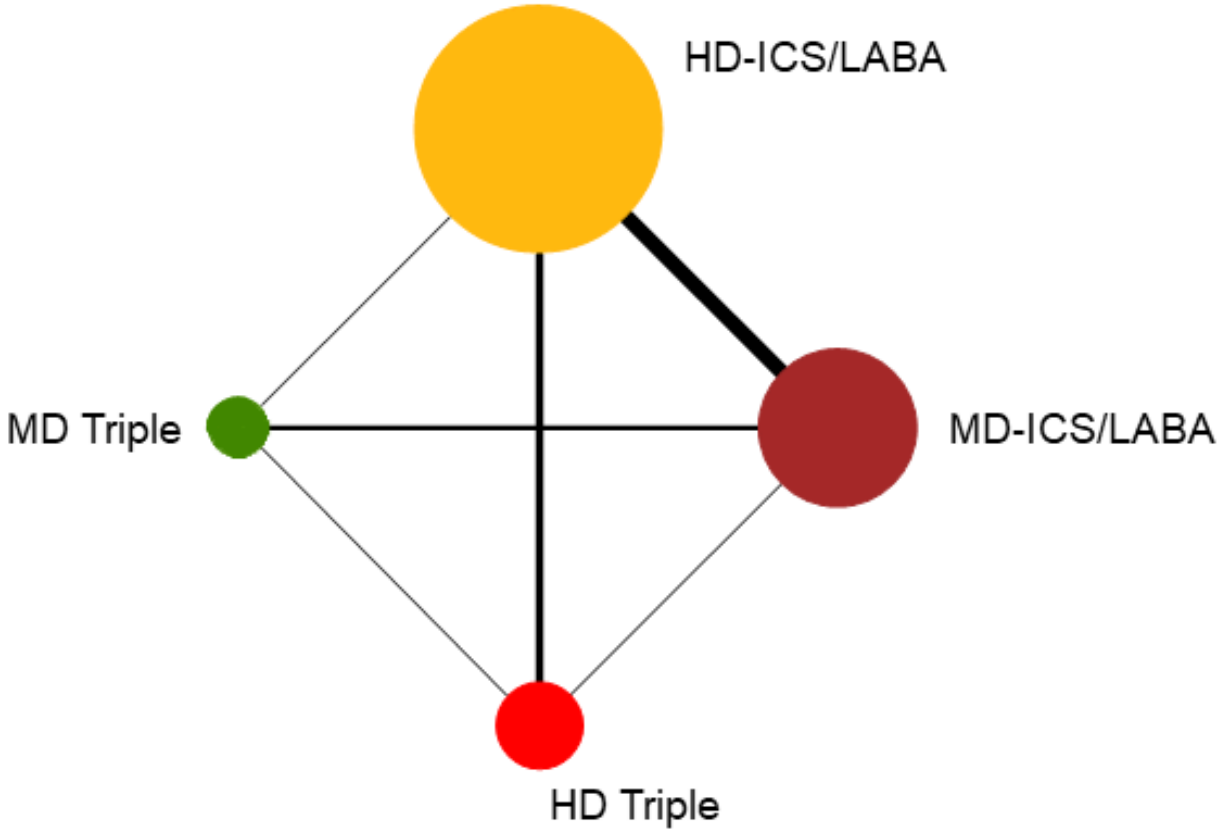
[1] Substantial heterogeneity I^2>= 50% to 90% in the direct pairwise comparison.

[2] Very serious imprecision. Due to wide confidence intervals and suboptimal sample sizes in the direct and/or indirect estimate(s).

[3] Based on the average rate in patients treated with MD-ICS/LABA in the included studies.

CrI: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA:** long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 1. Network diagram for severe exacerbations for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 2. Asthma exacerbations - pairwise comparisons

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence	What happens
		With active control	With experimental comparator	Difference		

Severe exacerbations - HD-ICA/LABA vs MD-ICS LABA № of participants: 4492 (5 RCTs) Follow up: 3 to 12 months	**RR 1.49** (0.74 to 3.01)	0.8%	**1.1%** (0.6 to 2.3)	**0.4% more** (0.2 fewer to 1.5 more)	⨁⨁⨁◯ Moderate[a]	HD-ICA/LABA likely results in little to no difference in severe exacerbations compared to MD-ICS LABA.
Severe exacerbations - MD TRIPLE vs MD-ICS/LABA № of participants: 813 (1 RCT) Follow up: 12 months	**RR 1.00** (0.35 to 2.83)	1.7%	**1.7%** (0.6 to 4.9)	**0.0% fewer** (1.1 fewer to 3.1 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD TRIPLE results in little to no difference in severe exacerbations compared to MD-ICS/LABA.
Severe exacerbations - HD TRIPLE vs MD-ICS/LABA № of participants: 815 (1 RCT) Follow up: 12 months	**RR 0.57** (0.17 to 1.93)	1.7%	**1.0%** (0.3 to 3.3)	**0.7% fewer** (1.4 fewer to 1.6 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that HD TRIPLE results in little to no difference in severe exacerbations compared to MD-ICS/LABA.
Severe exacerbations - MD TRIPLE vs HD-ICS/LABA № of participants: 812 (1 RCT) Follow up: 12 months	**RR 1.40** (0.45 to 4.37)	1.2%	**1.7%** (0.6 to 5.4)	**0.5% more** (0.7 fewer to 4.2 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that MD TRIPLE results in little to no difference in severe exacerbations compared to HD-ICS/LABA.
Severe exacerbations - HD TRIPLE vs HD-ICS/LABA № of participants: 1727 (2 RCTs) Follow up: 12 months	**RR 0.80** (0.45 to 1.42)	2.9%	**2.3%** (1.3 to 4.1)	**0.6% fewer** (1.6 fewer to 1.2 more)	⨁⨁⨁◯ Moderate[b]	HD TRIPLE likely results in little to no difference in severe exacerbations compared to HD-ICS LABA.
Severe exacerbations - HD TRIPLE vs MD TRIPLE № of participants: 814 (1 RCT) Follow up: 12 months	**RR 0.57** (0.17 to 1.93)	1.7%	**1.0%** (0.3 to 3.3)	**0.7% fewer** (1.4 fewer to 1.6 more)	⨁⨁◯◯ Low[b, c]	The evidence suggests that HD TRIPLE results in little to no difference in severe exacerbations compared to MD TRIPLE.
Severe exacerbations - TRIPLE vs DUAL № of participants: 2540 (2 RCTs)	**RR 0.84** (0.51 to 1.40)	2.5%	**2.1%** (1.3 to 3.5)	**0.4% fewer** (1.2 fewer to 1 more)	⨁⨁⨁◯ Moderate[d]	TRIPLE likely results in little to no difference in severe exacerbations compared to DUAL.

Follow up: 12 months						
Moderate to severe exacerbations - HD-ICS/LABA vs MD-ICS/LABA № of participants: 5452 (6 RCTs) Follow up: 3 to 12 months	**RR 0.93** (0.82 to 1.05)	15.0%	**14.0%** (12.3 to 15.8)	**1.1% fewer** (2.7 fewer to 0.8 more)	⊕⊕⊕⊕ High	HD-ICS/LABA results in little to no difference in moderate to severe exacerbations compared to MD-ICS/LABA.
Moderate to severe exacerbations - MD TRIPLE vs MD-ICS/LABA № of participants: 3184 (3 RCTs) Follow up: 12 months	**RR 0.86** (0.75 to 0.99)	22.8%	**19.6%** (17.1 to 22.6)	**3.2% fewer** (5.7 fewer to 0.2 fewer)	⊕⊕⊕○ Moderate[b]	MD TRIPLE likely reduces moderate to severe exacerbations compared to MD-ICS/LABA.
Moderate to severe exacerbations - HD TRIPLE vs MD-ICS/LABA № of participants: 2037 (2 RCTs) Follow up: 12 months	**RR 0.78** (0.66 to 0.92)	24.0%	**18.7%** (15.8 to 22)	**5.3% fewer** (8.1 fewer to 1.9 fewer)	⊕⊕⊕⊕ High	HD TRIPLE reduces moderate to severe exacerbations compared to MD-ICS/LABA.
Moderate to severe exacerbations - MD TRIPLE vs HD-ICS/LABA № of participants: 2651 (2 RCTs) Follow up: 12 months	**RR 1.05** (0.78 to 1.41)	23.4%	**24.6%** (18.2 to 33)	**1.2% more** (5.1 fewer to 9.6 more)	⊕⊕○○ Low[a, d]	MD TRIPLE may result in little to no difference in moderate to severe exacerbations compared to HD-ICS/LABA.
Moderate to severe exacerbations - HD TRIPLE vs HD-ICS/LABA № of participants: 4989 (4 RCTs) Follow up: 12 months	**RR 0.83** (0.75 to 0.92)	25.2%	**20.9%** (18.9 to 23.2)	**4.3% fewer** (6.3 fewer to 2 fewer)	⊕⊕⊕⊕ High	HD TRIPLE reduces moderate to severe exacerbations compared to HD-ICS/LABA.
Moderate to severe exacerbations - HD TRIPLE vs MD TRIPLE № of participants: 3470 (3 RCTs) Follow up: 6 to 12 months	**RR 0.85** (0.72 to 1.01)	15.2%	**12.9%** (10.9 to 15.3)	**2.3% fewer** (4.2 fewer to 0.2 more)	⊕⊕⊕○ Moderate[e]	HD TRIPLE likely results in a slight reduction in moderate to severe exacerbations compared to MD TRIPLE.
Moderate to severe exacerbations - TRIPLE vs DUAL № of participants: 8173	**RR 0.85** (0.78 to 0.92)	24.3%	**20.6%** (18.9 to 22.3)	**3.6% fewer** (5.3 fewer to 1.9 fewer)	⊕⊕⊕⊕ High	TRIPLE reduces moderate to severe exacerbations compared to DUAL.

(5 RCTs)

Follow up: 12 months

*__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).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Substantial heterogeneity I2 ≥ 50% to 90%

b. Optimal information size is not met (Guyatt 2011b)

c. Total size of less than 1000 participants may suggest small study effect (Dechartres 2013)

d. Confidence interval includes a clinically important difference.

e. Confidence interval includes the null effect.

CI: confidence interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **RCT**: randomised controlled trial; **RR:** risk ratio.

Summary of findings 3. NMA Summary of Findings for moderate to severe (steroid-requiring) exacerbations

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Moderate to severe exacerbations

Setting(s): Outpatient

Geometry of the Network in Figure 2*****

Total studies: 10 RCTs **Total Participants**: 12407	**Hazard ratio**** **(95% CrI)**	**Anticipated absolute effect at the end of 1 year***(95% CrI)**		**Certainty of the evidence**	**Ranking****** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			

HD-ICS/LABA (Direct evidence; 6 RCTs; 5452 participants)	**0.90** (0.77 to 1.04)	176 per 1000	20 per 1000 fewer (from 45 fewer to 8 more)	⊕⊕⊕⊕ **High**	**3.0** (2.0 to 4.0)	Little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3184 participants)	**0.84** (0.71 to 0.99)	165 per 1000	31 per 1000 fewer (from 2 fewer to 57 fewer)	⊕⊕⊕○ **Moderate** Due to imprecision[1]	**2.0** (2.0 to 3.0)	Probably superior
HD-TRIPLE (Direct evidence; 2 RCTs; 2037 participants)	**0.69** (0.58 to 0.82)	135 per 1000	61 per 1000 fewer (from 35 fewer to 82 fewer)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 1.0)	Superior
MD-ICS/LABA	Reference Comparator	196 per 1000[2]	Reference Comparator	Reference Comparator	**4.0** (3.0 to 4.0)	Reference Comparator
HD Triple vs. MD Triple						
HD-TRIPLE (Direct evidence; 3 RCTs; 3470 participants)	**0.83** (0.69 to 0.996)	162 per 1000	34 per 1000 fewer (from 1 fewer to 61 fewer)	⊕⊕⊕○ **Moderate** Due to imprecision[1]	NA	Probably superior
MD Triple	Reference Comparator	196 per 1000[3]	Reference Comparator	Reference Comparator	NA	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as hazard ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect (exacerbation rate at 1 year). Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

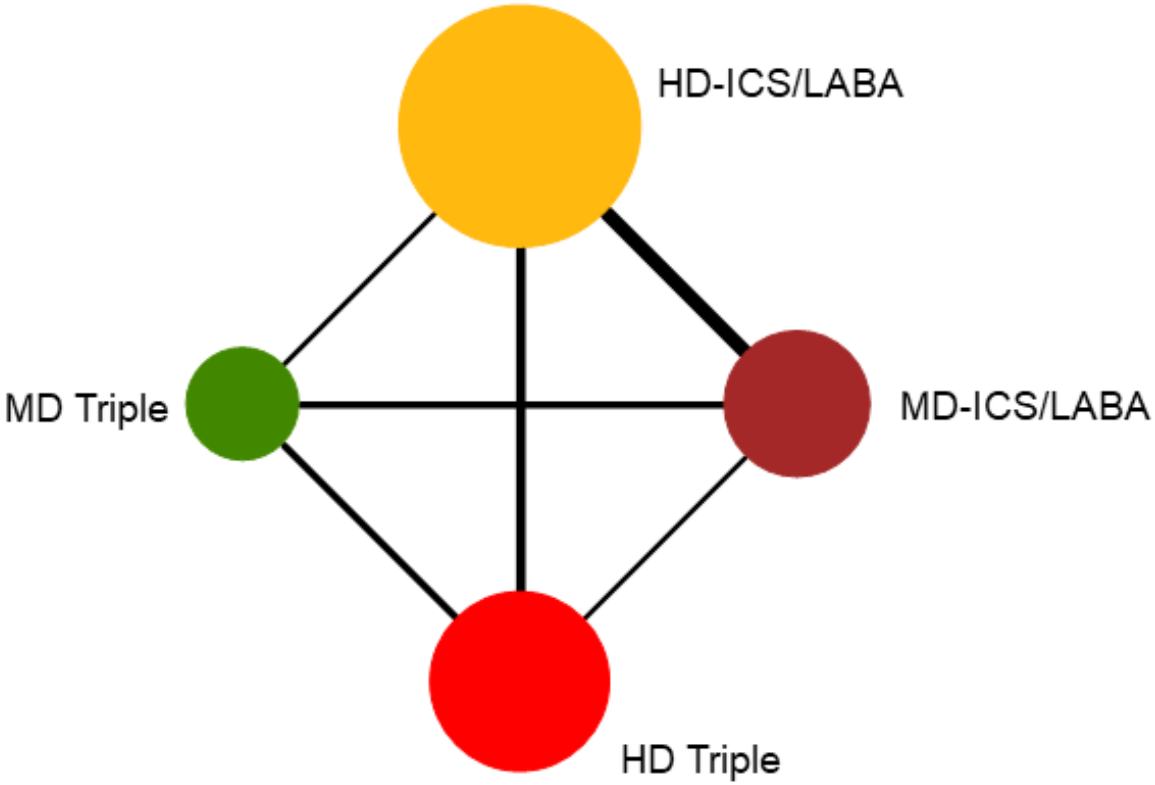
[1] Serious imprecision. Due to suboptimal sample size(s) in the direct and/or indirect estimate(s).

[2] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

[3] Based on the average rate in participants treated with MD Triple in the included studies.

CrI: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta-2 agonist; **MD**: medium dose; **NA**: not applicable; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 2. Network diagram for moderate to severe exacerbations for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 4. NMA Summary of Findings for change from baseline in ACQ scores at 3 months

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Change from baseline in ACQ scores at 3 months

Geometry of the Network in Figure 3*****

Setting(s): Outpatient

Total studies: 4 RCTs **Total Participants**: 4529	**Relative effect** **(95% CrI)**	**Anticipated absolute effect**(95% CrI)**		**Certainty of the evidence**	**Ranking***** **(95% CrI)**	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA*[1]**			
HD-ICS/LABA (Direct evidence; 3 RCTs; 2450 participants)	**0.01** (-0.05 to 0.07)	**0.72** (0.67 to 0.78)	Change from baseline in ACQ score was 0.01 lower (0.07 lower to 0.05 higher)	⨁⨁⨁◯ **Moderate** Due to imprecision[2]	**4.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[4]
MD-TRIPLE (Direct evidence; 1 RCT; 768 participants)	**-0.06** (-0.14 to 0.03)	**0.78** (0.70 to 0.87)	Change from baseline in ACQ score was 0.06 higher (0.03 lower to 0.14 higher)	⨁⨁◯◯ **Low** Due to imprecision[3]	**2.0** (1.0 to 4.0)	Suggest little or no clinically meaningful difference[4]
HD-TRIPLE (Direct evidence; 1 RCT; 764 participants)	**-0.09** (-0.18 to - 0.01)	**0.82** (0.74 to 0.90)	Change from baseline in ACQ score was 0.09 higher (0.01 higher to 0.18 higher)	⨁⨁◯◯ **Low** Due to imprecision[3]	**1.0** (1.0 to 2.0)	Suggest little or no clinically meaningful difference[4]
MD-ICS/LABA	Reference Comparator[1]	**0.72**	Reference Comparator	Reference Comparator	**3.0** (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The mean change from baseline in ACQ scores was 0.72with MD-ICS/LABA.

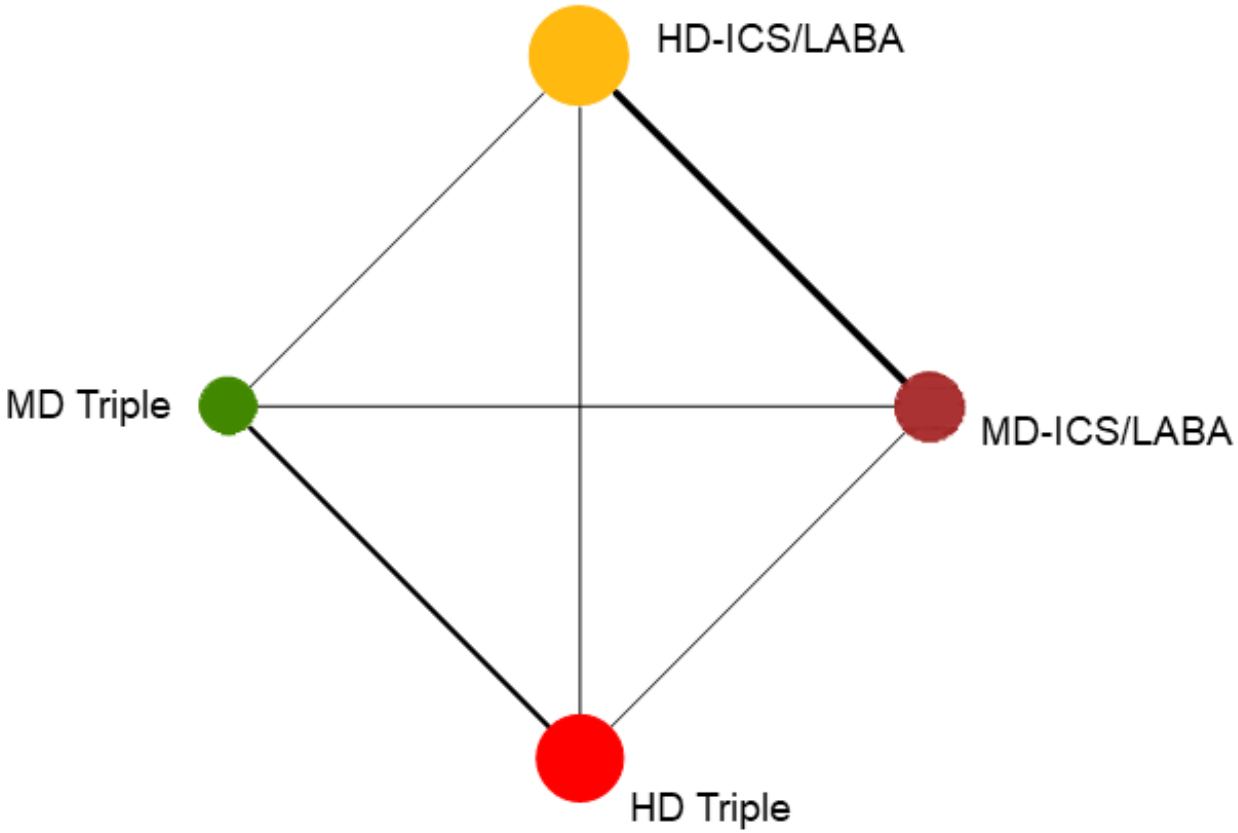
[2] Serious imprecision. Due to small sample sizes in the direct and/or indirect estimate(s).

[3] Very serious imprecision. Due to very small sample sizes in the direct and/or indirect estimate(s).

[4] Minimal clinically important difference is 0.5.

ACQ: Asthma Control Questionnaire; **CrI:** credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta-2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 3. Network diagram for change from baseline ACQ score at 3 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 5. NMA Summary of Findings for change from baseline in ACQ scores at 6 months

Patient or population: Adolescents and adults with symptomatic asthma

Geometry of the Network in Figure 4*

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Change from baseline in ACQ scores at 6 months

Setting(s): Outpatient

Total studies: 6 RCTs **Total Participants**: 7957	**Relative effect** **(95% CrI)**	**Anticipated absolute effect**(95% CrI)**		**Certainty of the evidence**	**Ranking***** **(95% CrI)**	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA[1]***			
HD-ICS/LABA (Direct evidence; 3 RCTs; 3762 participants)	**-0.03** (-0.09 to 0.02)	**0.90** (0.84 to 0.95)	Change from baseline in ACQ score was 0.03 higher (0.02 lower to 0.09 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**3.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
MD-TRIPLE (Direct evidence; 2 RCTs; 1961 participants)	**-0.07** (-0.13 to 0.00)	**0.93** (0.86 to 1.00)	Change from baseline in ACQ score was 0.07 higher (0.00 lower to 0.13 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**2.0** (1.0 to 3.0)	Probably little or no clinically meaningful difference[3]
HD-TRIPLE (Direct evidence; 2 RCTs; 1952 participants)	**-0.10** (-0.16 to -0.03)	**0.96** (0.90 to 1.02)	Change from baseline in ACQ score was 0.1 higher (0.03 higher to 0.16 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**1.0** (1.0 to 2.0)	Probably little or no clinically meaningful difference[3]
MD-ICS/LABA	Reference Comparator[1]	**0.86**	Reference Comparator	Reference Comparator	**4.0** (3.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

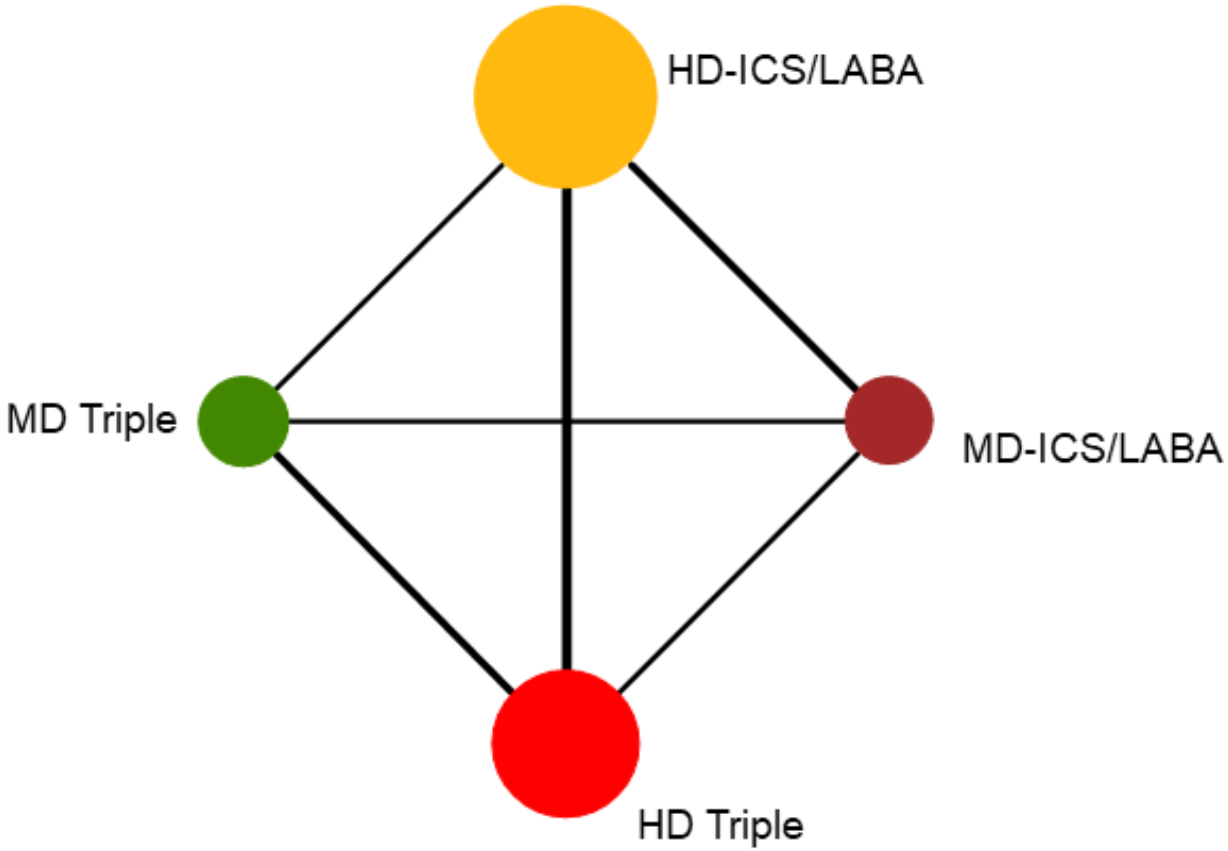
[1] The mean change from baseline in ACQ scores was 0.86 with MD-ICS/LABA.

[2] Serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).

[3] Minimal clinically important difference is 0.5.

ACQ: Asthma Control Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 4. Network diagram for change from baseline ACQ score at 6 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 6. NMA Summary of Findings for change from baseline in ACQ scores at 12 months

Patient or population: Adolescents and adults with symptomatic asthma	**Geometry of the Network in** Figure 5*
Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE	
Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)	
Outcome: Change from baseline in ACQ scores at 12 months	

Setting(s): Outpatient

Total studies: 5 RCTs **Total Participants**: 5440	**Relative effect** **(95% CrI)**	**Anticipated absolute effect**(95% CrI)**		**Certainty of the evidence**	**Ranking***** **(95% CrI)**	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA[1]***			
HD-ICS/LABA (Direct evidence; 3 RCTs; 3152 participants)	**0.00** (-0.06 to 0.06)	**1.00** (0.94 to 1.06)	Change from baseline in ACQ score was 0.00 (0.06 lower to 0.06 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**3.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
MD-TRIPLE (Direct evidence; 2 RCTs; 1366 participants)	**0.02** (-0.07 to 0.11)	**0.98** (0.89 to 1.07)	Change from baseline in ACQ score was 0.08 higher (0.01 lower to 0.17 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**4.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
HD-TRIPLE (Direct evidence; 2 RCTs; 1379 participants)	**-0.08** (-0.16 to 0.00)	**1.08** (1.00 to 1.16)	Change from baseline in ACQ score was 0.08 higher (0.00 lower to 0.16 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**1.0** (1.0 to 2.0)	Probably little or no clinically meaningful difference[3]
MD-ICS/LABA	Reference Comparator[1]	**1.00**	Reference Comparator	Reference Comparator	**3.0** (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

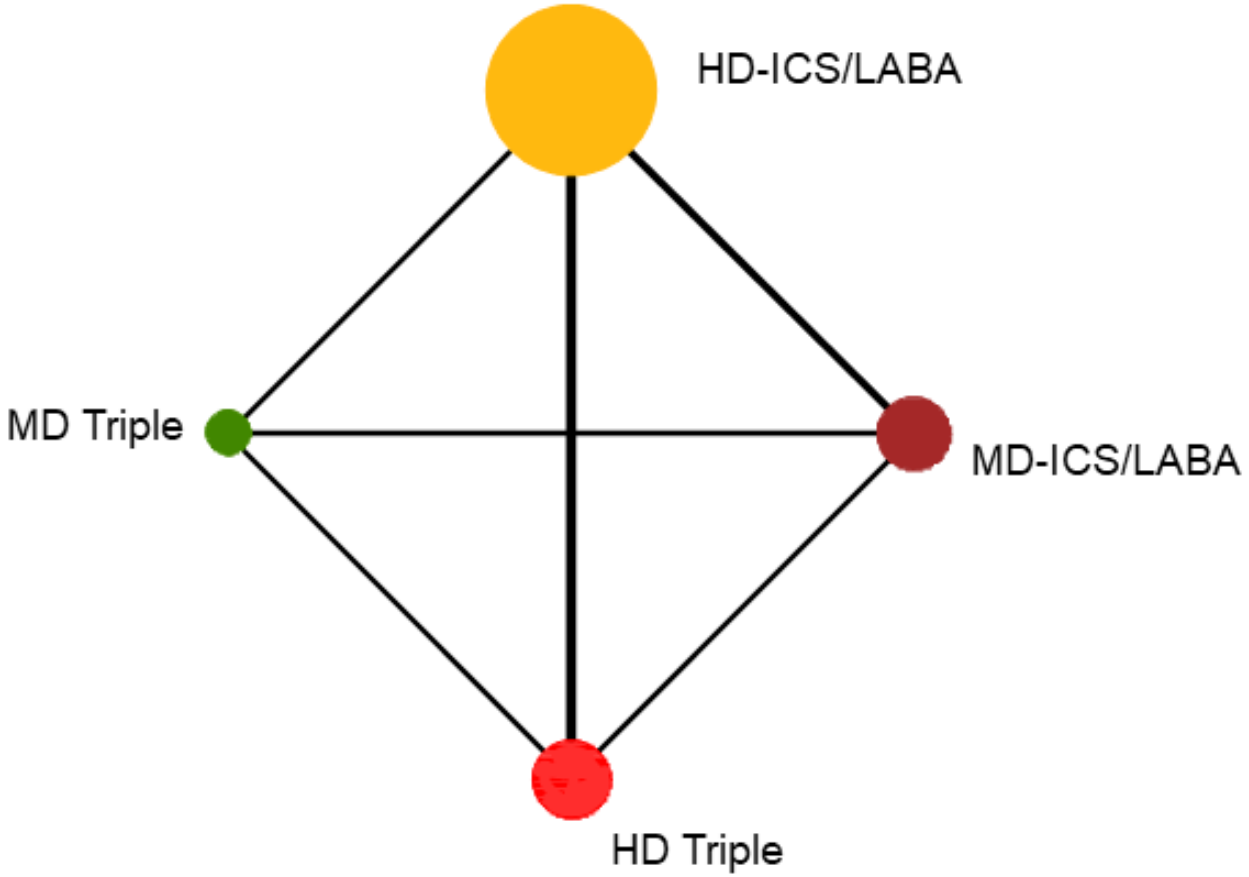
[1] The mean change from baseline in ACQ scores was 1.00with MD-ICS/LABA.

[2] Serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).

[3] Minimal clinically important difference is 0.5.

ACQ: Asthma Control Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 5. Network diagram for change from baseline ACQ score at 12 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 7. Asthma Control Questionnaire: change from baseline - pairwise comparisons ‡

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*		Certainty of the evidence	What happens†
		With active control	Difference		

CFB in ACQ at 3 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 2450 (3 RCTs)	-	-0.72	MD **0.01 higher** (0.05 lower to 0.07 higher)	⊕⊕⊕○ Moderate[a]	HD-ICS/LABA likely results in little to no difference in CFB in ACQ at 3 months compared to MD-ICS/LABA.
CFB in ACQ at 3 months - MD TRIPLE vs MD-ICS/LABA № of participants: 768 (1 RCT)	-	-0.58	MD **0.06 lower** (0.16 lower to 0.04 higher)	⊕⊕○○ Low[a, b]	The evidence suggests that MD TRIPLE results in little to no difference in CFB in ACQ at 3 months compared to MD-ICS/LABA.
CFB in ACQ at 3 months - HD TRIPLE vs MD-ICS/LABA № of participants: 764 (1 RCT)	-	-0.58	MD **0.12 lower** (0.22 lower to 0.02 lower)	⊕⊕○○ Low[a, b]	The evidence suggests that HD TRIPLE results in little to no difference in CFB in ACQ at 3 months compared to MD-ICS/LABA.
CFB in ACQ at 3 months - MD TRIPLE vs HD-ICS/LABA № of participants: 771 (1 RCT)	-	-0.61	MD **0.04 lower** (0.14 lower to 0.06 higher)	⊕⊕○○ Low[a, b]	The evidence suggests that MD TRIPLE results in little to no difference in CFB in ACQ at 3 months compared to HD-ICS/LABA.
CFB in ACQ at 3 months - HD TRIPLE vs HD-ICS/LABA № of participants: 767 (1 RCT)	-	-0.61	MD **0.09 lower** (0.19 lower to 0.01 higher)	⊕⊕○○ Low[a, b]	The evidence suggests that HD TRIPLE results in little to no difference in CFB in ACQ at 3 months compared to HD-ICS/LABA.
CFB in ACQ at 3 months - HD TRIPLE vs MD TRIPLE № of participants: 2079 (2 RCTs)	-	-0.85	MD **0.04 lower** (0.11 lower to 0.03 higher)	⊕⊕⊕○ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 3 months compared to MD TRIPLE.
CFB in ACQ at 3 months - TRIPLE vs DUAL № of participants: 1535 (1 RCT)	-	-0.59	MD **0.08 lower** (0.15 lower to 0.01 lower)	⊕⊕⊕○ Moderate[a]	TRIPLE likely results in little to no difference in CFB in ACQ at 3 months compared to DUAL.
CFB in ACQ at 6 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 3762 (3 RCTs)	-	-0.86	MD **0.04 lower** (0.12 lower to 0.04 higher)	⊕⊕⊕○ Moderate[c]	HD-ICS/LABA likely results in little to no difference in CFB in ACQ at 6 months compared to MD-ICS/LABA.
CFB in ACQ at 6 months - MD TRIPLE vs MD-ICS/LABA № of participants: 1961 (2 RCTs)	-	-0.79	MD **0.09 lower** (0.17 lower to 0.02 lower)	⊕⊕⊕○ Moderate[a]	MD TRIPLE likely results in little to no difference in CFB in ACQ at 6 months compared to MD-ICS/LABA.

CFB in ACQ at 6 months - HD TRIPLE vs MD-ICS/LABA № of participants: 1952 (2 RCTs)	-	-0.79	MD **0.11 lower** (0.18 lower to 0.04 lower)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 6 months compared to MD-ICS/LABA.
CFB in ACQ at 6 months - MD TRIPLE vs HD-ICS/LABA № of participants: 2561 (2 RCTs)	-	-0.91	MD **0.01 lower** (0.08 lower to 0.06 higher)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in CFB in ACQ at 6 months compared to HD-ICS/LABA.
CFB in ACQ at 6 months - HD TRIPLE vs HD-ICS/LABA № of participants: 3459 (3 RCTs)	-	-0.82	MD **0.06 lower** (0.15 lower to 0.03 higher)	⊕⊕◯◯ Low[a, c]	The evidence suggests that HD TRIPLE results in little to no difference in CFB in ACQ at 6 months compared to HD-ICS/LABA.
CFB in ACQ at 6 months - HD TRIPLE vs MD TRIPLE № of participants: 3288 (3 RCTs)	-	-0.94	MD **0.02 lower** (0.08 lower to 0.04 higher)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 6 months compared to MD-ICS/LABA.
CFB in ACQ at 6 months - TRIPLE vs DUAL № of participants: 5408 (4 RCTs)	-	-0.81	MD **0.07 lower** (0.14 lower to 0.01 lower)	⊕⊕⊕◯ Moderate[a]	TRIPLE likely results in little to no difference in CFB in ACQ at 6 months compared to DUAL.
CFB in ACQ at 12 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 3152 (3 RCTs)	-	-1.00	MD **0** (0.12 lower to 0.12 higher)	⊕⊕◯◯ Low[a, c, d]	The evidence suggests that HD-ICS/LABA results in little to no difference in CFB in ACQ at 12 months compared to MD-ICS/LABA.
CFB in ACQ at 12 months - MD TRIPLE vs MD-ICS/LABA № of participants: 1366 (2 RCTs)	-	-0.93	MD **0.01 lower** (0.11 lower to 0.08 higher)	⊕⊕⊕◯ Moderate[a, d]	MD TRIPLE likely results in little to no difference in CFB in ACQ at 12 months compared to MD-ICS/LABA.
CFB in ACQ at 12 months - HD TRIPLE vs MD-ICS/LABA № of participants: 1379 (2 RCTs)	-	-0.93	MD **0.09 lower** (0.23 lower to 0.06 higher)	⊕⊕⊕◯ Moderate[a, d]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 12 months compared to MD-ICS/LABA.
CFB in ACQ at 12 months - MD TRIPLE vs HD-ICS/LABA № of participants: 1967 (2 RCTs)	-	-1.03	MD **0.01 higher** (0.2 lower to 0.21 higher)	⊕⊕◯◯ Low[a, c, d]	The evidence suggests that MD TRIPLE results in little to no difference in CFB in ACQ at 12 months compared to HD-ICS/LABA.

CFB in ACQ at 12 months - HD TRIPLE vs HD-ICS/LABA № of participants: 2887 (3 RCTs)	-	-0.89	MD **0.07 lower** (0.15 lower to 0)	⊕⊕⊕○ Moderate[a, d]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 12 months compared to HD-ICS/LABA.
CFB in ACQ at 12 months - HD TRIPLE vs MD TRIPLE № of participants: 1381 (2 RCTs)	-	-0.94	MD **0.07 lower** (0.23 lower to 0.09 higher)	⊕⊕⊕○ Moderate[a, d]	HD TRIPLE likely results in little to no difference in CFB in ACQ at 12 months compared to MD TRIPLE.
CFB in ACQ at 12 months - DUAL vs TRIPLE № of participants: 4253 (4 RCTs)	-	-0.91	MD **0.04 lower** (0.1 lower to 0.02 higher)	⊕⊕⊕○ Moderate[a, d]	TRIPLE likely results in little to no difference in CFB in ACQ at 12 months compared to DUAL.

‡ ACQ scores range from 0 to 6 with lower scores indicating better asthma control.

*__The effect in the intervention group__ (and its 95% confidence interval) is based on the assumed effect in the comparison group and the **relative effect** of the intervention (and its 95% CI).
† Minimal Clinically Important Difference is 0.5

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Optimal information size is not met (Guyatt 2011b)

b. Total size of less than 1000 participants may suggest small study effect (Dechartres 2013)

c. Substantial heterogeneity I2 ≥ 50% to 90%

d. Lee 2020 had very high attrition rates and is considered at high risk of bias. However, excluding the study did not change the results.

ACQ:Asthma Control Questionnaire; **CFB**: change from baseline; **CI:** confidence interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD:** mean difference; **MD**: medium dose; **RCT**: randomised controlled trial.

Summary of findings 8. NMA Summary of Findings for change from baseline in AQLQ scores at 6 months

Patient or population: Adolescents and adults with symptomatic asthma

Geometry of the Network in Figure 6*

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Change from baseline in AQLQ score at 6 months

Setting(s): Outpatient

Total studies: 4 RCTs **Total Participants**: 3454	**Relative effect** (95% CrI)	**Anticipated absolute effect**(95% CrI)**		**Certainty of the evidence**	**Ranking*** (95% CrI)	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA*[1]**			
HD-ICS/LABA (Direct evidence; 1 RCT; 1223 participants)	**-0.06** (-0.14 to 0.03)	**0.71** (0.63 to 0.80)	Change from baseline in AQLQ score was 0.06 lower (0.14 lower to 0.03 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**4.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[4]
MD-TRIPLE (Direct evidence; 0 RCTs; 0 participants)	**0.03** (-0.23 to 0.29)	**0.80** (0.54 to 1.06)	Change from baseline in AQLQ score was 0.03 higher (0.23 lower to 0.29 higher)	⊕⊕◯◯ **Low** Due to imprecision[3]	**2.0** (1.0 to 4.0)	Suggest little or no clinically meaningful difference[4]
HD-TRIPLE (Direct evidence; 0 RCTs; 0 participants)	**0.11** (-0.09 to 0.30)	**0.88** (0.68 to 1.07)	Change from baseline in AQLQ score was 0.11 higher (0.09 lower to 0.30 higher)	⊕⊕◯◯ **Low** Due to imprecision[3]	**1.0** (1.0 to 3.0)	Suggest little or no clinically meaningful difference[4]
MD-ICS/LABA	Reference Comparator[1]	**0.77**	Reference Comparator	Reference Comparator	**3.0** (1.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted.

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] The mean change from baseline in AQLQ scores was 0.77 with MD-ICS/LABA.

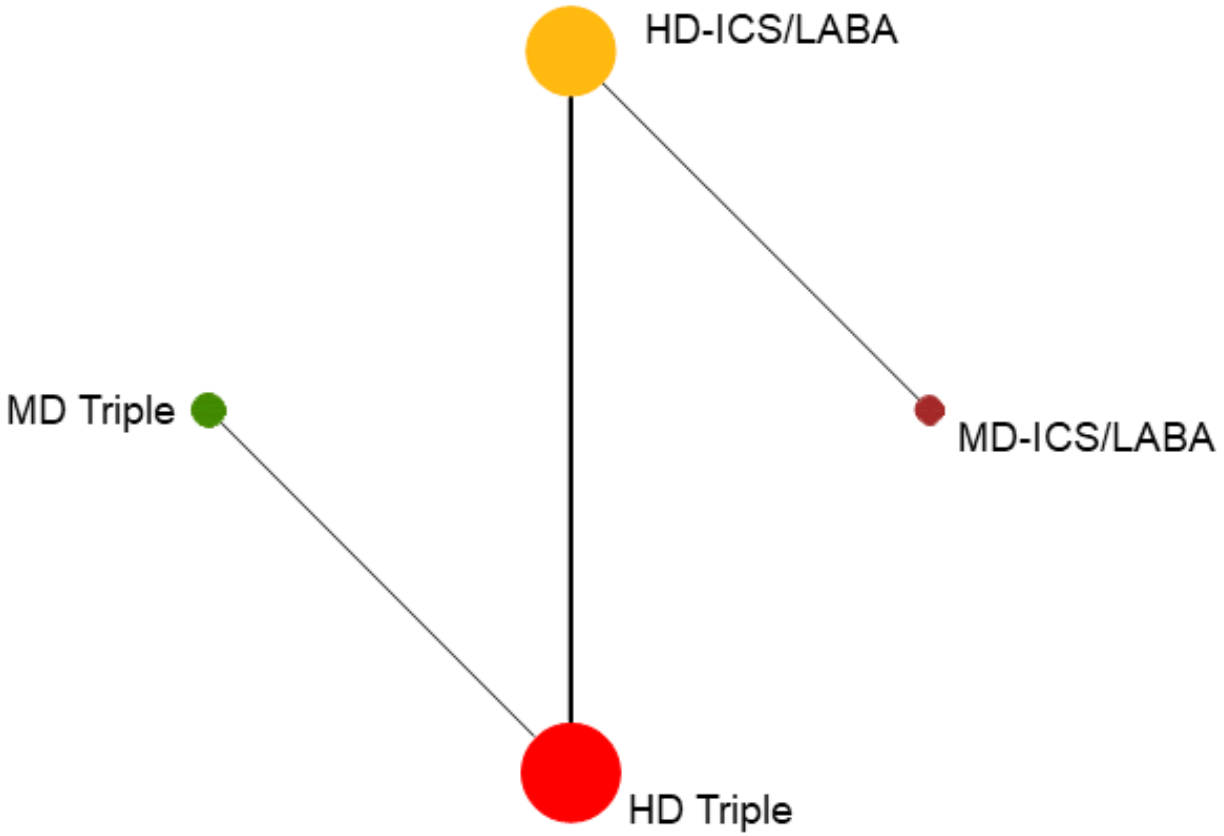
[2] Serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).

[3] Very serious imprecision due to very small sample sizes in the indirect estimate.

[4] Minimal clinically important difference is 0.5.

AQLQ: Asthma Quality of Life Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 6. Network diagram for change from baseline AQLQ scores at 6 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 9. NMA Summary of Findings for change from baseline in AQLQ scores at 12 months

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Change from baseline in AQLQ score at 12 months

Geometry of the Network in Figure 7*****

Setting(s): Outpatient

Total studies: 4 RCTs **Total Participants**: 4809	**Relative effect** **(95% CrI)**	**Anticipated absolute effect**(95% CrI)**		**Certainty of the evidence**	**Ranking***** **(95% CrI)**	**Interpretation of Findings**
		With intervention	***Difference compared to MD-ICS/LABA[1]***			
HD-ICS/LABA (Direct evidence; 2 RCTs; 2815 participants)	**-0.02** (-0.09 to 0.04)	**0.81** (0.74 to 0.87)	Change from baseline in AQLQ score was 0.02 lower (0.09 lower to 0.04 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**3.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
MD-TRIPLE (Direct evidence; 1 RCT; 1071 participants)	**-0.08** (-0.17 to 0.02)	**0.75** (0.66 to 0.85)	Change from baseline in AQLQ score was 0.08 lower (0.17 lower to 0.12 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**4.0** (2.0 to 4.0)	Probably little or no clinically meaningful difference[3]
HD-TRIPLE (Direct evidence; 1 RCT; 1088 participants)	**0.05** (-0.04 to 0.13)	**0.88** (0.79 to 0.13)	Change from baseline in AQLQ score was 0.05 higher (0.04 lower to 0.13 higher)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**1.0** (1.0 to 3.0)	Probably little or no clinically meaningful difference[3]
MD-ICS/LABA	Reference Comparator[1]	**0.83**	Reference Comparator	Reference Comparator	**2.0** (1.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Estimates are reported as mean difference and credible interval (CrI). Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Ranking and confidence intervals for efficacy outcome are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

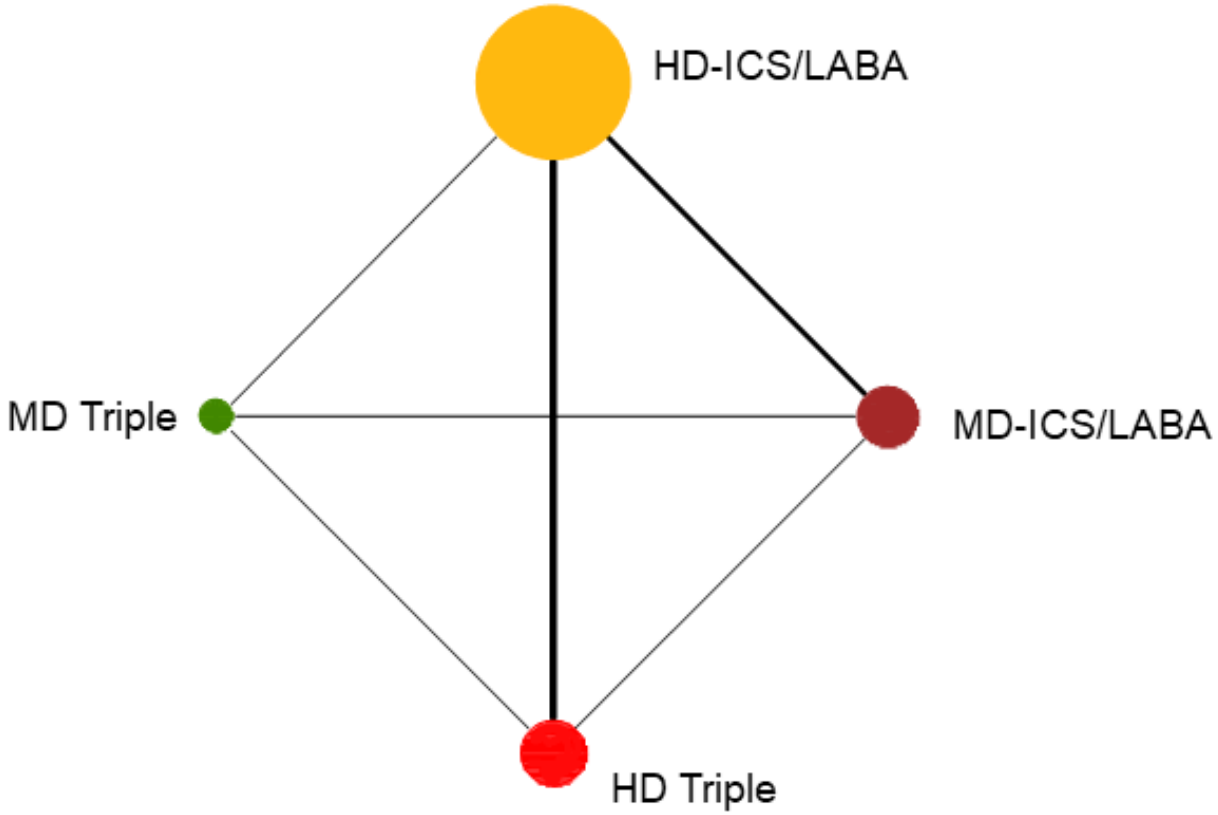
[1] The mean change from baseline in ACQ scores was 0.83 with MD-ICS/LABA.

[2] Serious imprecision due to small sample sizes in the direct and/or indirect estimate(s).

[3] Minimal clinically important difference is 0.5.

AQLQ: Asthma Quality of Life Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 7. Network diagram for change from baseline AQLQ scores at 12 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 10. Asthma Quality of Life Questionnaire: change from baseline - pairwise comparisons ‡

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)*		Certainty of the evidence	What happens†
		With active control	Difference		

CFB in AQLQ at 6 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 1223 (1 RCT)	-	0.77	MD **0.06 lower** (0.14 lower to 0.03 higher)	⊕⊕⊕◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in CFB in AQLQ at 6 months compared to MD-ICS/LABA.
CFB in AQLQ at 6 months - HD TRIPLE vs HD-ICS/LABA № of participants: 907 (2 RCTs)	- -	0.32 -	MD **0.16 higher** (0.01 lower to 0.34 higher)	⊕⊕◯◯ Low[a, b]	The evidence suggests that HD TRIPLE results in little to no difference in CFB in AQLQ at 6 months compared to HD-ICS/LABA.
CFB in AQLQ at 6 months - HD TRIPLE vs MD TRIPLE № of participants: 1426 (1 RCT)	-	0.71	MD **0.08 higher** (0.09 lower to 0.25 higher)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in AQLQ at 6 months compared to MD-ICS/LABA.
CFB in AQLQ at 6 months - TRIPLE vs DUAL № of participants: 907 (2 RCTs)	-	0.32	MD **0.16 higher** (0.01 lower to 0.34 higher)	⊕⊕◯◯ Low[a]	The evidence suggests that TRIPLE results in little to no difference in CFB in AQLQ at 6 months compared to DUAL.
CFB in AQLQ at 12 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 2815 (2 RCTs)	-	0.83	MD **0.02 lower** (0.08 lower to 0.04 higher)	⊕⊕⊕◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in CFB in AQLQ at 12 months compared to MD-ICS/LABA.
CFB in AQLQ at 12 months - MD TRIPLE vs MD-ICS/LABA № of participants: 1071 (1 RCT)	-	0.81	MD **0.05 lower** (0.15 lower to 0.05 higher)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in CFB in AQLQ at 12 months compared to MD-ICS/LABA.
CFB in AQLQ at 12 months - HD TRIPLE vs MD-ICS/LABA № of participants: 1088 (1 RCT)	-	0.81	MD **0.06 higher** (0.04 lower to 0.16 higher)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in AQLQ at 12 months compared to MD-ICS/LABA.
CFB in AQLQ at 12 months - MD TRIPLE vs HD-ICS/LABA № of participants: 1628 (1 RCT)	-	0.83	MD **0.07 lower** (0.16 lower to 0.02 higher)	⊕⊕⊕◯ Moderate[a]	HD-ICS/LABA likely results in little to no difference in CFB in AQLQ at 12 months compared to MD-ICS/LABA.
CFB in AQLQ at 12 months - HD TRIPLE vs HD-ICS/LABA № of participants: 2552 (3 RCTs)	-	0.70	MD **0.06 higher** (0.02 lower to 0.14 higher)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in CFB in AQLQ at 12 months compared to HD-ICS/LABA.

CFB in AQLQ at 12 months - HD TRIPLE vs MD TRIPLE № of participants: 1087 (1 RCT)	-	0.76	MD **0.11 higher** (0.01 higher to 0.21 higher)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in CFB in AQLQ at 12 months compared to MD TRIPLE.
CFB in AQLQ at 12 months - TRIPLE vs DUAL № of participants: 3623 (3 RCTs)	-	0.73	MD **0.01 higher** (0.05 lower to 0.07 higher)	⊕⊕⊕◯ Moderate[a]	TRIPLE likely results in little to no difference in CFB in AQLQ at 12 months compared to DUAL.

‡ AQLQ scores range from 1 to 7 with higher scores indicating better asthma control.

***The effect in the intervention group** (and its 95% confidence interval) is based on the assumed effect in the comparison group and the **relative effect** of the intervention (and its 95% CI).
† Minimal Clinically Important Difference is 0.5

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Optimal information size is not met (Guyatt 2011b)

b. Total size of less than 1000 participants may suggest small study effect (Dechartres 2013)

AQLQ: Asthma Quality of Life Questionnaire; **CFB**: change from baseline; **CI:** confidence interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD:** mean difference; **MD**: medium dose; **RCT**: randomised controlled trial.

Summary of findings 11. NMA Summary of Findings for ACQ responders at 6 months

Patient or population: Adolescents and adults with symptomatic asthma

Geometry of the Network in Figure 8*

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: ACQ responders at 6 months

Setting(s): Outpatient

Total studies: 7 RCTs **Total Participants**: 10453	**Risk ratio** **(95% CrI)**	**Anticipated absolute effect*** (95% CrI)**		**Certainty of the evidence**	**Ranking**** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			
HD-ICS/LABA (Direct evidence; 3 RCTs; 3700 participants)	**1.05** (0.92 to 1.20)	632 per 1000	12 per 1000 more (from 19 fewer to 43 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**3.0** (3.0 to 4.0)	Probably little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3063 participants)	**1.25** (1.09 to 1.44)	670 per 1000	50 per 1000 more (from 19 more to 81 more)	⊕⊕◯◯ **Low** Due to imprecision[1] and heterogeneity[2]	**1.0** (1.0 to 2.0)	Possibly superior
HD-TRIPLE (Direct evidence; 2 RCTs; 1916 participants)	**1.25** (1.07 to 1.45)	670 per 1000	50 per 1000 more (19 more to 81 more)	⊕⊕◯◯ **Low** Due to imprecision[1] and heterogeneity[2]	**2.0** (1.0 to 2.0)	Possibly superior
MD-ICS/LABA	Reference Comparator	620 per 1000[3]	Reference Comparator	Reference Comparator	**4.0** (3.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

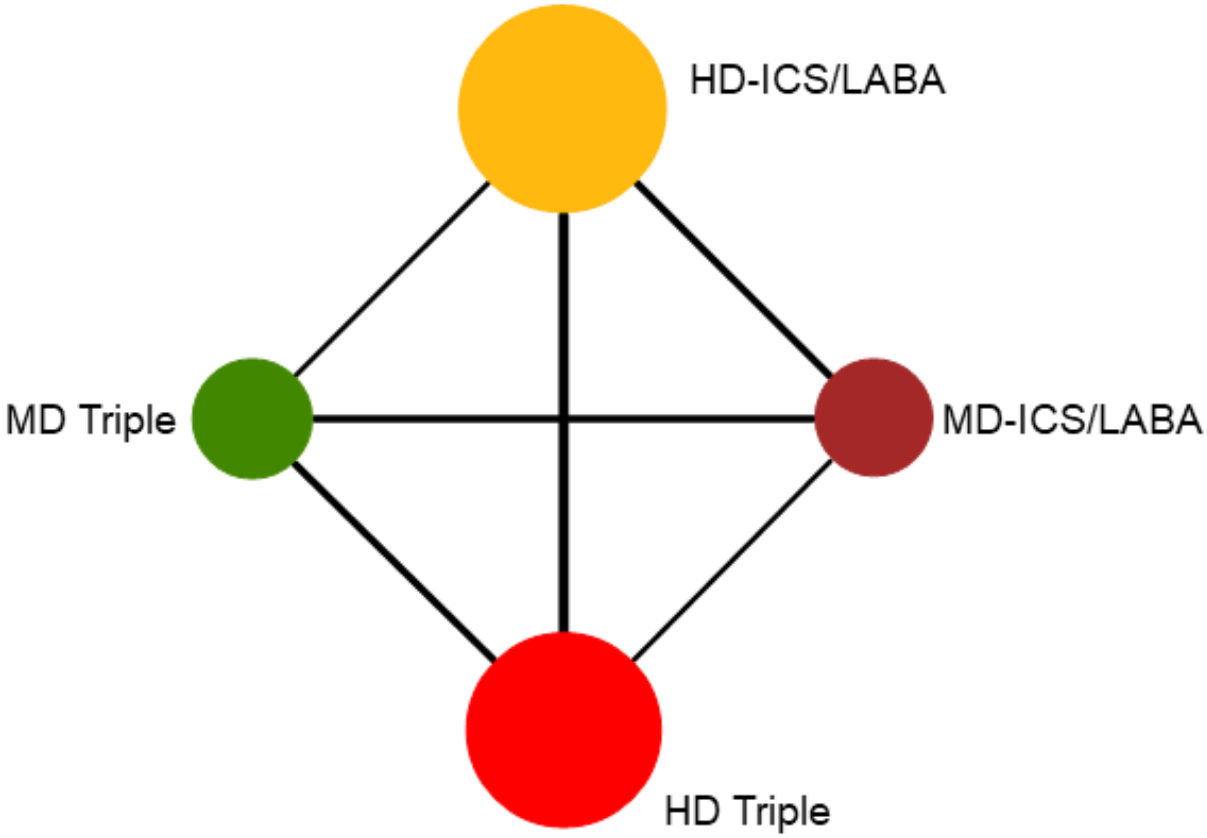
[1] Serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).

[2] Serious heterogeneity in the direct estimate.

[3] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

ACQ: Asthma Control Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 8. Network diagram for ACQ Responders at 6 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 12. NMA Summary of Findings for ACQ responders at 12 months

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: ACQ responders at 12 months

Geometry of the Network in Figure 9*****

Total studies: 5 RCTs **Total Participants**: 7391	**Risk ratio**** (95% CrI)	**Anticipated absolute effect***(95% CrI)**		**Certainty of the evidence**	**Ranking****** (95% CrI)	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			
HD-ICS/LABA (Direct evidence; 2 RCTs; 2817 participants)	**1.00** (0.94 to 1.05)	676 per 1000	0 per 1000 fewer (from 41 fewer to 30 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**3.0** (2.0 to 4.0)	Probably little or no difference
MD-TRIPLE (Direct evidence; 2 RCTs; 2237 participants)	**0.99** (0.94 to 1.05)	669 per 1000	7 per 1000 more (from 41 fewer to 34 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**3.0** (2.0 to 4.0)	Probably little or no difference
HD-TRIPLE (Direct evidence; 1 RCT; 1088 participants)	**1.08** (1.02 to 1.14)	730 per 1000	54 per 1000 more (14 more to 95 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[2]	**1.0** (1.0 to 1.0)	Probably superior
MD-ICS/LABA	Reference Comparator	676 per 1000[3]	Reference Comparator	Reference Comparator	**3.0** (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

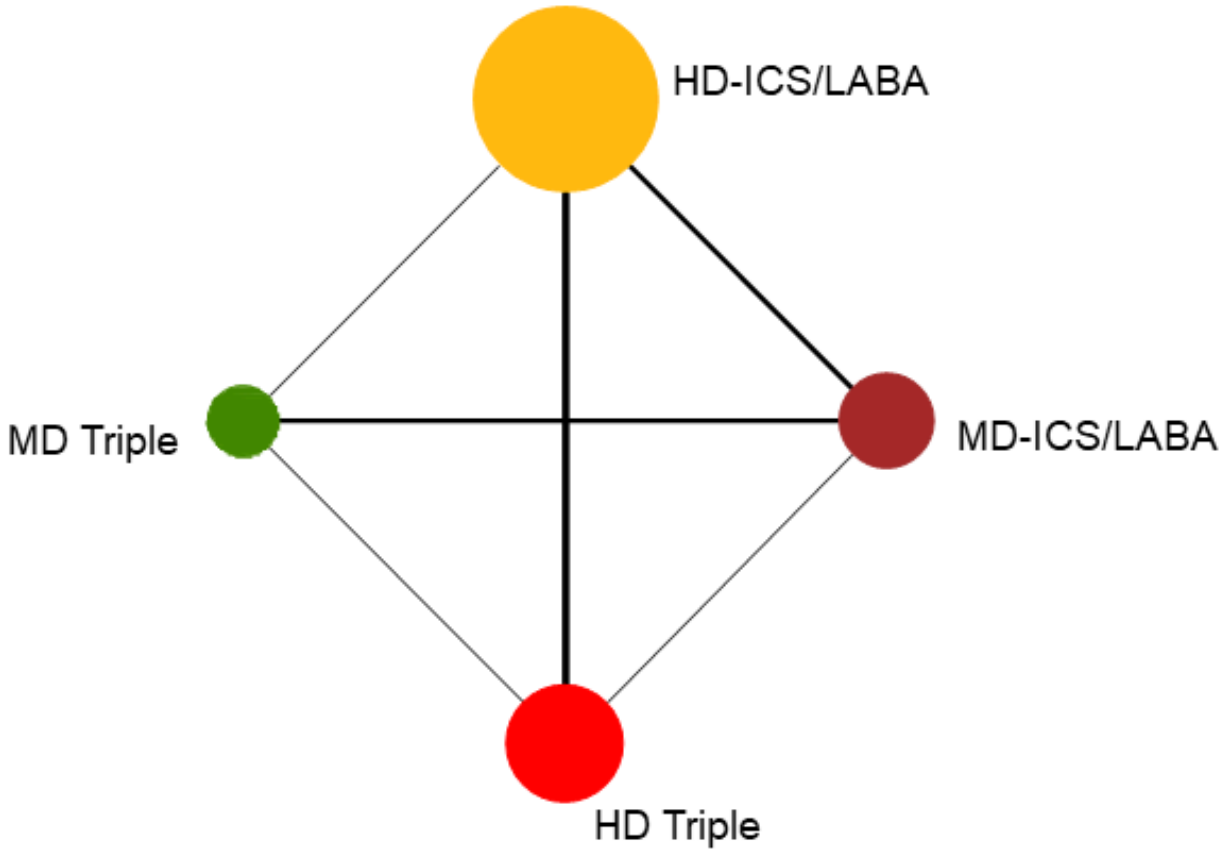
[1] Serious imprecision due to suboptimal sample size in the direct and/or indirect estimate(s).

[2] Serious imprecision due 95% CI or CrI including the null effect in the direct and/or indirect estimate(s).

[3] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

ACQ: Asthma Control Questionnaire; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 9. Network diagram for ACQ responders at 12 months for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 13. Asthma Control Questionnaire responders - pairwise comparisons

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence	What happens
		With active control	With experimental comparator	Difference		

ACQ responders at 6 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 3700 (3 RCTs)	**RR 1.02** (0.96 to 1.08)	66.8%	**68.1%** (64.1 to 72.2)	**1.3% more** (2.7 fewer to 5.3 more)	⊕⊕⊕○ Moderate[a, b]	HD-ICS/LABA likely results in little to no difference in ACQ responders at 6 months compared to MD-ICS/LABA.
ACQ responders at 6 months - MD TRIPLE vs MD-ICS/LABA № of participants: 3063 (3 RCTs)	**RR 1.09** (0.99 to 1.19)	58.3%	**63.5%** (57.7 to 69.3)	**5.2% more** (0.6 fewer to 11.1 more)	⊕⊕○○ Low[c, d]	The evidence suggests MD TRIPLE increases ACQ responders at 6 months compared to MD-ICS/LABA.
ACQ responders at 6 months - HD TRIPLE vs MD-ICS/LABA № of participants: 1916 (2 RCTs)	**RR 1.11** (0.91 to 1.35)	62.8%	**69.7%** (57.2 to 84.8)	**6.9% more** (5.7 fewer to 22 more)	⊕○○○ Very low[e, f]	HD TRIPLE may increase ACQ responders at 6 months compared to MD-ICS/LABA, but the evidence is very uncertain.
ACQ responders at 6 months - MD TRIPLE vs HD-ICS/LABA № of participants: 2480 (2 RCTs)	**RR 1.02** (0.97 to 1.08)	67.5%	**68.9%** (65.5 to 72.9)	**1.4% more** (2 fewer to 5.4 more)	⊕⊕⊕○ Moderate[b]	MD TRIPLE likely results in little to no difference in ACQ responders at 6 months compared to HD-ICS/LABA.
ACQ responders at 6 months - HD TRIPLE vs HD-ICS/LABA № of participants: 4818 (4 RCTs)	**RR 1.07** (1.01 to 1.14)	61.2%	**65.5%** (61.8 to 69.8)	**4.3% more** (0.6 more to 8.6 more)	⊕⊕⊕○ Moderate[b]	HD TRIPLE likely results in little to no difference in ACQ responders at 6 months compared to HD-ICS/LABA.
ACQ responders at 6 months - HD TRIPLE vs MD TRIPLE № of participants: 2821 (3 RCTs)	**RR 0.99** (0.95 to 1.03)	73.2%	**72.5%** (69.6 to 75.4)	**0.7% fewer** (3.7 fewer to 2.2 more)	⊕⊕⊕○ Moderate[b]	HD TRIPLE likely results in little to no difference in ACQ responders at 6 months compared to MD TRIPLE.
ACQ responders at 6 months - TRIPLE vs DUAL № of participants: 7881 (5 RCTs)	**RR 1.09** (1.02 to 1.15)	60.1%	**65.5%** (61.3 to 69.1)	**5.4% more** (1.2 more to 9 more)	⊕⊕○○ Low[b, c]	The evidence suggests TRIPLE increases ACQ responders at 6 months compared to DUAL.
ACQ responders at 12 months - HD-ICS/LABA vs MD-ICS/LABA № of participants: 2817 (2 RCTs)	**RR 0.99** (0.90 to 1.07)	77.0%	**76.2%** (69.3 to 82.3)	**0.8% fewer** (7.7 fewer to 5.4 more)	⊕⊕○○ Low[a, b, c]	HD-ICS/LABA likely results in little to no difference in ACQ responders at 12 months compared to MD-ICS/LABA.
ACQ responders at 12 months - MD TRIPLE vs MD-ICS/LABA № of participants: 2222 (2 RCTs)	**RR 1.01** (0.95 to 1.07)	65.9%	**66.6%** (62.6 to 70.6)	**0.7% more** (3.3 fewer to 4.6 more)	⊕⊕⊕○ Moderate[b]	MD TRIPLE likely results in little to no difference in ACQ responders at 12 months compared to MD-ICS/LABA.

ACQ responders at 12 months - HD TRIPLE vs MD-ICS/LABA № of participants: 1088 (1 RCT)	**RR 1.08** (1.01 to 1.15)	73.1%	**79.0%** (73.9 to 84.1)	**5.9% more** (0.7 more to 11 more)	⊕⊕⊕◯ Moderate[b]	HD TRIPLE likely results in an increase in ACQ responders at 12 months compared to MD-ICS/LABA.
ACQ responders at 12 months - MD TRIPLE vs HD-ICS/LABA № of participants: 1631 (1 RCT)	**RR 0.97** (0.91 to 1.03)	75.3%	**73.1%** (68.5 to 77.6)	**2.3% fewer** (6.8 fewer to 2.3 more)	⊕⊕⊕◯ Moderate[b]	MD TRIPLE likely results in little to no difference in ACQ responders at 12 months compared to HD-ICS/LABA.
ACQ responders at 12 months - HD TRIPLE vs HD-ICS/LABA № of participants: 3982 (3 RCTs)	**RR 1.11** (0.99 to 1.23)	64.2%	**71.3%** (63.6 to 79)	**7.1% more** (0.6 fewer to 14.8 more)	⊕◯◯◯ Very low[b, c, d]	HD TRIPLE may increase ACQ responders at 12 months compared to HD-ICS/LABA, but the evidence is very uncertain.
ACQ responders at 12 months - HD TRIPLE vs MD TRIPLE № of participants: 1089 (1 RCT)	**RR 1.08** (1.01 to 1.16)	72.8%	**78.6%** (73.5 to 84.5)	**5.8% more** (0.7 more to 11.6 more)	⊕⊕⊕◯ Moderate[b]	HD TRIPLE likely increases ACQ responders at 12 months compared to MD TRIPLE.
ACQ responders at 12 months - TRIPLE vs DUAL № of participants: 6204 (4 RCTs)	**RR 1.07** (0.99 to 1.17)	64.8%	**69.4%** (64.2 to 75.8)	**4.5% more** (0.6 fewer to 11 more)	⊕◯◯◯ Very low[b, c, d]	TRIPLE may increase ACQ responders at 12 months compared to DUAL, but the evidence is very uncertain.

*__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).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. van Zyl-Smit 2020 had very high attrition rates and is considered at high risk of bias. However, excluding the study did not change the results.

b. Optimal information size is not met (Guyatt 2011b)

c. Substantial heterogeneity I2 ≥ 50% to 90%

d. Confidence interval includes the line of no effect

e. Considerable heterogeneity. I2 ≥75% to 100%

f. Confidence intervals include clinically important outcomes.

ACQ: Asthma Control Questionnaire; **CI:** confidence interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **RCT**: randomised controlled trial; **RR:** risk ratio.

Summary of findings 14. NMA Summary of Findings for all-cause SAEs

Patient or population: Adolescents and adults with symptomatic asthma

Geometry of the Network in Figure 10*****

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: All-cause serious adverse events (SAEs)

Setting(s): Outpatient

Total studies: 13 RCTs **Total Participants**: 144476	**Risk ratio**** **(95% CrI)**	**Anticipated absolute effect***(95% CrI)**		**Certainty of the evidence**	**Ranking****** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			
HD-ICS/LABA (Direct evidence; 8 RCTs; 7511 participants)	**1.06** (0.86 to 1.33)	54 per 1000	3 per 1000 more (from 7 fewer to 16 more)	⊕⊕⊕⊕ **High**	**3.0** (1.0 to 4.0)	Little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3187 participants)	**1.10** (0.84 to 1.45)	56 per 1000	5 per 1000 more (from 8 fewer to 21 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**3.0** (1.0 to 4.0)	Probably little or no difference
HD-TRIPLE (Direct evidence; 2 RCT; 2039 participants)	**1.05** (0.81 to 1.64)	54 per 1000	3 per 1000 more (from 10 fewer to 33 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**2.0** (1.0 to 4.0)	Probably little or no difference
MD-ICS/LABA	Reference Comparator	51 per 1000[2]	Reference Comparator	Reference Comparator	**2.0** (1.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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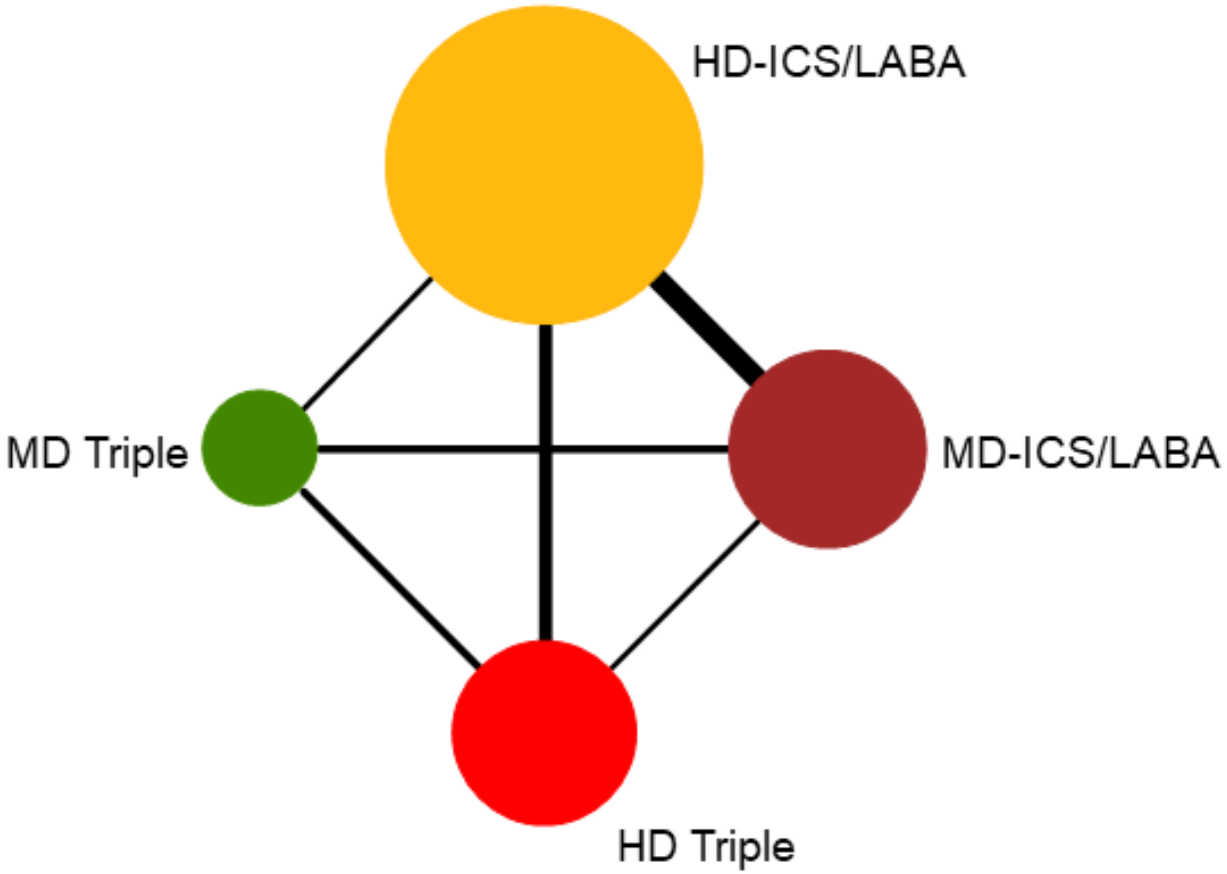
Explanatory Footnotes

[1] Serious imprecision due to wide confidence intervals in the direct and/or indirect estimate(s).

[2] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

CrI: credible interval; **H**D: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial; **SAE**: serious adverse event.

Figure 10. Network diagram for all-cause SAEs for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 15. Serious adverse events, adverse events, and dropouts due to adverse event - pairwise comparisons

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence	What happens
		With active control	With experimental comparator	Difference		

All cause SAEs - HD-ICS/LABA vs MD-ICS LABA № of participants: 7511 (8 RCTs) Follow up: 3 to 12 months	**RR 1.03** (0.83 to 1.29)	4.4%	**4.5%** (3.6 to 5.6)	**0.1% more** (0.7 fewer to 1.3 more)	⊕⊕⊕⊕ High	HD-ICS/LABA results in little to no difference in all cause SAEs compared to MD-ICS LABA.
All cause SAEs - MD TRIPLE vs MD-ICS/LABA № of participants: 3187 (3 RCTs) Follow up: 12 months	**RR 1.13** (0.85 to 1.50)	5.3%	**6.0%** (4.5 to 8)	**0.7% more** (0.8 fewer to 2.7 more)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in all cause SAEs compared to MD-ICS/LABA.
All cause SAEs - HD TRIPLE vs MD-ICS/LABA № of participants: 2039 (2 RCTs) Follow up: 12 months	**RR 1.05** (0.76 to 1.47)	6.2%	**6.5%** (4.7 to 9.1)	**0.3% more** (1.5 fewer to 2.9 more)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in all cause SAEs compared to MD-ICS/LABA.
All cause SAEs - MD TRIPLE vs HD-ICS/LABA № of participants: 2660 (2 RCTs) Follow up: 12 months	**RR 1.08** (0.81 to 1.44)	6.8%	**7.4%** (5.5 to 9.9)	**0.5% more** (1.3 fewer to 3 more)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in all cause SAEs compared to HD-ICS/LABA.
All cause SAEs - HD TRIPLE vs HD-ICS/LABA № of participants: 5004 (4 RCTs) Follow up: 12 months	**RR 0.95** (0.77 to 1.18)	6.9%	**6.6%** (5.3 to 8.2)	**0.3% fewer** (1.6 fewer to 1.2 more)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in all cause SAEs compared to HD-ICS/LABA.
All cause SAEs - HD TRIPLE vs MD TRIPLE № of participants: 2998 (3 RCTs) Follow up: 6 to 12 months	**RR 0.96** (0.72 to 1.27)	6.0%	**5.8%** (4.3 to 7.6)	**0.2% fewer** (1.7 fewer to 1.6 more)	⊕⊕⊕◯ Moderate[a]	HD TRIPLE likely results in little to no difference in all cause SAEs compared to MD TRIPLE.
All cause SAEs - TRIPLE vs DUAL № of participants: 8192 (6 RCTs)	**RR 1.03** (0.87 to 1.21)	6.3%	**6.5%** (5.5 to 7.7)	**0.2% more** (0.8 fewer to 1.3 more)	⊕⊕⊕⊕ High	TRIPLE results in little to no difference in all cause SAEs compared to DUAL.

Follow up: 12 months						
Asthma-related SAEs - HD-ICS/LABA vs MD-ICS LABA № of participants: 6244 (6 RCTs) Follow up: 3 to 12 months	**RR 1.33** (0.80 to 2.21)	1.1%	**1.5%** (0.9 to 2.5)	**0.4% more** (0.2 fewer to 1.4 more)	⊕⊕⊕⊕ High	HD-ICS/LABA results in little to no difference in asthma-related SAEs compared to MD-ICS LABA.
Asthma-related SAEs - MD TRIPLE vs MD-ICS/LABA № of participants: 3188 (3 RCTs) Follow up: 12 months	**RR 1.52** (0.85 to 2.69)	1.2%	**1.8%** (1 to 3.2)	**0.6% more** (0.2 fewer to 2 more)	⊕⊕⊕◯ Moderate[a]	MD TRIPLE likely results in little to no difference in asthma-related SAEs compared to MD-ICS/LABA.
Asthma-related SAEs - HD TRIPLE vs MD-ICS/LABA № of participants: 2039 (2 RCTs) Follow up: 12 months	**RR 0.86** (0.41 to 1.80)	1.5%	**1.3%** (0.6 to 2.7)	**0.2% fewer** (0.9 fewer to 1.2 more)	⊕⊕⊕⊕ High	HD TRIPLE results in little to no difference in asthma-related SAEs compared to MD-ICS LABA.
Asthma-related SAEs - MD TRIPLE vs HD-ICS/LABA № of participants: 2660 (2 RCTs) Follow up: 12 months	**RR 1.35** (0.77 to 2.36)	1.6%	**2.2%** (1.3 to 3.9)	**0.6% more** (0.4 fewer to 2.2 more)	⊕⊕⊕◯ Moderate[a]	Safety outcomes likely results in little to no difference in asthma-related SAEs - MD TRIPLE vs HD-ICS/LABA.
Asthma-related SAEs - HD TRIPLE vs HD-ICS/LABA № of participants: 5004 (4 RCTs) Follow up: 12 months	**RR 0.86** (0.58 to 1.27)	2.2%	**1.9%** (1.3 to 2.8)	**0.3% fewer** (0.9 fewer to 0.6 more)	⊕⊕⊕⊕ High	HD TRIPLE results in little to no difference in asthma-related SAEs compared to HD-ICS LABA.
Asthma-related SAEs - HD TRIPLE vs MD TRIPLE № of participants: 3472 (3 RCTs) Follow up: 6 to 12 months	**RR 0.57** (0.31 to 1.05)	1.7%	**1.0%** (0.5 to 1.8)	**0.7% fewer** (1.2 fewer to 0.1 more)	⊕⊕⊕⊕ High	HD TRIPLE results in little to no difference in asthma-related SAEs compared to MD TRIPLE.
Asthma-related SAEs - TRIPLE vs DUAL № of participants: 8192	**RR 1.04** (0.76 to 1.42)	1.8%	**1.9%** (1.4 to 2.6)	**0.1% more** (0.4 fewer to 0.8 more)	⊕⊕⊕⊕ High[b]	TRIPLE results in little to no difference in asthma-related SAEs compared to DUAL.

(6 RCTs) Follow up: 12 months						
All cause AEs - HD-ICS/LABA vs MD-ICS LABA № of participants: 5949 (7 RCTs) Follow up: 3 to 12 months	**RR 1.01** (0.97 to 1.06)	43.8%	**44.3%** (42.5 to 46.4)	**0.4% more** (1.3 fewer to 2.6 more)	⊕⊕⊕⊕ High	HD-ICS/LABA results in little to no difference in all cause AEs compared to MD-ICS LABA.
All cause AEs - MD TRIPLE vs MD-ICS/LABA № of participants: 3188 (3 RCTs) Follow up: 12 months	**RR 0.96** (0.91 to 1.00)	61.9%	**59.4%** (56.3 to 61.9)	**2.5% fewer** (5.6 fewer to 0 fewer)	⊕⊕⊕◯ Moderate[c]	MD TRIPLE likely results in a slight reduction in all cause AEs compared to MD-ICS/LABA.
All cause AEs - HD TRIPLE vs MD-ICS/LABA № of participants: 2039 (2 RCTs) Follow up: 12 months	**RR 0.92** (0.85 to 1.00)	52.0%	**47.9%** (44.2 to 52)	**4.2% fewer** (7.8 fewer to 0 fewer)	⊕⊕⊕◯ Moderate[c]	HD TRIPLE likely results in a reduction in all cause AEs compared to MD-ICS/LABA.
All cause AEs - MD TRIPLE vs HD-ICS/LABA № of participants: 2659 (2 RCTs) Follow up: 12 months	**RR 0.99** (0.83 to 1.18)	56.1%	**55.5%** (46.5 to 66.2)	**0.6% fewer** (9.5 fewer to 10.1 more)	⊕⊕◯◯ Low[a, b]	The evidence suggests that MD TRIPLE results in little to no difference in all cause AEs compared to HD-ICS/LABA.
All cause AEs - HD TRIPLE vs HD-ICS/LABA № of participants: 5004 (4 RCTs) Follow up: 12 months	**RR 0.91** (0.87 to 0.96)	63.0%	**57.3%** (54.8 to 60.5)	**5.7% fewer** (8.2 fewer to 2.5 fewer)	⊕⊕⊕⊕ High	HD TRIPLE results in a reduction in all cause AEs -compared to HD-ICS/LABA.
All cause AEs - HD TRIPLE vs MD TRIPLE № of participants: 3473 (3 RCTs) Follow up: 6 to 12 months	**RR 0.95** (0.90 to 1.02)	51.7%	**49.1%** (46.5 to 52.7)	**2.6% fewer** (5.2 fewer to 1 more)	⊕⊕⊕◯ Moderate[c]	HD TRIPLE likely results in a slight reduction in all cause AEs -compared to MD TRIPLE.

All cause AEs - TRIPLE vs DUAL № of participants: 8192 (6 RCTs) Follow up: 12 months	**RR 0.93** (0.90 to 0.96)	62.6%	**58.2%** (56.3 to 60.1)	**4.4% fewer** (6.3 fewer to 2.5 fewer)	⊕⊕⊕⊕ High	TRIPLE results in a reduction in all cause AEs compared to DUAL.
Dropouts due to adverse event - HD-ICS/LABA vs MD-ICS LABA № of participants: 5969 (7 RCTs) Follow up: 3 to 12 months	**RR 1.00** (0.68 to 1.48)	1.8%	**1.8%** (1.2 to 2.7)	**0.0% fewer** (0.6 fewer to 0.9 more)	⊕⊕⊕⊕ High	HD ICS/LABA results in little to no difference in dropouts due to adverse event compared to MD-ICS LABA.
Dropouts due to adverse event - MD TRIPLE vs MD-ICS/LABA № of participants: 3205 (3 RCTs) Follow up: 12 months	**RR 0.42** (0.08 to 2.14)	2.1%	**0.9%** (0.2 to 4.4)	**1.2% fewer** (1.9 fewer to 2.4 more)	⊕◯◯◯ Very low[b, d, e]	The evidence is very uncertain about the effect of MD TRIPLE on dropouts due to adverse event compared to MD-ICS/LABA.
Dropouts due to adverse event - HD TRIPLE vs MD-ICS/LABA № of participants: 2670 (2 RCTs) Follow up: 12 months	**RR 0.47** (0.19 to 1.18)	2.9%	**1.3%** (0.5 to 3.4)	**1.5% fewer** (2.3 fewer to 0.5 more)	⊕⊕⊕◯ Moderate[e]	HD TRIPLE likely results in a slight reduction in dropouts due to adverse event compared to MD-ICS/LABA.
Dropouts due to adverse event - MD TRIPLE vs HD-ICS/LABA № of participants: 2668 (2 RCTs) Follow up: 12 months	**RR 1.24** (0.76 to 2.02)	2.4%	**3.0%** (1.9 to 4.9)	**0.6% more** (0.6 fewer to 2.5 more)	⊕⊕⊕◯ Moderate[e]	MD TRIPLE likely results in little to no difference in dropouts due to adverse event compared to HD-ICS/LABA.
Dropouts due to adverse event - HD TRIPLE vs HD-ICS/LABA № of participants: 5018 (4 RCTs) Follow up: 12 months	**RR 0.60** (0.38 to 0.95)	2.3%	**1.4%** (0.9 to 2.2)	**0.9% fewer** (1.4 fewer to 0.1 fewer)	⊕⊕⊕⊕ High	HD TRIPLE results in a slight reduction in dropouts due to adverse event compared to HD-ICS/LABA.
Dropouts due to adverse event - HD TRIPLE vs MD TRIPLE № of participants: 1765 (2 RCTs)	**RR 1.00** (0.29 to 3.44)	0.6%	**0.6%** (0.2 to 2)	**0.0% fewer** (0.4 fewer to 1.4 more)	⊕⊕⊕◯ Moderate[e]	HD TRIPLE likely results in little to no difference in dropouts due to adverse event compared to MD TRIPLE.

Follow up: 6 to 12 months						
Dropouts due to adverse event - TRIPLE vs DUAL № of participants: 8223 (5 RCTs) Follow up: 12 months	**RR 0.59** (0.33 to 1.03)	2.2%	**1.3%** (0.7 to 2.3)	**0.9% fewer** (1.5 fewer to 0.1 more)	⊕⊕⊕◯ Moderate[c]	TRIPLE likely results in a slight reduction in dropouts due to adverse event compared to DUAL.

*__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).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Confidence interval includes a clinically important difference.

b. Substantial heterogeneity I2 ≥ 50% to 90%

c. Confidence interval includes the line of no effect.

d. Optimal information size is not met (Guyatt 2011b)

e. Very wide confidence interval.

AE: adverse event; **CI:** confidence interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **LD**: low dose; **MD**: medium dose; **RCT**: randomised controlled trial; **RR:** risk ratio; **SAE**: serious adverse event.

Summary of findings 16. NMA Summary of Findings for asthma-related SAEs

Patient or population: Adolescent sand adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: Asthma-related serious adverse events (SAEs)

Setting(s): Outpatient

Geometry of the Network in Figure 11*

Total studies: 11 RCTs **Total Participants**: 13209	**Relative risk** **(95% CrI)**	**Anticipated absolute effect***(95% CrI)		**Certainty of the evidence**	**Ranking**** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			
HD-ICS/LABA (Direct evidence; 6 RCTs; 6244 participants)	**1.27** (0.79 to 2.05)	13 per 1000	3 per 1000 more (from 2 fewer to 12 more)	⊕⊕⊕⊕ **High**	**3.0** (1.0 to 4.0)	Little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3188 participants)	**1.70** (0.99 to 1.8)	18 per 1000	8 per 1000 more (from 0 fewer to 9 more)	⊕⊕⊕◯ **Moderate** Due to imprecision[1]	**4.0** (2.0 to 4.0)	Probably little or no difference
HD-TRIPLE (Direct evidence; 2 RCTs; 2039 participants)	**1.05** (0.60 to 1.80)	11 per 1000	1 per 1000 more (from 4 fewer to 9 more)	⊕⊕⊕⊕ **High**	**2.0** (1.0 to 3.0)	Little or no difference
MD-ICS/LABA	Reference Comparator	10 per 1000[2]	Reference Comparator	Reference Comparator	**1.0** (1.0 to 3.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two risks by calculating the difference between the risk of the intervention group with the risk of the control group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

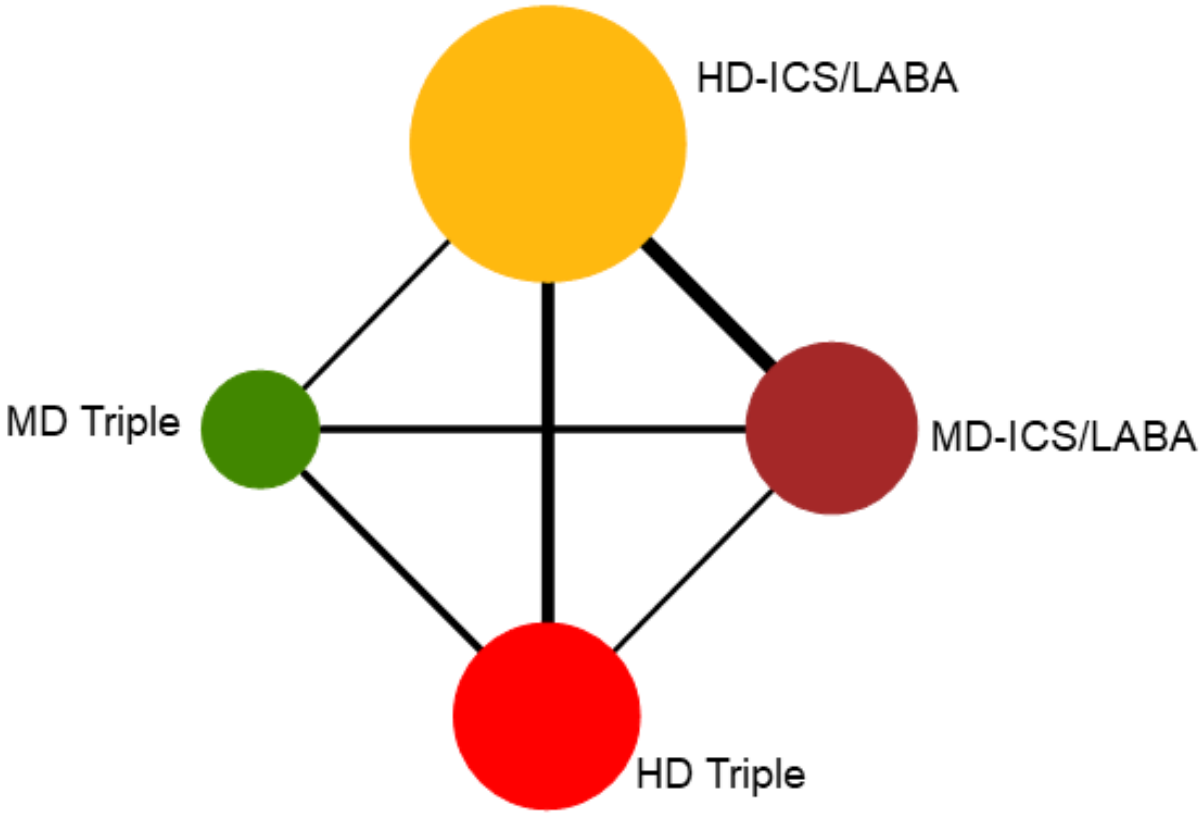
Explanatory Footnotes

[1] Serious imprecision due to wide confidence intervals in the direct and/or indirect estimate(s).

[2] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

CrI: credible interval; **H**D: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial; **SAE**: serious adverse event.

Figure 11. Network diagram for asthma-related SAEs for grouped interventions The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 17. NMA Summary of Findings for all-cause AEs

Patient or population: Adolescents and adults with symptomatic asthma

Interventions: HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE

Comparator (reference): Medium-Dose ICS/LABA (MD-ICS/LABA)

Outcome: All-cause adverse events (AEs)

Geometry of the Network in Figure 12*****

Setting(s): Outpatient

Total studies: 12 RCTs **Total Participants**: 12915	**Relative effect** **(95% CrI)**	**Anticipated absolute effect***(95% CrI)		**Certainty of the evidence**	**Ranking**** **(95% CrI)**	**Interpretation of Findings**
		With intervention	**Difference compared to MD-ICS/LABA**			
HD-ICS/LABA (Direct evidence; 7 RCTs; 5949 participants)	**1.00** (0.89 to 1.12)	508 per 1000	0 per 1000 more (from 29 fewer to 28 more)	⊕⊕⊕⊕ **High**	**3.0** (2.0 to 4.0)	Little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3188 participants)	**0.89** (0.78 to 1.02)	479 per 1000	29 per 1000 fewer (from 62 fewer to 5 more)	⊕⊕⊕○ **Moderate** Due to imprecision[1]	**2.0** (1.0 to 3.0)	Probably little or no difference
HD-TRIPLE (Direct evidence; 2 RCTs; 2039 participants)	**0.79** (0.69 to 0.90)	449 per 1000	59 per 1000 fewer (from 26 fewer to 92 fewer)	⊕⊕⊕⊕ **High**	**1.0** (1.0 to 2.0)	Superior
MD-ICS/LABA	Reference Comparator	508 per 1000[2]	Reference Comparator	Reference Comparator	**3.0** (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

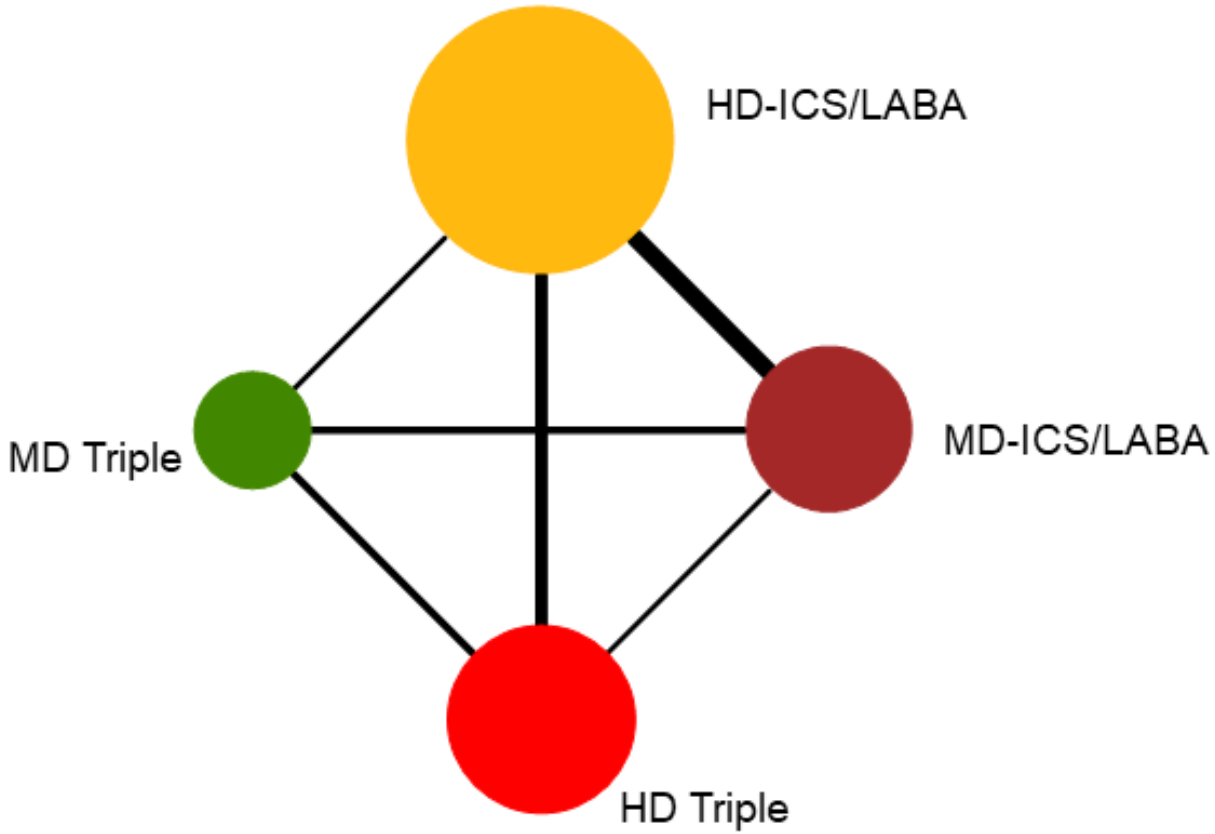
Explanatory Footnotes

[1] Serious imprecision due to 95% CIs including the null effect.

[2] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

AE: adverse event; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

Figure 12. Network diagram for all-cause AEs for grouped interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Summary of findings 18. NMA summary of findings table for dropouts due to AEs

-Patient or population: Adolescents and adults with symptomatic asthma **Interventions:** HD-ICS/LABA, MD-TRIPLE, HD-TRIPLE **Comparator (reference):** Medium-Dose ICS/LABA (MD-ICS/LABA) **Outcome:** Dropouts due to adverse events (AEs)	**Geometry of the Network in-** Figure 13*

Setting(s): Outpatient

Total studies: 12 RCTs Total Participants: 12915	Risk ratio** (95% CrI)	Anticipated absolute effect***(95% CrI)		Certainty of the evidence	Ranking**** (95% CrI)	Interpretation of Findings
		With intervention	Difference compared to MD-ICS/LABA			
HD-ICS/LABA (Direct evidence; 7 RCTs; 5969 participants)	0.91 (0.64 to 1.36)	15 per 1000	1 per 1000 fewer (from 6 fewer to 5 more)	⊕⊕⊕⊕ High	3.0 (2.0 to 4.0)	Little or no difference
MD-TRIPLE (Direct evidence; 3 RCTs; 3205 participants)	0.88 (0.53 to 1.43)	14 per 1000	2 per 1000 fewer (from 8 fewer to 7 more)	⊕⊕⊕◯ Moderate Due to imprecision[1]	3.0 (2.0 to 4.0)	Probably little or no difference
HD-TRIPLE (Direct evidence; 2 RCTs; 2051 participants)	0.50 (0.30 to 0.84)	8 per 1000	8 per 1000 fewer (from 11 fewer to 3 fewer)	⊕⊕⊕◯ Moderate Due to imprecision[1]	1.0 (1.0 to 2.0)	Probably superior
MD-ICS/LABA	Reference Comparator	16 per 1000[2]	Reference Comparator	Reference Comparator	4.0 (2.0 to 4.0)	Reference Comparator

NMA-SoF table definitions

* The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted, respectively.

** Network Meta-Analysis estimates are reported as risk ratio. Results are expressed in credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted.

*** Anticipated absolute effect. Anticipated absolute effect compares two rates by calculating the difference between the rates of the intervention group with the rate of MD-ICS/LABA group.

**** Median and credible intervals are presented. Rank statistics is defined as the probabilities that a treatment out of *n* treatments in a network meta-analysis is the best, the second, the third and so on until the least effective treatment.

GRADE Working Group grades of evidence (or certainty in the evidence)

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanatory Footnotes

[1] Serious imprecision due to wide confidence intervals in the direct and/or indirect estimate(s).

[2] Based on the average rate in participants treated with MD-ICS/LABA in the included studies.

AE: adverse event; **CrI**: credible interval; **HD**: high dose; **ICS**: inhaled corticosteroids; **LABA**: long-acting beta-2 agonist; **MD**: medium dose; **NMA**: network meta-analysis; **RCT**: randomised controlled trial.

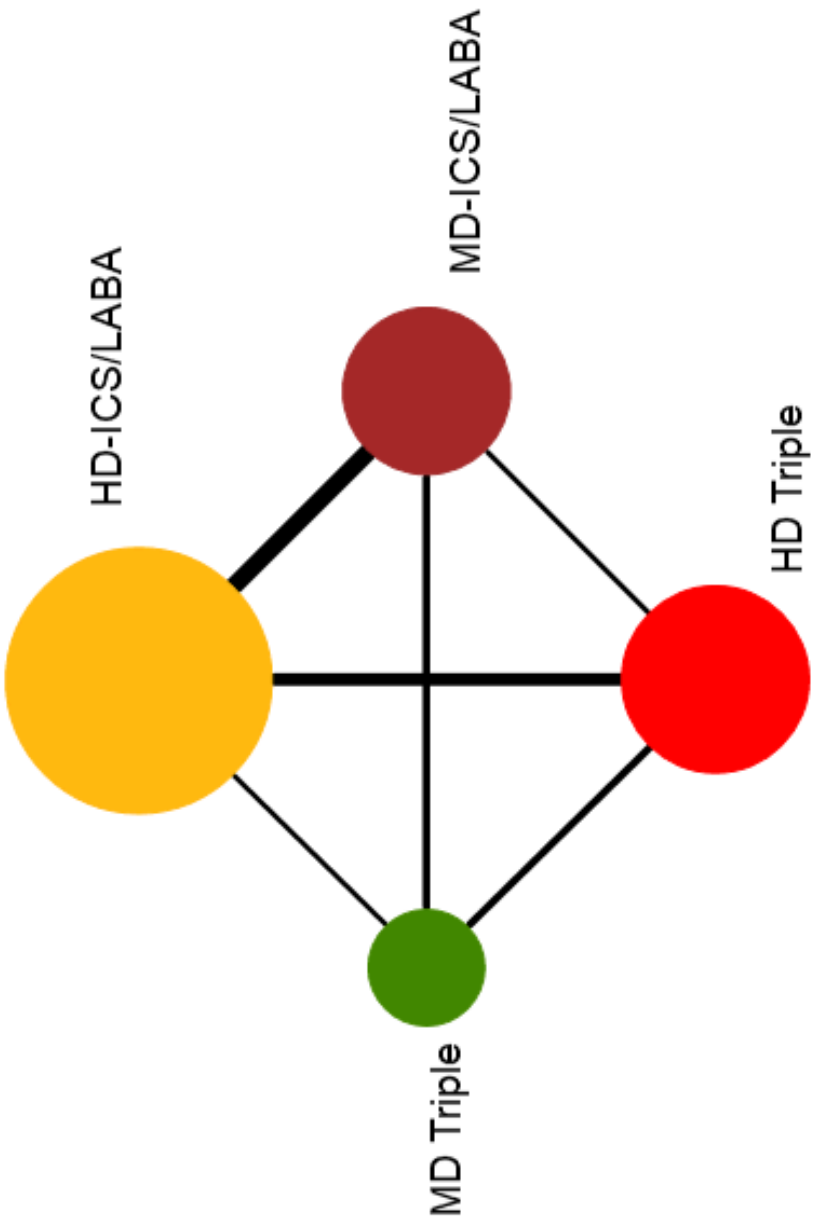


Figure 13. Network diagram for drop-outs due to AEs for grouped interventions. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory airway disease characterised by reversible airway obstruction. The disease often starts in childhood, although it can be first diagnosed during adulthood. It is characterised by symptoms such as wheezing, shortness of breath, coughing and chest tightness. These symptoms are usually reversible with bronchodilator therapy and inhaled corticosteroids (ICS). Asthma is a common condition with global prevalence rates ranging from 7% to 25% (Sears 2014). It affects as many as 339 million people with estimated annual deaths of 420,000 worldwide (Global Asthma Report 2018). It also has significant economic impacts and accounts for 1.1% of global disability-adjusted life years (Soriano 2017). The main objectives in asthma management are to achieve symptom control, reduce exacerbations, and meet patient and family expectations (GINA 2021).

Description of the intervention

Management of asthma involves a series of stepwise therapies depending on the severity of the disease. Initial therapy typically starts with a short-acting beta$_2$-agonist as needed (step 1), and a daily low-dose (LD) ICS is added for persistent symptoms (step 2) (O'Byrne 2019). Subsequently, a long-acting beta$_2$-agonist (LABA), such as formoterol, typically is added to LD- to medium-dose (MD) ICS if needed (steps 3 and 4) (Ducharme 2010; Sobieraj 2018a). Current guidelines recommend adding a long-acting muscarinic antagonist (LAMA) or a biologic agent and/or consideration of high dose ICS-LABA (step 5), when asthma is not controlled with MD-ICS/LABA combination therapy (GINA 2021).

How the intervention might work

Inhaled corticosteroids work by their anti-inflammatory effects in reducing bronchial hyper-responsiveness and mucus hypersecretion (Barnes 2010). They are currently the first-line therapeutic agents in the management of persistent asthma.

The LABA class of medications works by stimulation of the beta$_2$ receptors on smooth muscles of the airways, which results in prolonged bronchodilation and a membrane stabilisation effect (Derom 1992; Kips 2001). LABA therapy plays a role in the treatment of asthma. However, it has long been established that LABA should play an adjunctive role with ICS as LABA was found to be inferior to ICS in the management of asthma when used as monotherapy (Haahtela 1991). Therefore, in the management of asthma, LABA medications are not utilised until failure with ICS monotherapy has been identified.

Long-acting muscarinic antagonists (LAMAs) inhibit the action of acetylcholine at muscarinic receptors in bronchial smooth muscle and submucosal glands, resulting in bronchodilation as well as decreased mucus production (Gosens 2018). Their side effects are related to anticholinergic effects and typically comprise dry mouth, urinary retention and mydriasis (dilated pupils) (McIvor 2014). These side effects can impact participants' adherence and potentially affect outcomes. Recent evidence has suggested a role for LAMAs in the treatment of persistent asthma not controlled with ICS/LABA (Aalbers 2017; Kerstjens 2012). The premise of the addition of LAMA is to synergistically increase bronchodilation and thus alleviate asthma symptoms.

Why it is important to do this review

A recent meta-analysis by Sobieraj and colleagues demonstrated that addition of a LAMA to ICS compared to ICS alone reduced asthma exacerbations (Sobieraj 2018a). Other studies also support the benefit of LAMA when added to ICS (Anderson 2015; Befekadu 2014). However, ICS/LABA/LAMA or ICS/LAMA combinations failed to show any benefit compared to ICS/LABA (Sobieraj 2018b). This review involved a network meta-analysis assessing outcomes in people with asthma whose symptoms are not well-controlled with an ICS/LABA combination by comparing higher dose ICS/LABA and triple therapy (ICS/LABA/LAMA). If a triple combination (ICS/LABA/LAMA) is no more effective than a medium dose (MD) or high-dose (HD) ICS/LABA combination, healthcare providers could consider other options such as a biologic agent (step 6) when an MD- or HD-ICS/LABA combination fails.

There is a question of whether there are added benefits of HD versus MD ICS and a concern for increased side effects with higher-dose ICS (Beasley 2019; Kew 2016; Zhang 2019). Inhaled corticosteroids are associated with systemic adverse events driven by increased dosages. These include osteoporosis, cataracts, skin changes (thinning and bruising) and adrenal suppression (Pandya 2014). Most studies comparing dual and triple combination therapies did not consider ICS doses (i.e. low-, medium- and high-doses) in their combinations. Therefore, this review also analysed the impact of HD versus MD ICS within the dual and triple combination therapies. If this review confirms the notion that an HD ICS increases side effects with no additional benefits compared with an MD ICS in combination inhalers, healthcare providers could be discouraged from using an HD ICS in combination inhalers.

OBJECTIVES

To assess the effectiveness and safety of dual and triple combination inhaler therapies, using a network-meta-analysis (NMA), compared with each other and with varying doses of inhaled corticosteroids (ICS) in adolescents and adults with uncontrolled asthma who have been treated with or are eligible for medium dose (MD)- ICS/long-acting beta$_2$-agonist (LABA) combination therapy.

METHODS

Criteria for considering studies for this review

Types of studies

We included pre-registered randomised controlled trials (RCTs) of at least 12 weeks of study duration. To minimise publication bias and selective reporting, studies could be either published or unpublished. We did not consider cluster or- cross-over RCTs to minimise unit of analysis errors, overestimating the treatment effects, and residual effects of crossed over inhaled corticosteroids (ICS) doses.

Types of participants

We included studies in adolescents and adults (age 12 years or older) with uncontrolled asthma who had been treated with or were eligible for MD-ICS/LABA combination therapy. In this review, uncontrolled asthma is defined as: Asthma Control Questionnaire (ACQ) score equal to or greater than 1.5 (Juniper 2006); Asthma Control Test (ACT) score less than 20 (Schatz 2006); persistent asthma (symptoms or rescue medication usage two days per week

or nighttime awakenings three times per month); or at least one asthma exacerbation in the past 12 months prior to randomisation (Gessner 2020; Kerstjens 2012; Papi 2007).

Types of interventions

We included studies comparing at least two of the following therapies.

- MD- or HD-ICS/LABA, a fixed dose (a combination of two active ingredients in a fixed ratio of doses) or free combination of two separate inhalers (beclomethasone/formoterol, budesonide/formoterol, ciclesonide/formoterol, fluticasone/formoterol, mometasone/formoterol, mometasone/indacaterol, fluticasone/salmeterol, fluticasone/vilanterol, etc.)
- ICS/LABA/LAMA, a fixed-dose (a combination of three active ingredients in a fixed ratio of doses) triple combination (fluticasone furoate/vilanterol/umeclidinium, mometasone/glycopyrronium/indacaterol (MF/GLY/IND), etc.), or an ICS/LABA fixed combination plus a LAMA (aclidinium, glycopyrronium, tiotropium, umeclidinium, etc.)

We classified doses of the ICS component in combination inhalers into low, medium, or high dose based on clinical comparability (BTS/SIGN 2019; GINA 2021). We considered fluticasone furoate 100 µg once daily a medium dose which was approximately equivalent to fluticasone propionate 250 µg twice daily according to the manufacturer's summary of product characteristics (Bernstein 2018; NICE 2018). We had originally classified MF/GLY/IND 160/50/150 µg and 80/50/150 µg as MD and LD Triple according to Vaidya 2016 which was later reclassified as HD and MD triple when new data became available (Buhl 2021).

We allowed the use of a short-acting bronchodilator, such as albuterol (salbutamol) and ipratropium as rescue treatment. Network diagrams of individual treatment and grouped comparisons in each outcome for the NMAs are presented in the Figures section.

Types of outcome measures

We analysed the following outcomes in this review.

Primary outcomes

1. Asthma exacerbations (moderate, defined as requiring a short course of oral corticosteroids and severe, defined as resulting in hospitalisation, mechanical ventilation, or death)

Secondary outcomes

1. Asthma Control Questionnaire (ACQ-7: seven item question) and its responders (Juniper 2006)
2. Asthma Quality of Life Questionnaire (AQLQ) (Juniper 1994)
3. All-cause adverse events (AEs) and serious adverse events (SAEs)
4. Asthma-related SAEs
5. Dropouts due to AEs

An SAE is defined by the US Food and Drug Administration (FDA) as any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or causes prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; may have caused a congenital anomaly or birth defect; or requires intervention to prevent permanent impairment or damage (FDA 2016).

Search methods for identification of studies

Electronic searches

We identified studies from searches of the following databases and trial registries.

1. Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies, 2008 to 18 February 2022.
2. Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, 2008 to 18 February 2022
3. MEDLINE Ovid SP 2008 to18 February 2022
4. Embase Ovid SP 2008 to 18 February 2022
5. Global Health Ovid SP 2008 to 18 February 2022
6. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
7. World Health Organisation International Clinical Trials Registry Platform (apps.who.int/trialsearch)

The database search strategies are listed in Appendix 1. The original search strategy was drafted in MEDLINE and adapted for use in the other databases. We structured the search strategy to search for articles containing terms for asthma, a LABA and an ICS. This structure facilitated searching for all the possible comparisons. The Cochrane Airways Information Specialist developed the search strategy in collaboration with the authors.

We searched all databases and trials registries from 2008, when the International Committee of Medical Journal Editors started to implement an updated policy requiring trial registration as a condition of publication, to 18 February 2022. There was no restriction on language or type of publication. We identified conference abstracts and grey literature to be hand searched through the Cochrane Airways Trials Register and the CENTRAL database.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for study information. We searched on PubMed for errata or retractions from included studies published in full text. We contacted investigators or study sponsors in order to obtain missing numerical outcome data as necessary.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd (http://crowd.cochrane.org) – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. More detailed information about the Screen4Me components can be found in these publications: Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

Following this initial assessment, two review authors (YO, TM) independently screened titles and abstracts of the search results using Covidence and coded them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve'. We retrieved the full-text study reports of all potentially eligible studies and two review authors (YO, TM) independently screened them for inclusion, recording the reasons for exclusion of ineligible studies. We resolved any disagreement through discussion or, if required, we consulted a third review author (TP). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We used a data collection form for study characteristics and outcome data, which had been piloted on at least one study in the review. Three review authors (YO, TM, TP) extracted the following study characteristics from the included studies.

1. Methods: study design, total duration of study, details of any 'run-in' period, study centres and location, study setting, withdrawals, and date of study.
2. Participants: number, mean age, age range, gender, race, smoking history, exacerbation history, diagnostic criteria, baseline lung function, and inclusion and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We used change from baseline (CFB) data, i.e., the difference between baseline and post-intervention values at 3, 6, and 12 months.
5. Notes: funding for studies, website address for industry generated reports (e.g., Clinical Study Report), and trial registration number.

Two review authors (YO, TM) independently extracted outcome data from the included studies. We chose estimated effects of intervention in the following order of preference: (1) full intention-to-treat analysis (ITT); (2) modified ITT; (3) per-protocol analysis. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third review author (TP). One review author (YO) transferred data into the Review Manager file (Review Manager 2020). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (TM) spot-checked study characteristics for accuracy.

Assessment of risk of bias in included studies

Two review authors (YO, TM) independently assessed risk of bias for each study using the criteria outlined in the revised Cochrane risk of bias 2 (RoB 2) tool (Higgins 2019; Sterne 2019). We used the RoB 2 Excel tool to implement RoB 2 and presented consensus decisions for signalling questions in a general repository as supplemental data to be transparent. We assessed the risk of bias according to the following domains in all outcome measures and time points as necessary.

1. Randomisation processes
2. Deviations from intended interventions
3. Missing outcome data
4. Measurement of outcome
5. Selective outcome reporting

We categorised each domain as being 'high risk', 'low risk' or 'some concerns' using the algorithms proposed in RoB 2. We assessed overall risk of bias and considered a study: to be at high risk of bias when at least one domain was judged as being at high risk; to be at low risk when all domains were judged as being at low risk (Guyatt 2011a), and to raise some concerns when at least one domain was judged to raise some concerns but no domains were judged as being at high risk of bias. We resolved any disagreement through discussion or, if required, we consulted a third review author (TP).

Assessment of bias in conducting the systematic review

We conducted this review according to the previously published protocol (Oba 2020) and justified any deviations from it in the 'Differences between protocol and review' section of this review. We used the overall risk of bias judgements in the GRADE approach and summary of finding tables (Guyatt 2011b).

Network meta-analysis

We compared each pair of treatments by estimating a hazard ratio (HR) for time-to-event outcomes (e.g. asthma exacerbations), a mean difference for continuous outcomes, and an odds ratio (OR) for dichotomous outcomes, along with their 95% credible intervals (CrIs).

We used a shared parameter model for exacerbation outcomes, whereby data on the log hazard ratio (lnHR) were modelled with the assumption that continuous treatment differences (lnHR and standard error)(SE) had a normal likelihood. When lnHR data were not available, or when appropriate covariance matrices could not be extracted or calculated for studies with more than two arms, we modelled data on dichotomous data at a given time as lnHR by using a binomial likelihood with a cloglog link. We used HR data in preference to dichotomous data when available and considered only the HR for the first event for exacerbation outcomes. When there were no dichotomous data available for a multi-arm study for which a covariance matrix could not be calculated, we included unconnected pairwise comparisons as separate studies.

We used a normal likelihood with an identity link for continuous outcomes and a binomial likelihood with a logit link for dichotomous outcomes.

Direct pairwise meta-analysis

We analysed dichotomous data as risk ratio (RR) or risk difference (RD) and continuous data as the mean difference(MD) along with their 95% confidence intervals (CIs).

Unit of analysis issues

For dichotomous outcomes, we used participants, rather than events, as the unit of analysis (i.e. number of participants admitted to hospital, rather than number of admissions).

Dealing with missing data

We contacted investigators or study sponsors in order to obtain missing numerical outcome data where possible (e.g. when a study

was identified as an abstract only). When this was not possible and a large proportion of data was missing, we considered the missing data would introduce serious bias using the criteria proposed by Guyatt 2017. We took this into consideration in the GRADE rating for the affected outcomes.

Network meta-analysis

We assessed heterogeneity by comparing the between-trials standard deviation (SD) to the size of relative treatment effects, on the log-scale for HRs and ORs. We assessed consistency between direct and indirect estimates by fitting node splitting models (van Valkenhoef 2016) and inspecting the resulting Bayesian p-values for inconsistency, as well as comparing the model fit and between-study heterogeneity to the standard NMA model. We extracted potential effect modifiers such as age, gender, race, smoking status, and exacerbation history. We assessed clinical heterogeneity by comparing them across different treatment comparisons. We qualitatively compared direct estimates from pairwise meta-analysis with NMA estimates to check for broad agreement.

Direct pairwise meta-analysis

We used the I^2 statistic to measure heterogeneity amongst the studies in each analysis with I^2 greater than 50% suggesting substantial heterogeneity (Deeks 2020). We also visually inspected forest plots and assess p values from the Chi^2 test to identify heterogeneity. We reported substantial heterogeneity when identified and rated down the certainty of evidence when appropriate (Guyatt 2011a).

Network meta-analysis

We minimised reporting bias from unpublished studies or selective outcome reporting by using a broad search strategy and by checking references of included studies and relevant systematic reviews. For each outcome, we estimated and presented the proportion of studies contributing data to the NMAs.

Direct pairwise meta-analysis

For pairwise meta-analyses, we assessed small-study and publication bias through visual inspection of a funnel plot if more than 10 studies were being pooled. We assumed the presence of small-study bias when the number of participants was fewer than 50 per study, 1000 per pooled analysis, or 100 per arm when no more than 10 studies could be pooled (Dechartres 2013; Nüesch 2010).

Network meta-analysis (NMA)

We conducted NMAs in OpenBUGS (version 3.2.3) and sampled 100,000 iterations for three chains after a burn-in of 50,000 iterations for exacerbations outcomes. NMAs for moderate-severe exacerbations were conducted in R (version 4.0.5) using the GeMTC package, as there were only dichotomous data for the outcome. Models were sampled over 100,000 iterations forfour4 chains, after a burn-in of 50,000 iterations. We used half-normal prior distributions (Röver 2021) for the between-study heterogeneity in severe exacerbations.

For continuous outcomes, we sampled over 100,000 iterations for four chains, after a burn-in of 50,000 iterations using R (version 4.0.5) with GeMTC package. We analysed group comparisons only as there were sufficient data to allow for individual treatment comparisons.

For dichotomous outcomes, we mostly conducted NMAs in R (version 4.0.5) using GeMTC package, but exceptions were made for individual treatment outcomes that reported zero counts for events (asthma-related SAEs and dropouts due to AEs). As the data for individual treatments were sparse, we added a continuity correction of 0.5 to make the models stable and ensure convergence when necessary. GeMTC does not allow a continuity correction to be added, so we fit these models in OpenBUGS. We sampled 100,000 iterations for four chains after a burn-in of 50,000 iterations for models in GeMTC and 100,000 iterations for three chains after a burn-in of 50,000 iterations for models in OpenBUGS. We used prior distributions for the comparison of pharmacological interventions for between-study heterogeneity as suggested by Turner and colleagues. (Turner 2015).

We included all eligible studies in the primary analysis as long as a trial was connected to the main network. We based model comparison on the Deviance Information Criterion (DIC) (Spiegelhalter 2002). Differences of three points or more were considered meaningful. If models differed by less than three points, we selected the simplest model. We also calculated the posterior mean of the residual deviance to assess model fit. We considered this adequate when the posterior mean of the residual deviance approximated the number of unconstrained data points (Dias 2013a).

We estimated the probability that each treatment group ranked at one of the five possible positions in the grouped comparisons and presented mean and median ranks along with their 95% CrIs for all the primary and secondary outcomes with rank one, meaning that group was best for that outcome. We presented specific methodological details for each analysis in the result sections.

Direct pairwise meta-analysis

We performed direct pairwise meta-analyses using a fixed-effect or random-effects model in case of significant heterogeneity (I^2 greater than 50%) using Review Manager 5.4 (Review Manager 2020). We undertook a pairwise meta-analysis only where this was meaningful; that is, if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Subgroup analysis and investigation of heterogeneity

We classified doses of the ICS component in combination inhalers into medium and high dose and the results were reported individually as well as combining MD- and HD-ICS formulations of each combination therapy (i.e., dual versus triple therapy). We performed a subgroup analysis for exacerbation outcomes separating studies which required a history exacerbation in the previous year vs. those that did not to assess clinical heterogeneity (intransitivity) in the NMAs.

Sensitivity analysis

We performed sensitivity analyses for all the primary and secondary outcomes excluding studies at high risk of bias from the overall analysis and analysed studies of different duration separately for continuous outcomes and ACQ responders. We identified studies at high risk of bias using RoB 2 as described

above. We used a model not used in the primary analysis (fixed-effect or random-effects) as a sensitivity analysis for all pairwise meta-analyses and some outcomes in the NMA depending on the model fit.

Threshold analysis

We conducted threshold analyses at the contrast level for the exacerbation outcomes as part of a sensitivity analysis (Phillippo 2018; Phillippo 2019) to examine the impact of potential bias on each treatment contrast of the group comparisons. We did not conduct a threshold analysis for individual treatment comparisons as there was too much uncertainty in the estimates.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables using the outcomes listed under Types of outcome measures. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it related to the studies that contributed data for the prespecified outcomes (Guyatt 2011b). We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020), using GRADEpro software (GRADEpro GDT). We estimated anticipated absolute effects from each reference comparator (active control) in the included studies. We justified all decisions to downgrade the certainty of evidence using footnotes, and we made comments to aid the reader's understanding of the review where necessary. We presented NMA-summary of findings tables, proposed by Yepes-Nuñez and colleagues, for all outcomes in the NMA (Yepes-Nuñez 2019). It consisted of details of questions and interventions for a specific outcome, relative effect estimates for each intervention, anticipated absolute effects, GRADE certainty of evidence, rank probabilities of the intervention, and interpretations of findings.

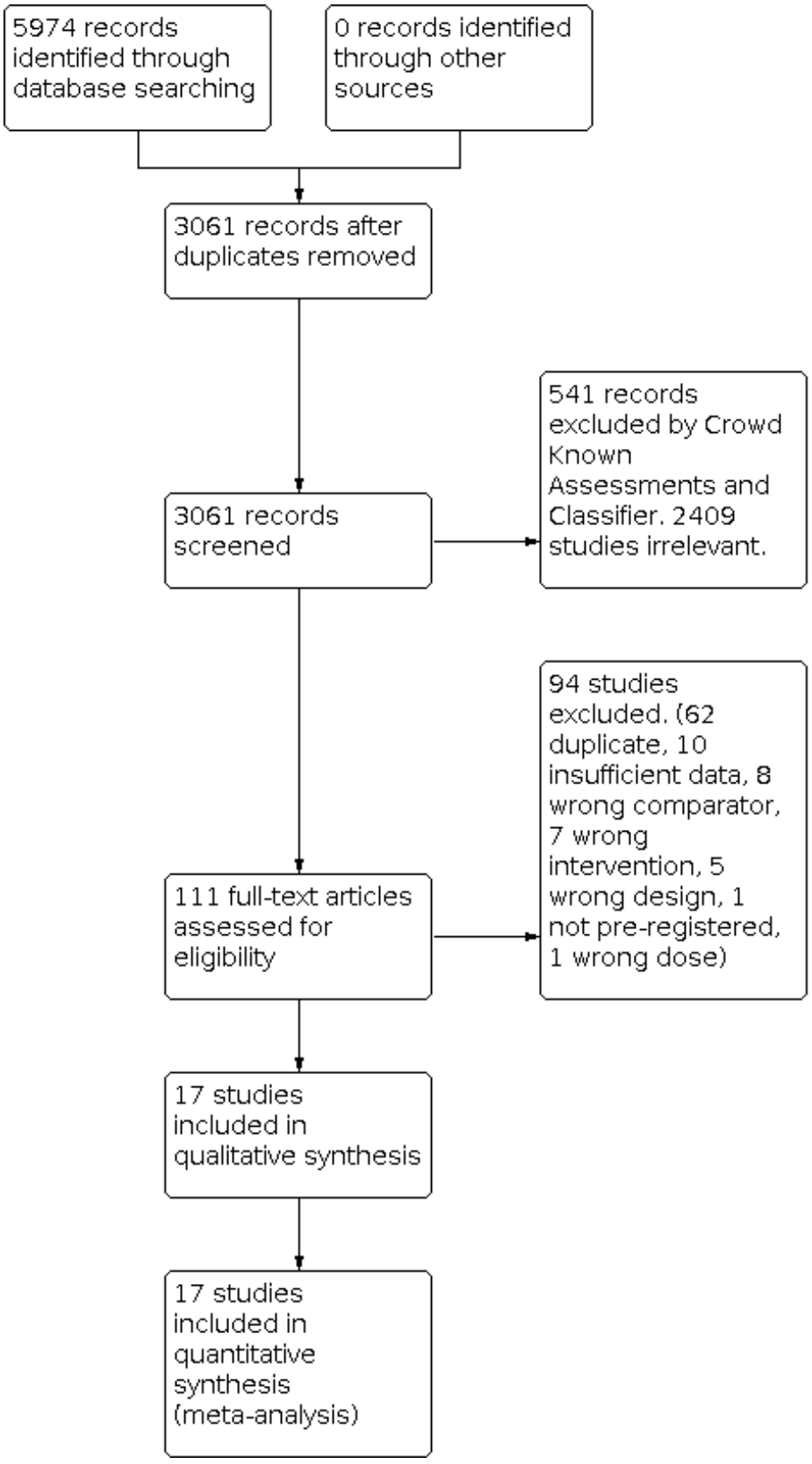
RESULTS

Description of studies

Results of the search

Database searching identified 5974 records, after we removed duplicates 3061records remained. The search was conducted up to 18 February 2022. 541 records were excluded by Crowd Known Assessments, and Classifier. We excluded 2402 studies on abstract review. We reviewed the remaining 118 studies for further details and excluded additional 101 studies for various reasons as shown in Figure 14.

Figure 14. PRISMA flow diagram



Included studies

We included 17 studies (19 trials) with a total of 17,161 participants. The study and patient characteristics including study durations, treatment arms, demographics of participants, and baseline pulmonary function are presented in Table 1 and details of each study are shown in Characteristics of included studies. The median duration of trials was 26 weeks (range 12 to 52). A history of at least one asthma exacerbation within the past year was required in five studies (Gessner 2020; Kerstjens 2012; Kerstjens 2020; Stempel 2016; Virchow 2019). Five studies only included an intra group comparison of MD-ICS/LABAs (Bernstein 2011; Bodzenta-Lukaszyk 2012; Cukier 2013; Papi 2007; Woodcock 2013). The number of included studies varied with each outcome due to data availability which is summarised in summary of findings tables. All studies were industry funded and conducted in multiple centres.

Participants

The mean age and proportion of male and white participants were 49.1 (standard deviation (SD) 15.0) years, 40 %, and 81 %, respectively. Current smokers were excluded in all studies. Previous smokers who had smoked 20 pack-years or greater were excluded in two studies (Busse 2008 and Gessner 2020) and those who had smoked 10 pack-years or greater were excluded in the rest. The mean forced expiratory volume in 1 second (FEV1) and FEV1 % predicted at the baseline were reported in 14 and 15 studies and 1.9 L and 61%, respectively.

Excluded studies

We excluded 94 studies after full-text review (Figure 14) which are recorded in Characteristics of excluded studies, with reasons for exclusion. We excluded Kerwin 2021 because ICS doses were not reported and glycopyrronium formulations used in the trial were not approved for clinical use or commercially available at the time of data extraction.

Risk of bias in included studies

Assessment of risk of bias in each study and outcome is available on the following website: https://www.dropbox.com/s/hi7z3h0ccabdhpb/RoB2%20Figure.xlsx?dl=0 and a summary is presented in Figure 15. ROB 2 judgements and supporting statements are reported in the analysis section for each study and outcome. There were no studies that we should clearly have excluded from this review because of differences in baseline characteristics or poor quality.

Figure 15. Summary of risk of bias assessment using Cochrane 'Risk of bias 2' tool. ACQ: Asthma Control Questionnaire; AE: adverse event; AQLQ: Asthma Quality of Life Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SAE: serious adverse event.

Figure 15. (Continued)

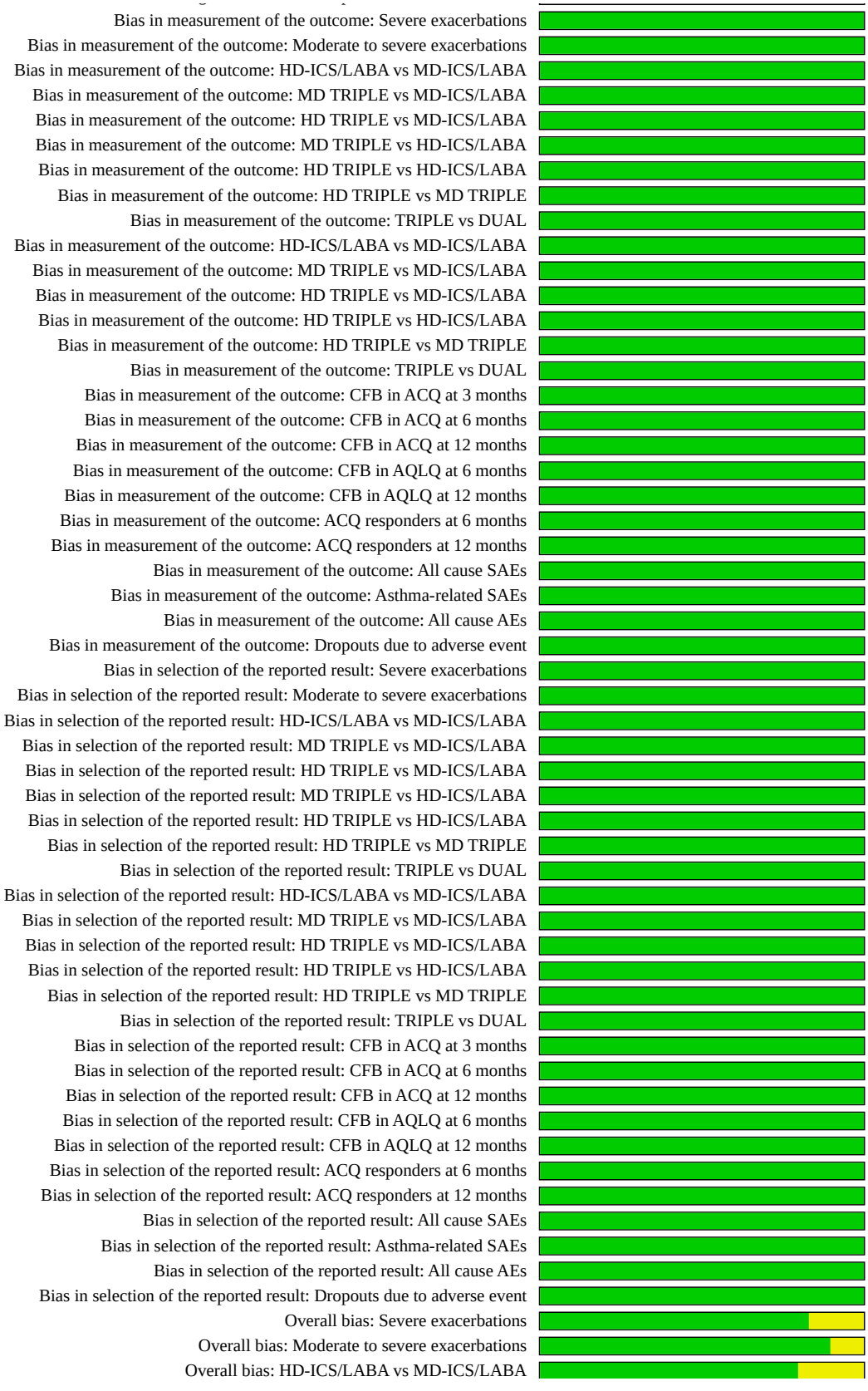
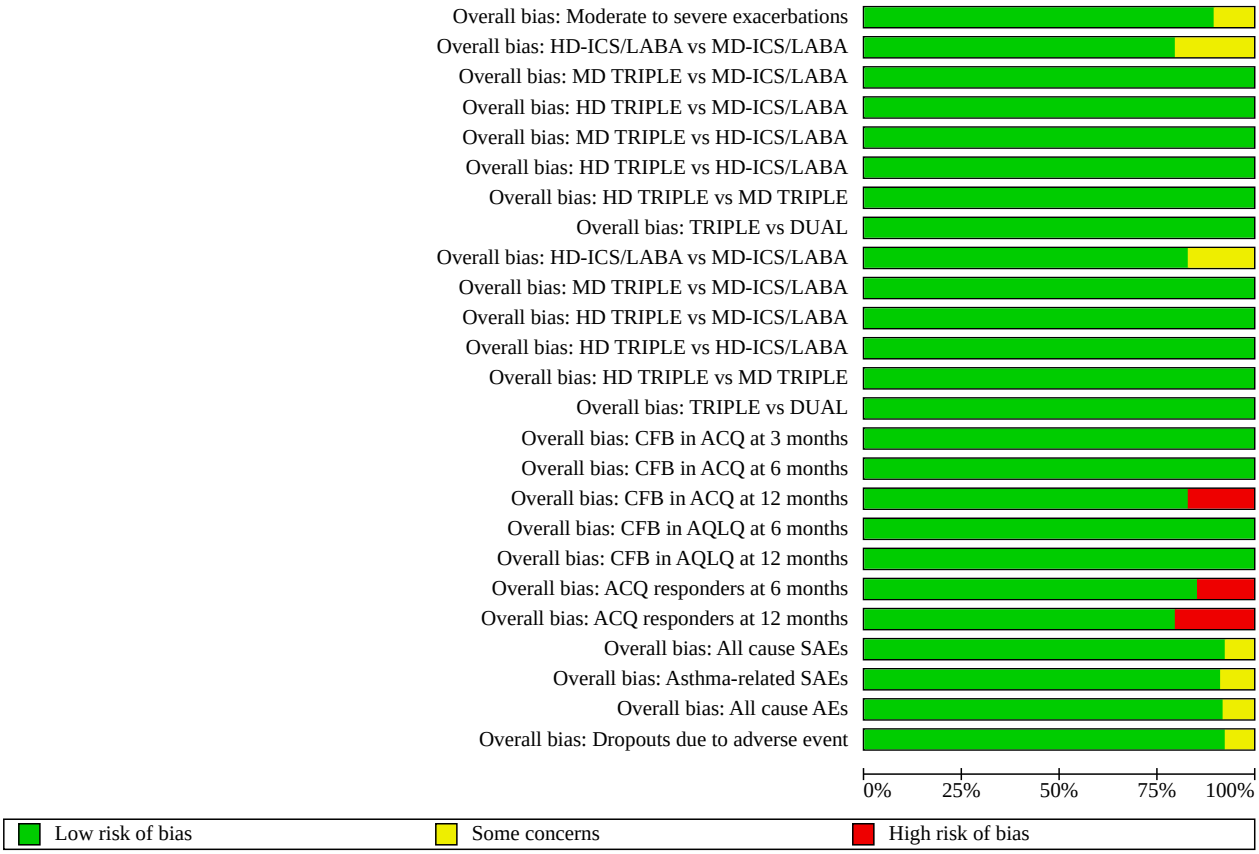


Figure 15. (Continued)



Allocation (selection bias)

All studies were randomised controlled trials (RCT)s and industry sponsored. We confirmed a random allocation sequence using a validated computerised system in 12 studies and assumed an industry-standard method was used forfive5 studies (Busse 2008; Cukier 2013; Kerstjens 2012; Mansfield 2017; Papi 2007). We considered them to be at low risk for random sequence generation and allocation concealment (concealment assumed by automatisation).

Blinding (performance bias and detection bias)

Three studies (Busse 2008; Cukier 2013; Mansfield 2017) were open label and judged to raise "some concerns". The rest of the studies were double-blinded which were rated as at low risk of bias (blinding of participants, personnel, and outcome assessors).

Incomplete outcome data (attrition bias)

Attrition rates for CFB in ACQ at 12 months in Lee 2020 and ACQ responders at 6 and 12 months in van Zyl-Smit 2020 were 80%, 18% to 23%, and 24%, respectively. We rated the risk of the bias to be high for these outcomes. We tested whether the above studies compromised the validity of the results by excluding them which is reported in the results section.

Selective reporting (reporting bias)

We included pre-registered trials only and all studies reported expected outcomes in publications or industry generated reports on their websites (e.g., Clinical Study Report).

Other potential sources of bias

Study characteristics across the treatment groups are presented in Table 2 for clinical heterogeneity assessment. The MD-ICS/LABA group had a lower proportion of participants who had an asthma exacerbation within the previous year (33%) compared to other groups (60% or greater). Otherwise, demographic and clinical characteristics of participants were similar across the treatment groups. We conducted a subgroup analysis for exacerbation outcomes separating studies requiring or not requiring a history of asthma exacerbation in the previous year and labelled them as high and low risk group, respectively.

Effects of interventions

See: **Summary of findings 1** NMA Summary of Findings for severe exacerbations (asthma-related hospitalisations); **Summary of findings 2** Asthma exacerbations - pairwise comparisons; **Summary of findings 3** NMA Summary of Findings for moderate to severe (steroid-requiring) exacerbations; **Summary of findings 4** NMA Summary of Findings for change from baseline in ACQ scores at 3 months; **Summary of findings 5** NMA Summary of Findings for change from baseline in ACQ scores at 6 months;

Summary of findings 6 NMA Summary of Findings for change from baseline in ACQ scores at 12 months; **Summary of findings 7** Asthma Control Questionnaire: change from baseline - pairwise comparisons ‡; **Summary of findings 8** NMA Summary of Findings for change from baseline in AQLQ scores at 6 months; **Summary of findings 9** NMA Summary of Findings for change from baseline in AQLQ scores at 12 months; **Summary of findings 10** Asthma Quality of Life Questionnaire: change from baseline - pairwise comparisons ‡; **Summary of findings 11** NMA Summary of Findings for ACQ responders at 6 months; **Summary of findings 12** NMA Summary of Findings for ACQ responders at 12 months; **Summary of findings 13** Asthma Control Questionnaire responders - pairwise comparisons; **Summary of findings 14** NMA Summary of Findings for all-cause SAEs; **Summary of findings 15** Serious adverse events, adverse events, and dropouts due to adverse event - pairwise comparisons; **Summary of findings 16** NMA Summary of Findings for asthma-related SAEs; **Summary of findings 17** NMA Summary of Findings for all-cause AEs; **Summary of findings 18** NMA summary of findings table for dropouts due to AEs

1. Primary outcome, asthma exacerbations

1.1 Severe asthma exacerbations (asthma-related hospitalisations)

1.1.1 Grouped treatments

For this outcome, 7 trials (6911 participants) comparing four treatments provided evidence as dichotomous data, and 1 trial (3072 participants) provided evidence as logHR data (Kerstjens 2020). A network diagram for the studies included in the NMA is presented in Figure 1.

A summary of the studies included in the analysis is presented in Appendix 2. Bernstein 2015 was excluded from the NMA, as both treatment arms reported zero events, effectively not contributing any evidence to the network. A single study (Kerstjens 2020) contributed logHR evidence on the LD Triple versus MD-ICS/LABA and MD Triple versus HD-ICS/LABA comparisons, but only two unconnected pairwise comparisons could be included in the NMA as there was no way to calculate the covariance matrix from the evidence available. These two comparisons were included as if they were from independent studies as they had no treatment arms in common.

1.1.1.1 Model selection and inconsistency checking

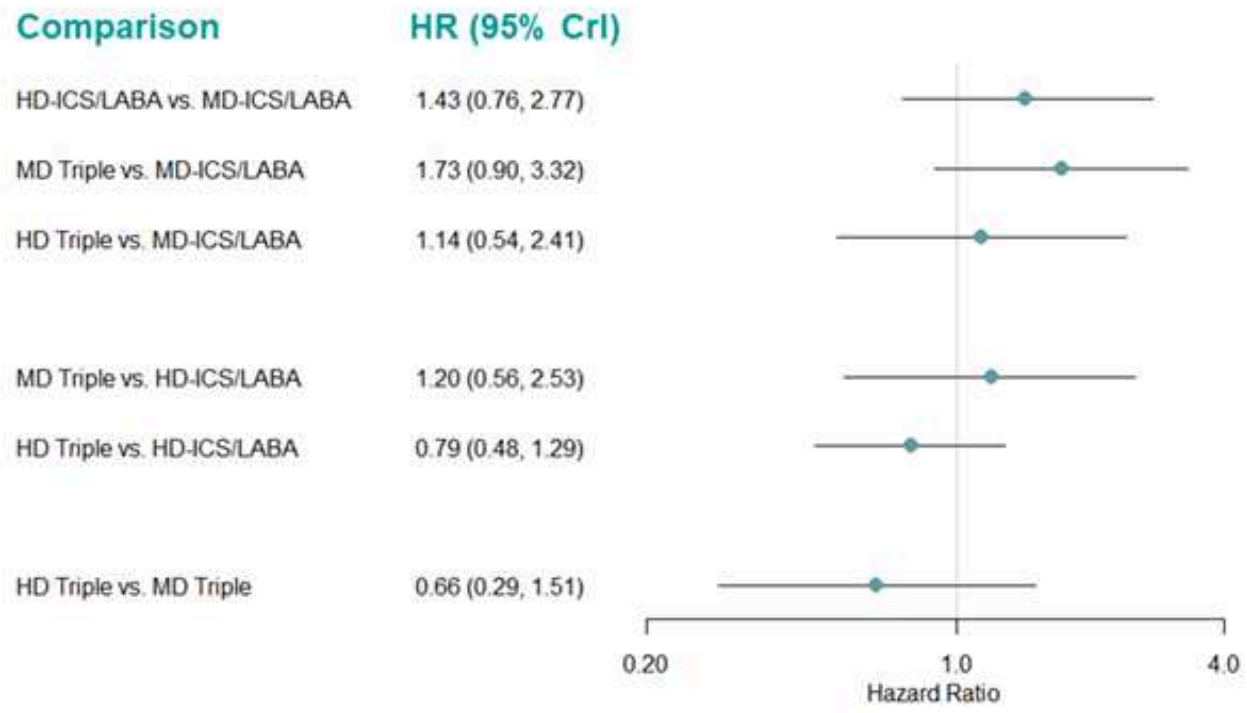
A half-normal (0.5^2) prior distribution was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both models fit the data well. The between-study heterogeneity was low but had a wide credible interval (CrI). As the difference in Deviance Information Criterion (DIC) between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen for the overall analysis, as well as the subgroup analyses. Results for the fixed-effect model are presented in Section 1.1.1.2.

A node-splitting model was fit to assess the inconsistency in the model. The results of the node-splitting model are presented in Table 3. There was no evidence to suggest there was any inconsistency in the model.

1.1.1.2 NMA results

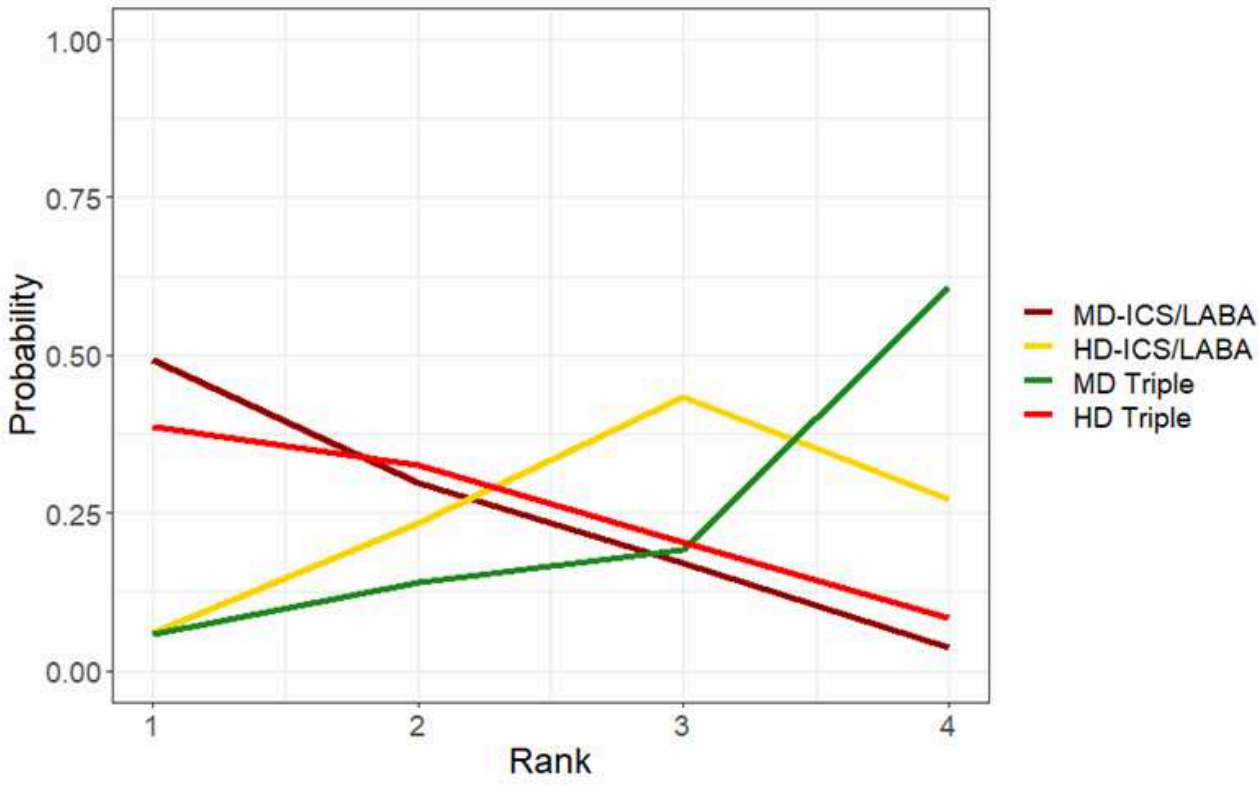
Hazard ratios (HRs) for severe exacerbations in grouped treatments are presented in Figure 16. The HRs for the comparison of all treatment groups against each other are reported in Table 4. There is insufficient evidence to suggest that there is a change in hazards of severe exacerbations for any of the treatment comparisons. An NMA summary of findings is presented in Summary of findings 1

Figure 16. Forest plot of hazard ratios for severe exacerbations for grouped treatments. Hazard ratios less than one favors the first named treatment. CrI: Credible Interval; HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 17, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 5. MD-ICS/LABA and HD Triple have a higher probability of being better than the other three treatments (median rank 1.0 [95% CrI 1 to 3] and 2 [1 to 4], respectively). However, treatment ranks are very uncertain, displaying wide credible intervals, and all treatments have rank probabilities of 50% and below.

Figure 17. Rank plots for grouped treatments for severe exacerbations (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

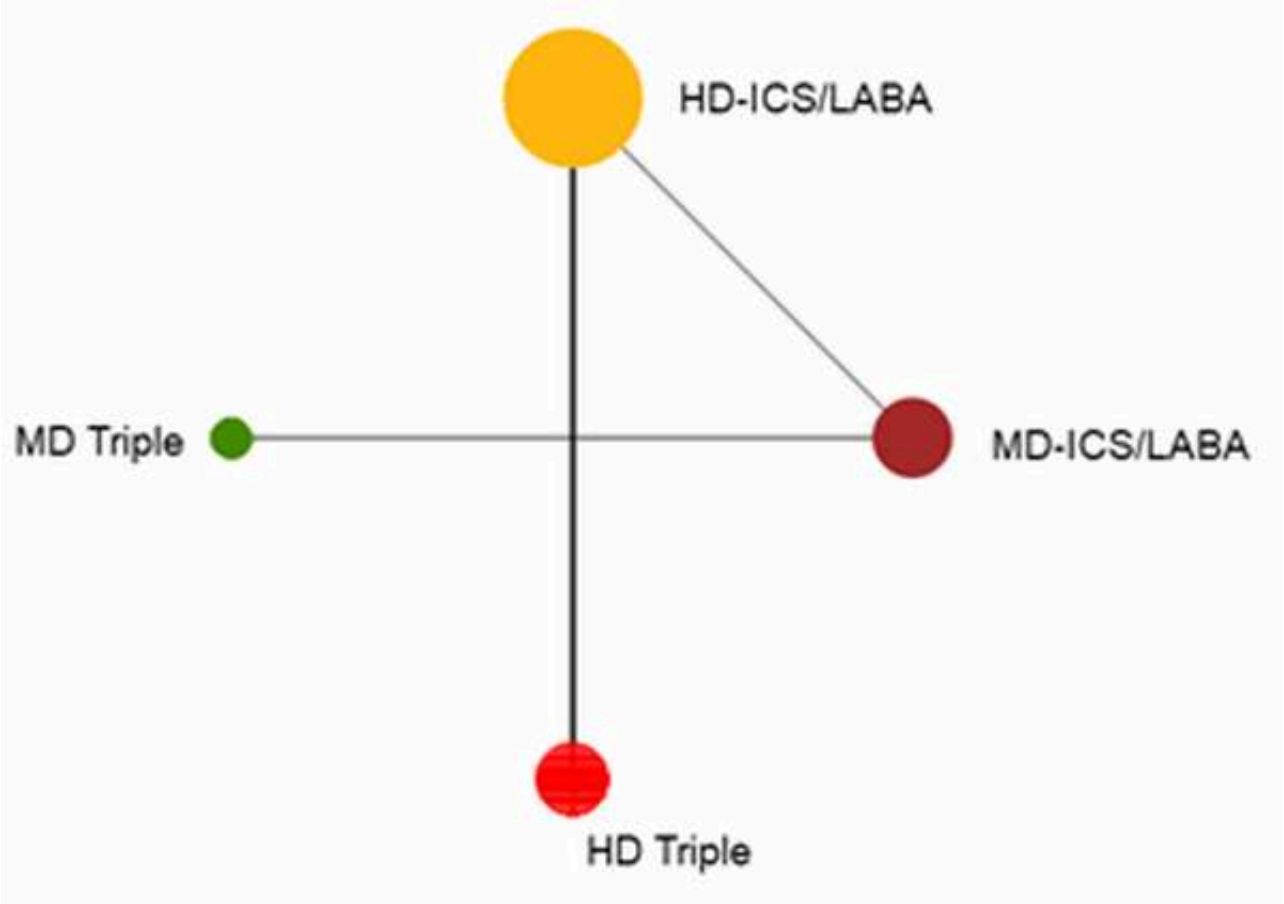


Results for the subgroups were largely consistent with the overall analysis (Table 4). The only exception is the comparison of HD-ICS/LABA vs. MD-ICS/LABA where HD-ICS/LABA increased the hazards of severe exacerbations compared to MD-ICS/LABA in the high-risk group (HR 13.4 [95% CrI 2.0 to 191.2]), although the credible interval indicates that this estimate is very uncertain. Due to the sparse nature of the network for the high-risk group, HRs for the HD-ICS/LABA vs. MD-ICS/LABA, HD Triple vs. MD-ICS/LABA, and HD Triple vs. MD Triple comparisons were extremely uncertain. Details of the subgroup analyses are described below.

1.1.1.2.1 High-risk subgroup

For this outcome, 5 trials (7063 participants) provided evidence as dichotomous data across four individual treatments. A network diagram for the studies included in the NMA is presented as Figure 18. This network is very sparse, treatments are only connected by a single study and there are no evidence loops.

Figure 18. Network diagram for severe exacerbations for high-risk individuals. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

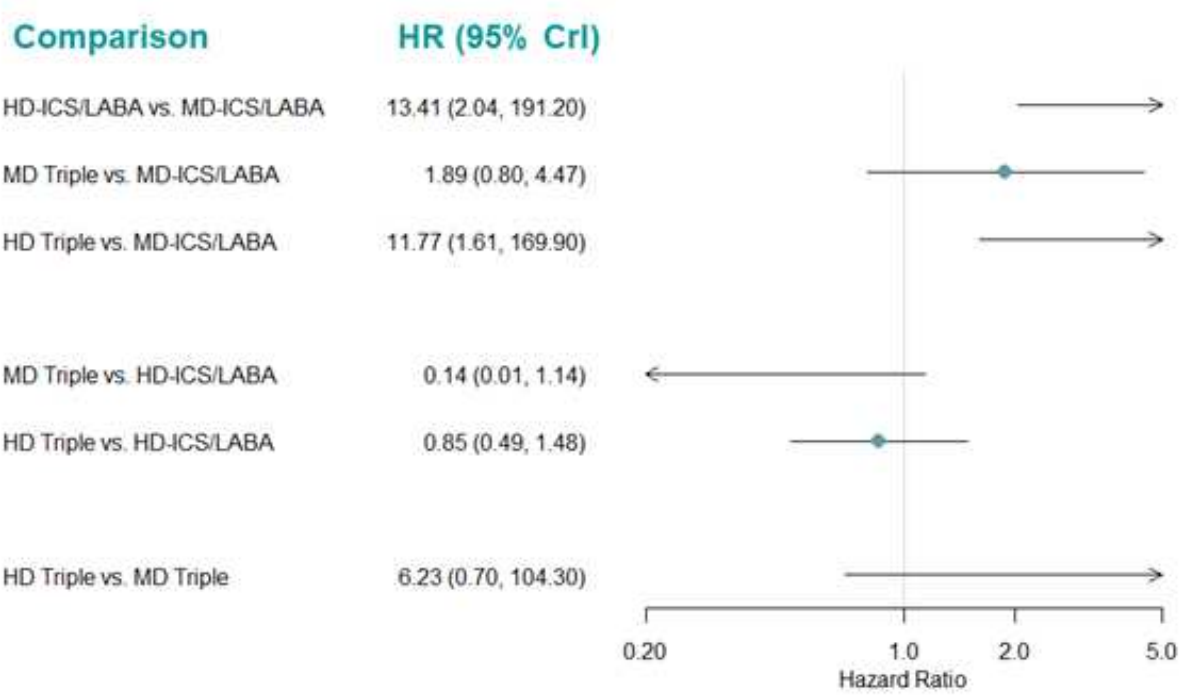


A summary of the studies included in the analysis is presented in Appendix 2. A single study (Kerstjens 2020) contributed logHR evidence, but only two unconnected pairwise comparisons were included in the NMA as independent studies as there was no way to calculate the covariance matrix from the evidence available.

A half-normal(0.50^2) prior distribution was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed- and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. There was moderate between-study heterogeneity with a wide 95% credible interval. As the difference in DIC between the fixed- and random-effects models was less than 3, the simpler fixed-effect model was chosen. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

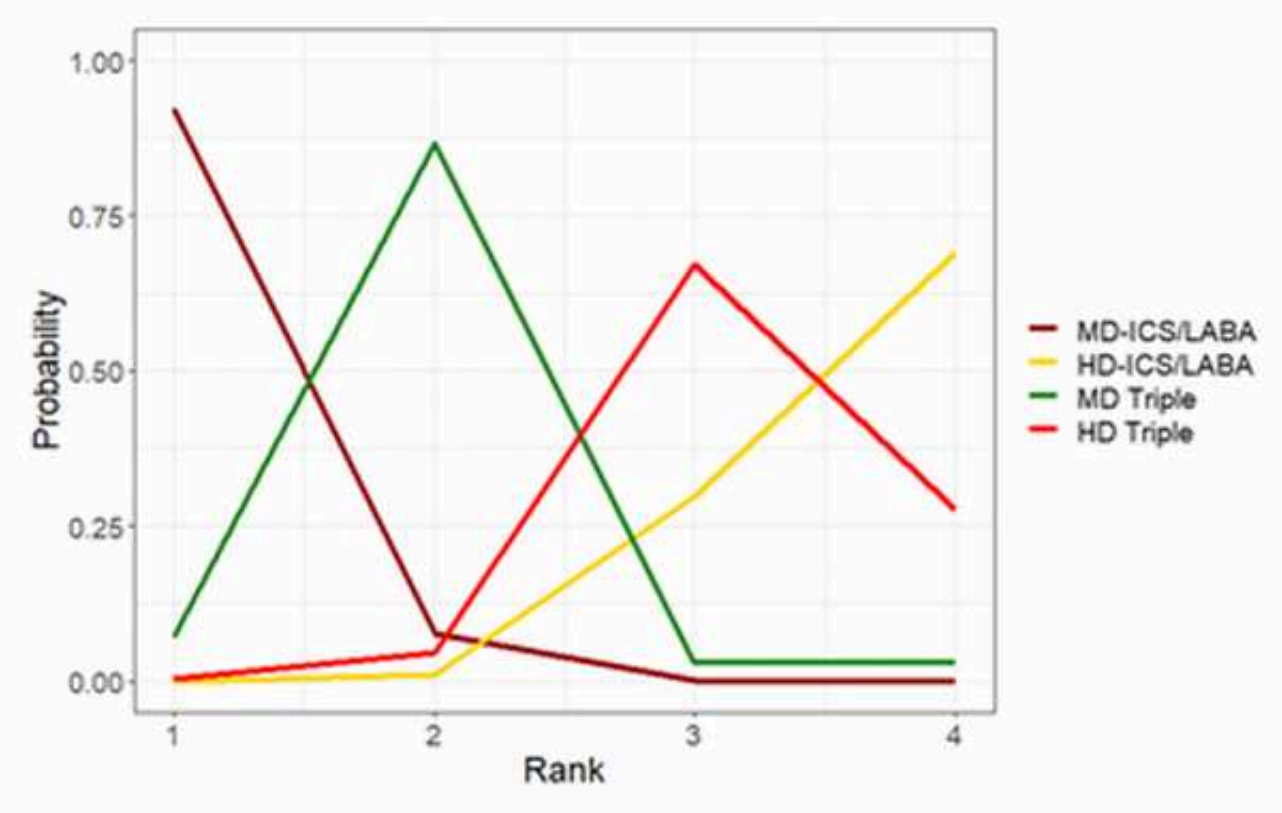
Hazard ratios for severe exacerbations in high-risk studies are presented in Figure 19. The HRs for the comparison of all treatment groups against each other are reported in Table 4. The impact of the sparse evidence, exhibited in the network diagram can be seen in the number of comparisons for which HRs were extremely uncertain (highlighted in yellow in Table 4).

Figure 19. Forest plot of hazard ratios for severe exacerbations for high-risk individuals. Hazard ratio less than one favours the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots are presented in Figure 20, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 5. MD-ICS/LABA had the highest probability of being ranked the best treatment (median rank 1 [95% CrI 1 to 2]). However, the 95% credible intervals for all other treatments are wide, reflecting the high uncertainty in the HRs estimated and treatment rankings.

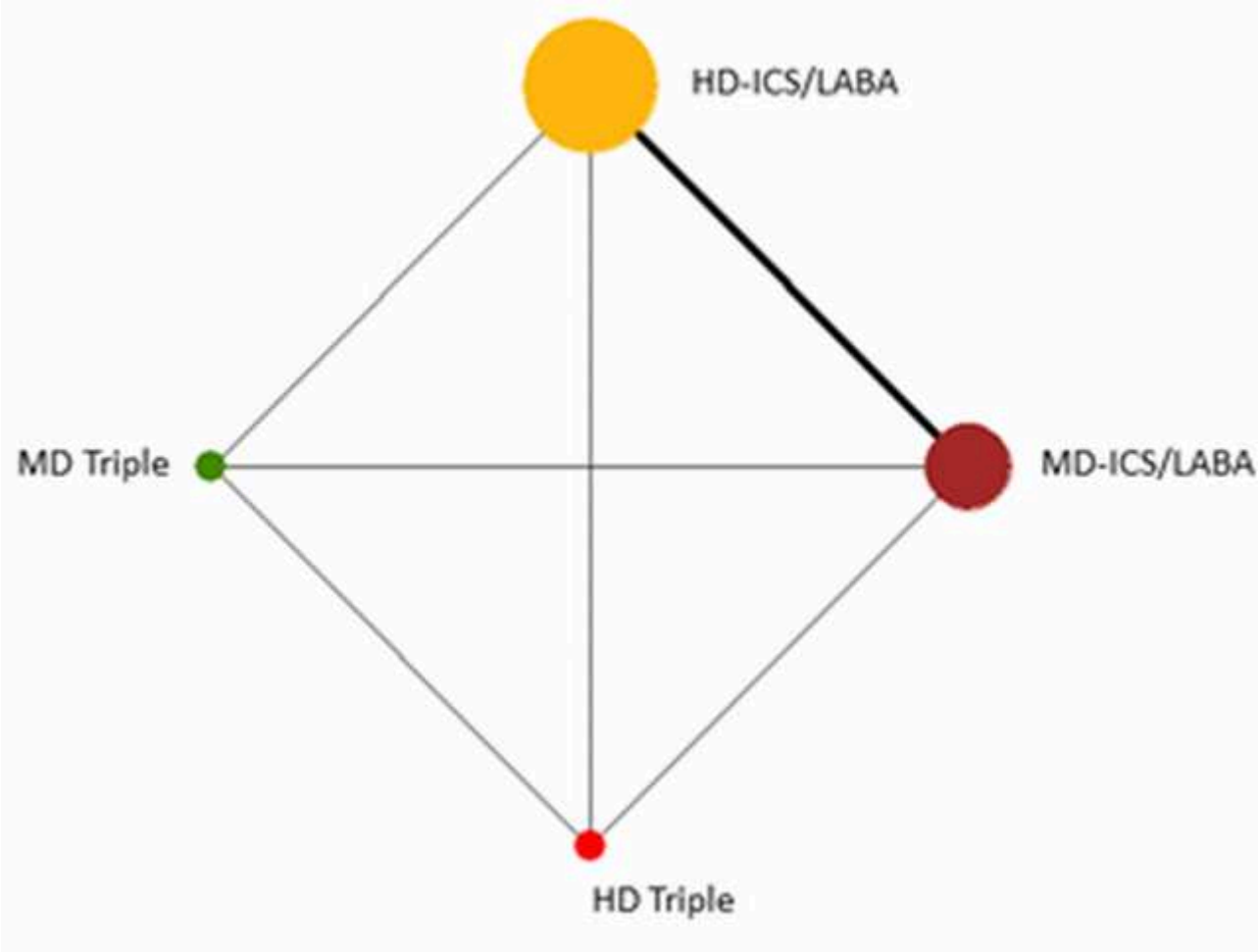
Figure 20. Rank plots for severe exacerbations for high-risk individuals. (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



1.1.1.2.2 Low-risk subgroup

For this outcome, 5 trials (4436 participants) comparing four treatments provided evidence as dichotomous data. A network diagram for the studies included in the NMA is presented in Figure 21. A summary of the studies included in the analysis is presented in Appendix 2. Bernstein 2015 was excluded from the NMA, as both treatment arms reported zero events, effectively not contributing any evidence to the network.

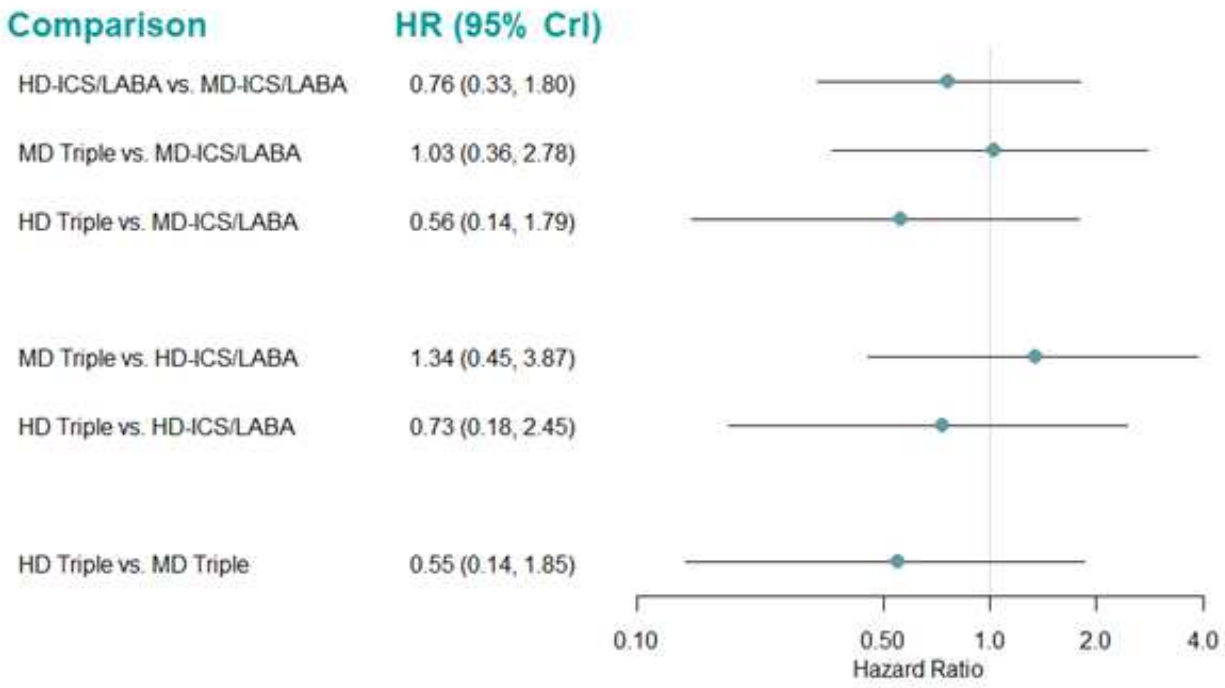
Figure 21. Network diagram for severe exacerbations for low-risk individuals. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



A half-normal(0.5^2) prior distribution was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both models fit the data well. There was moderate between-study heterogeneity, with a wide 95% credible interval. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. There is no potential for inconsistency in this network as there is no independent indirect evidence for any of the comparisons.

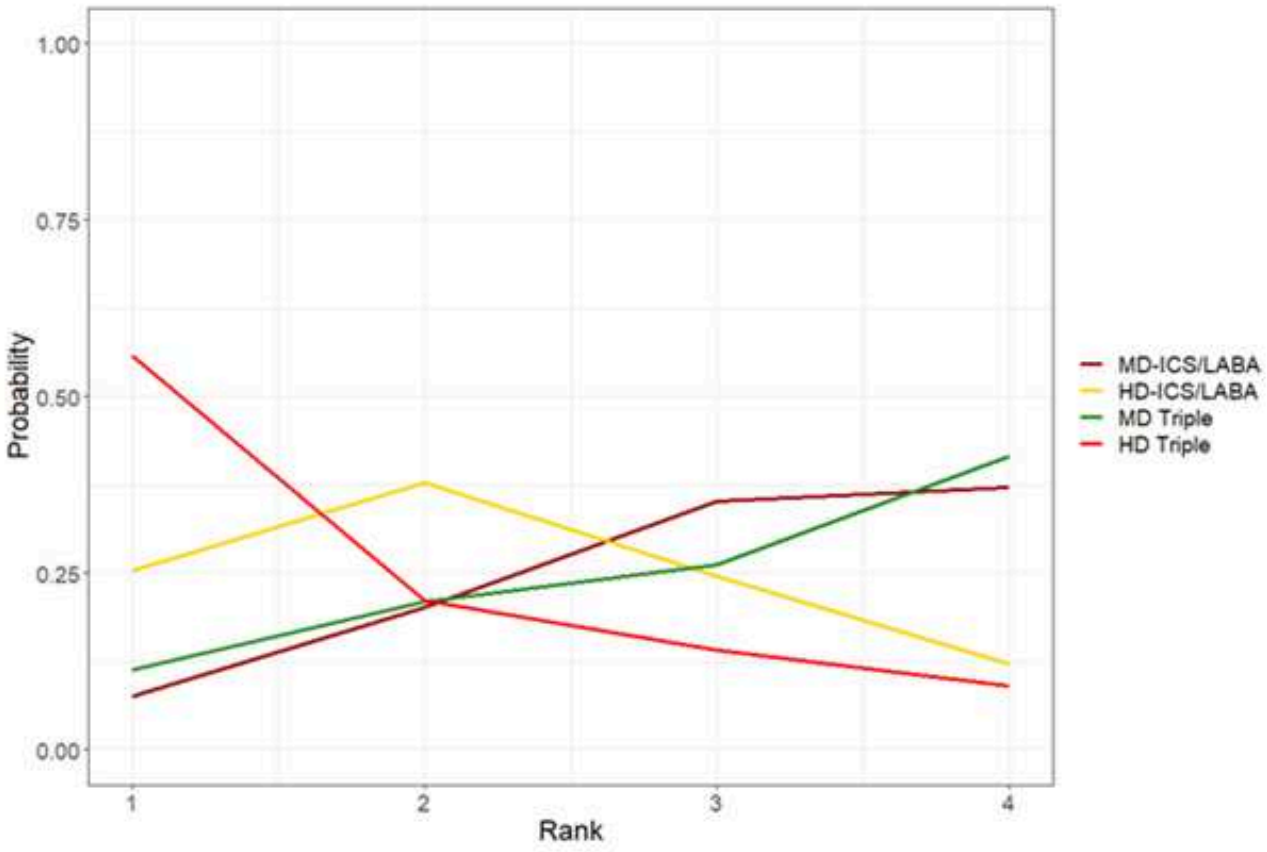
Hazard ratios for severe exacerbations in low-risk studies are presented in Figure 22. The HRs for the comparison of all treatment groups against each other are reported in Table 4. There is insufficient evidence to suggest that there is a change in hazards of severe exacerbations for any of the treatment comparisons.

Figure 22. Forest plot of hazard ratios for severe exacerbations for low-risk individuals. Hazard ratio less than one favours the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 23, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 5. HD Triple ranks higher than the other treatments (median rank 1 [95% CrI 1 to 4]), but the wide credible intervals demonstrate the uncertainty in treatment rankings.

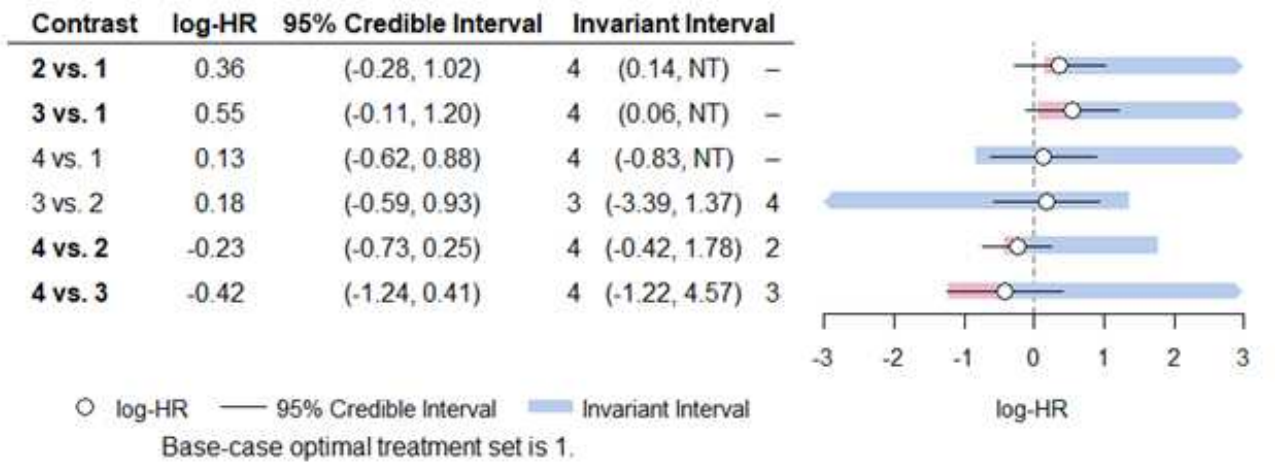
Figure 23. Rank plots for severe exacerbations for low-risk individuals. (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



1.1.1.3 Threshold analysis

The forest plot for the threshold analysis is presented in Figure 24 and the thresholds and new optimum treatments, based only on the treatment with the best relative effect, are presented in Table 6. Credible intervals for the HD-ICS/LABA vs. MD-ICS/LABA, MD Triple versus MD-ICS/LABA, HD Triple versus HD-ICS/LABA, and HD Triple versus MD Triple comparisons extend beyond the limits of the invariance intervals, suggesting the recommended treatment is sensitive to uncertainty in the data. The recommended treatment did seem to be sensitive to moderate potential bias in the negative direction for the HD-ICS/LABA vs. MD-ICS/LABA, MD Triple vs. MD-ICS/LABA, and HD Triple versus HD-ICS/LABA comparisons, which would make HD Triple the recommended treatment. This is consistent with the ranks discussed in Section 1.1.1.2, where HD Triple is ranked the next best treatment after MD-ICS/LABA.

Figure 24. Forest plot for threshold analysis for grouped treatments for severe exacerbations (fixed effect model) Treatment Codes: 1=MD-ICS/LABA, 2= HD-ICS/LABA, 3=MD Triple, 4= HD Triple. The optimum treatment for this analysis was MD-ICS/LABA. HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LD: low dose; MD: medium dose; NT: no threshold (no amount of change in this direction would change the recommendation).



1.1.1.4 Pairwise meta-analysis

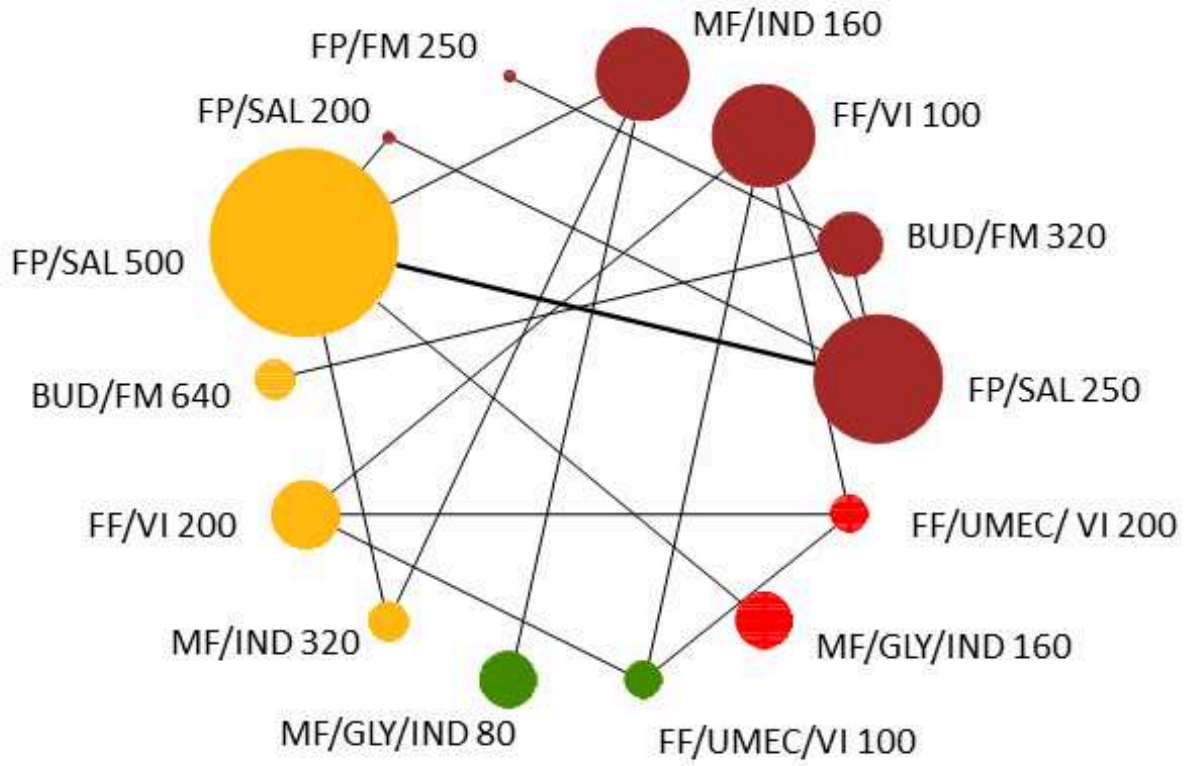
The evidence suggests there is little or no difference in severe exacerbations for any of the treatment comparisons (7 trials, 6911 participants; [low to moderate certainty]) (Analysis 1.1: Summary of findings 2). The results are qualitatively similar to those of the NMA as shown in Table 3. There is no difference in severe exacerbations comparing triple (ICS/LABA/LAMA) with dual therapy (ICS/LABA) when analysed combining MD- and HD-ICS formulations in each combination therapy. There was no difference in the results between fixed-effect and random-effects models.

The results of subgroup analyses are presented in Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5; Analysis 6.6; Analysis 6.7). The results are consistent with the whole group analysis except for HD-ICS/LABA vs. MD-ICS/LABA in the high-risk group in which HD-ICS/LABA was associated with a higher risk of severe exacerbations compared to MD-ICS/LABA (1 trial, 1562 participants; RR 8.27 [95% CI 1.09 to 62.72], Analysis 6.1).

1.1.2 Individual treatments

For this outcome, 9 trials (7217 participants) provided evidence as dichotomous data, and 1 trial (3072 participants) provided evidence as logHR data (Kerstjens 2020), comparing 14 treatments across the network. A network diagram for the studies included in the NMA is presented as Figure 25. A summary of the studies included in the analysis is presented in Appendix 4. The dichotomous study Bernstein 2015 was excluded from the NMA, as both treatment arms reported zero events, effectively not contributing any evidence to the network. A single study (Kerstjens 2020) contributed logHR evidence, but only two unconnected pairwise comparisons were included in the NMA as independent studies as there was no way to calculate the covariance matrix from the evidence available. We added a continuity correction of 0.5 to the zero count events to help improve model convergence due to the sparsity of the evidence in Mansfield 2017.

Figure 25. Network diagram for severe exacerbations for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. BUD:budesonide, CrI:Credible Interval, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI:vilanterol.



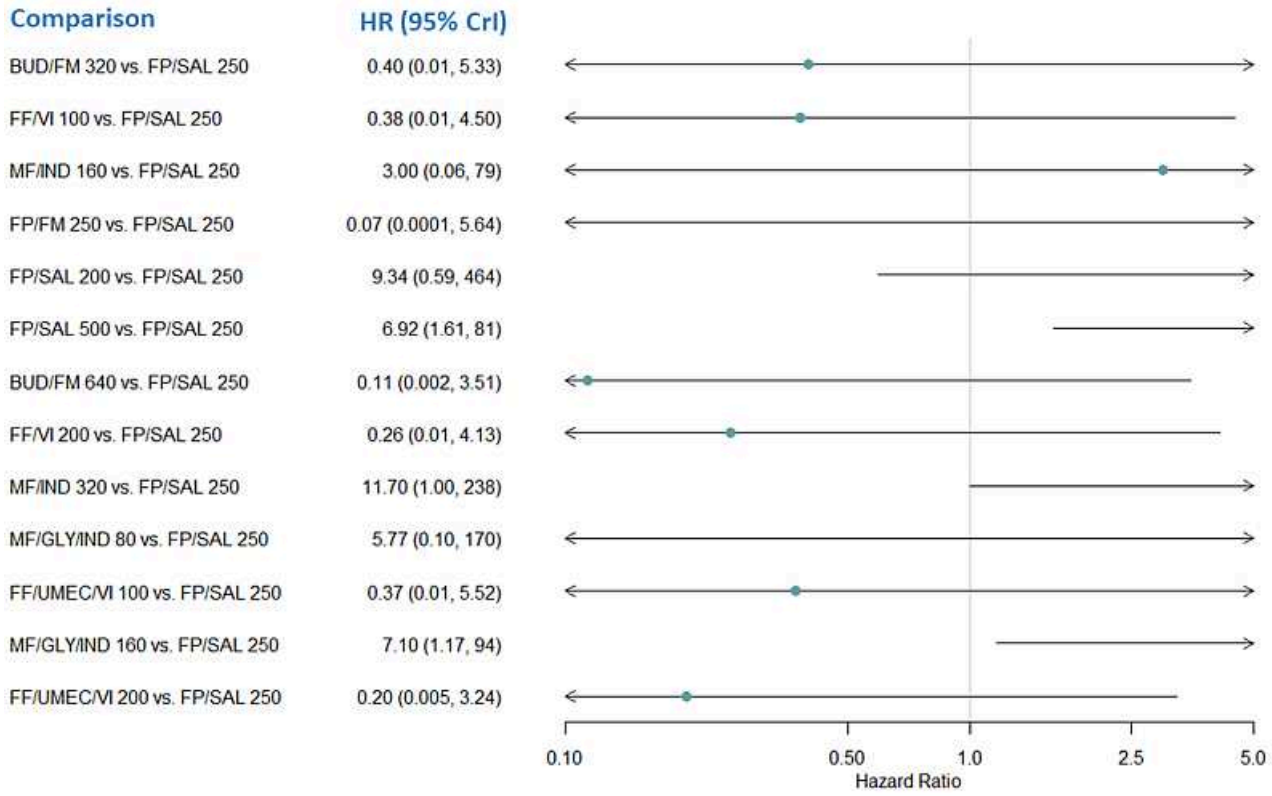
1.1.2.1 Model selection and inconsistency checking

A half-normal (0, 0.5^2) prior was used to model the between-study heterogeneity in the random-effects model (Röver 2021). Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low but with a wide credible interval. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 1.1.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

1.1.2.2 NMA results

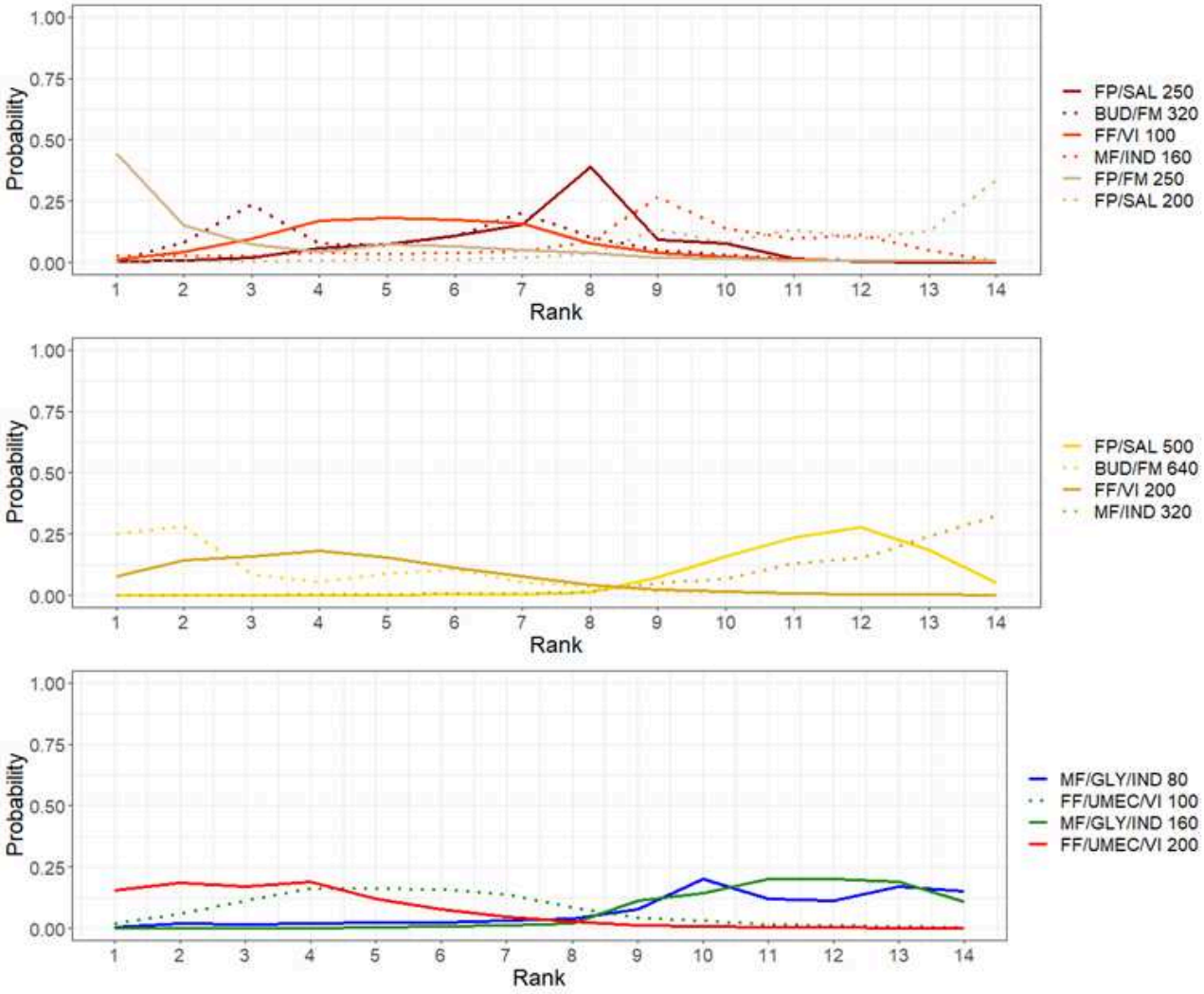
Hazard ratios for severe exacerbations in individual treatments, compared to fluticasone propionate/salmeterol (FP/SAL) 250/50 µg (MD-ICS/LABA) are presented in Figure 26. The HRs for the comparison of all treatment groups against each other are reported in Table 7. The impact of the sparse evidence available for each comparison can be seen in the number of comparisons for which the HRs are extremely uncertain (highlighted in yellow in Table 7).

Figure 26. Forest plot of hazard ratios relative to FP/SAL 250 for severe exacerbations for individual treatments. Hazard ratio less than one favors the first named treatment. BUD:budesonide, CrI:Credible Interval, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, HR: hazard ratio; IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, UMEC: umeclidinium, VI:vilanterol



The rank plots for individual treatments are presented in Figure 27, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 8. Overall, treatment ranks are very uncertain displaying wide credible intervals, and all treatments have rank probabilities of less than 50%.

Figure 27. Rank plots for individual treatments for severe exacerbations (fixed effect model). Line colors denote the treatment group. BUD:budesonide, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



1.2 Primary outcome: moderate to severe (steroid-requiring) asthma exacerbations

1.2.1 Grouped treatments

For this outcome, 10 trials (12,407 participants) comparing four treatments provided evidence as dichotomous data. A network diagram for the studies included in the NMA is presented as Figure 2. A summary of the studies included in the analysis is presented in Appendix 5.

1.2.1.1 Model selection and inconsistency checking

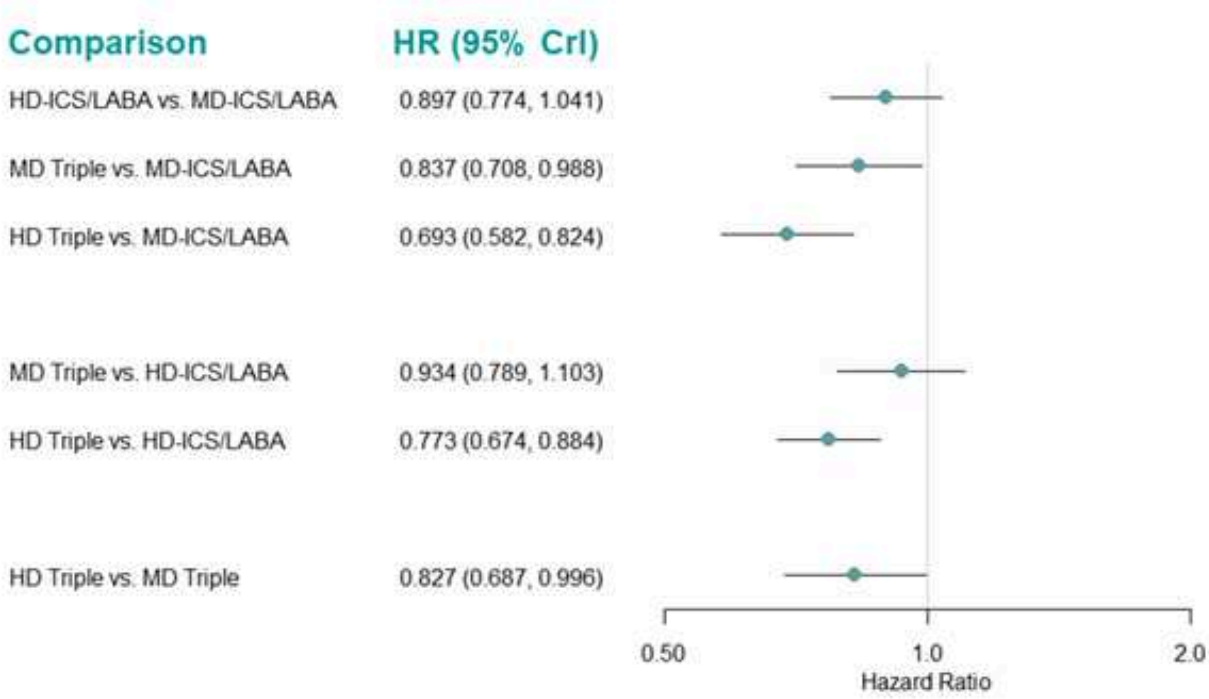
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen for the overall analysis, as well as the subgroup analyses. Results for the fixed-effect model are presented in Section 1.2.1.2.

A node-splitting model was fit to assess the inconsistency in the model. The results of the node-splitting model are presented in Table 9. There was no evidence to suggest any inconsistency in the model.

1.2.1.2 NMA results

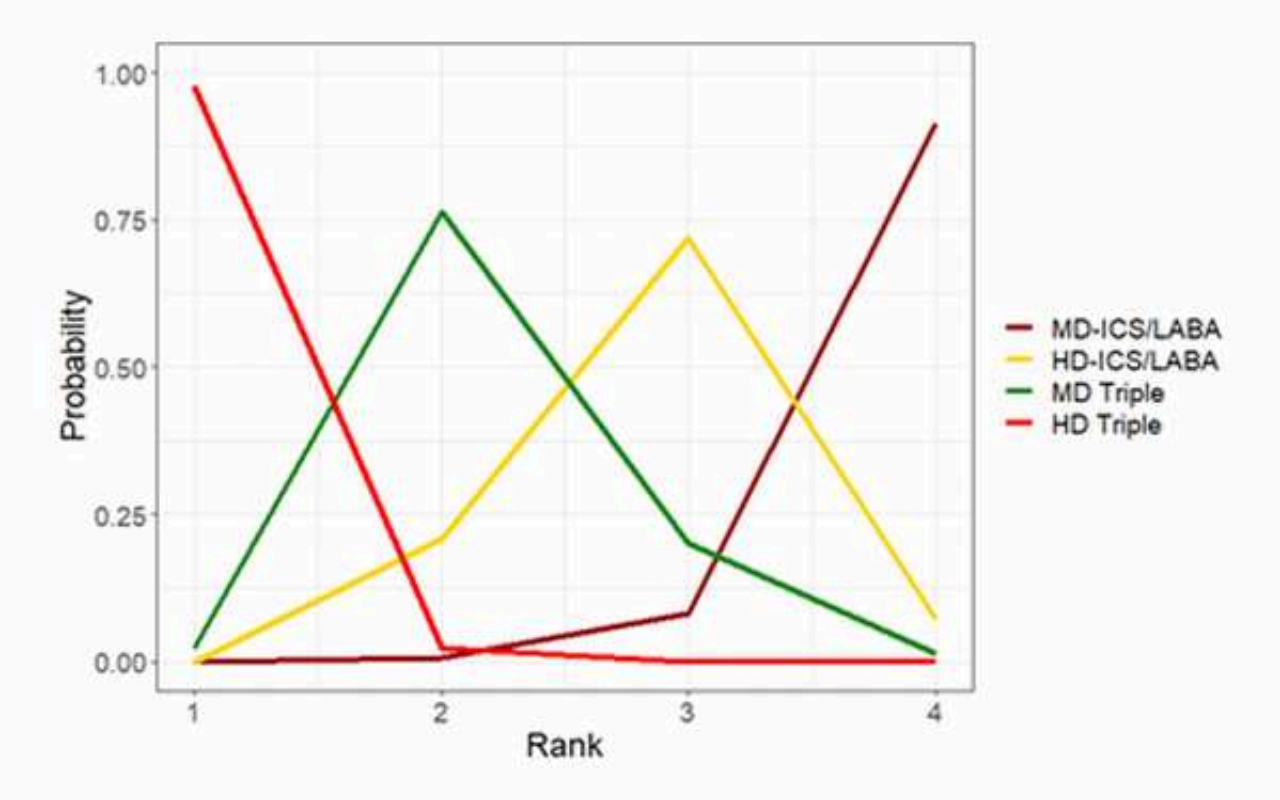
Hazard ratios for moderate to severe exacerbations in grouped treatments are presented in Figure 28. The HRs for the comparison of all treatment groups against each other are reported in Table 10. There is evidence to suggest that HD Triple reduces the hazards of moderate-severe exacerbations compared to MD-ICS/LABA and HD-ICS/LABA (HR 0.69 [95% CrI 0.58 to 0.82] and 0.93 [0.79 to 0.88], respectively). There is also marginal evidence to suggest that MD Triple reduces the hazards of moderate-severe exacerbations compared to MD-ICS/LABA (HR 0.84 [95% CrI 0.71 to 0.99] and HD Triple reduces the hazards of moderate-severe exacerbations compared to MD Triple (HR 0.83, 95% CrI [0.69 to 0.996], absolute risk reduction (ARR) 34 fewer per 1000 patients). An NMA summary of findings is presented in Summary of findings 3.

Figure 28. Forest plot of hazard ratios relative for moderate to severe exacerbations for grouped treatments. Hazard ratio less than one favors the first named treatment. CrI: Credible Interval; HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 29, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 11. HD Triple ranks higher than the other treatments (median rank 1 [95%CrI 1 to 1]).

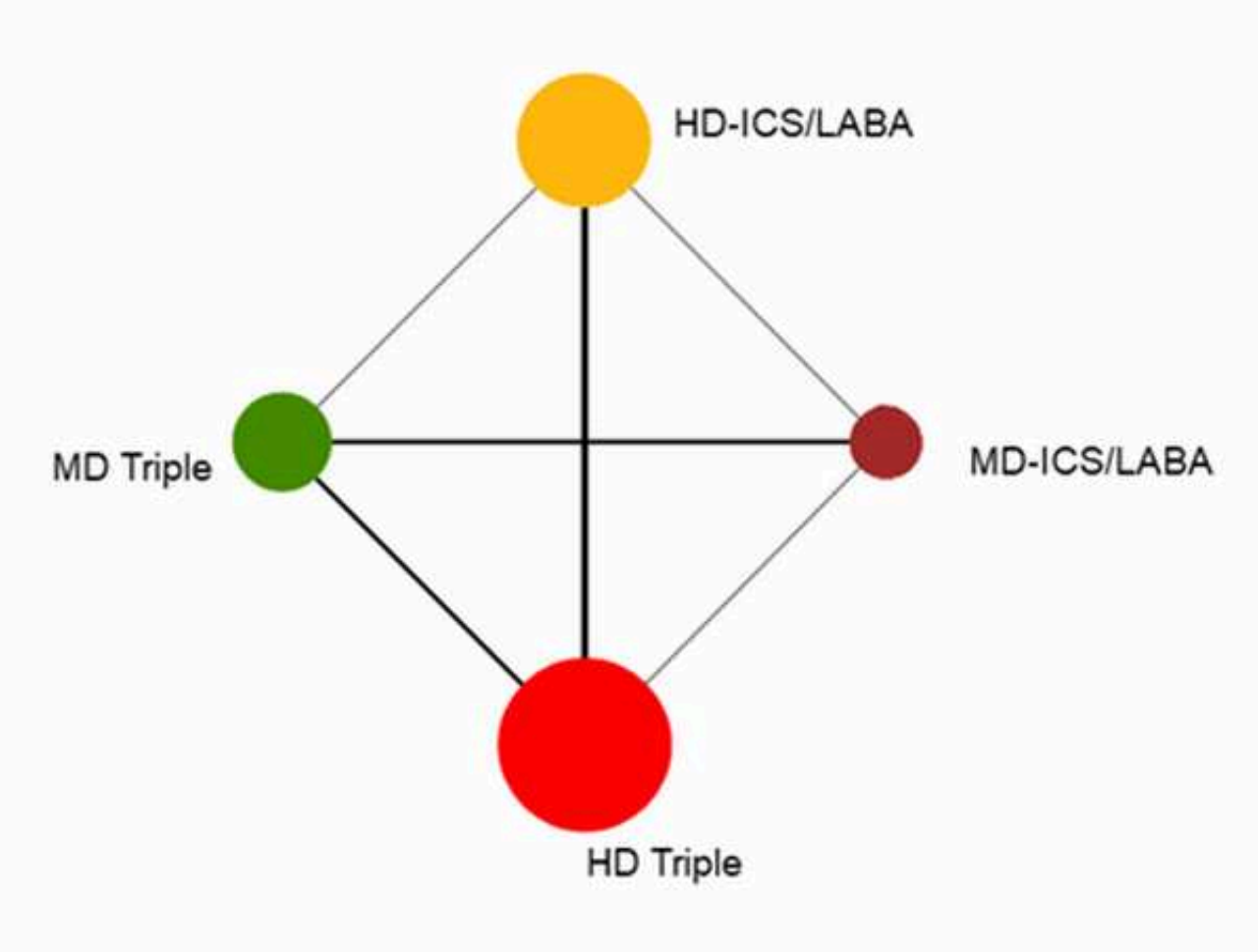
Figure 29. Rank plots for grouped treatments for moderate to severe exacerbations (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



1.2.1.2.1 High-risk subgroup

For this outcome, 5 trials (7063 participants) provided evidence as dichotomous data across four individual treatments. A network diagram for the studies included in the NMA is presented in Figure 30. A summary of the studies included in the analysis is presented in Appendix 5.

Figure 30. Network diagram for moderate to severe exacerbations for high-risk individuals. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

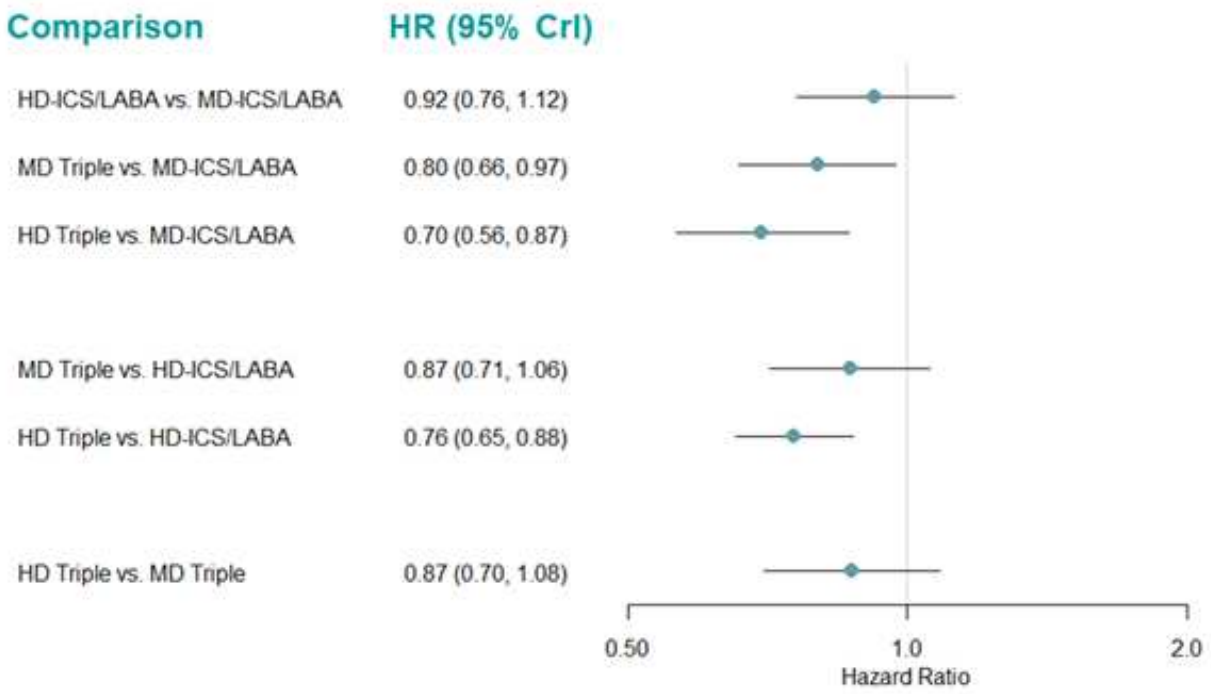


Model fit parameters for the fixed-effect- and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low, but the credible interval was wide. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen.

A node-splitting model was fit to assess the inconsistency in the model. The results of the node-splitting model are presented in Table 9. There was no evidence to suggest there was any inconsistency in the model.

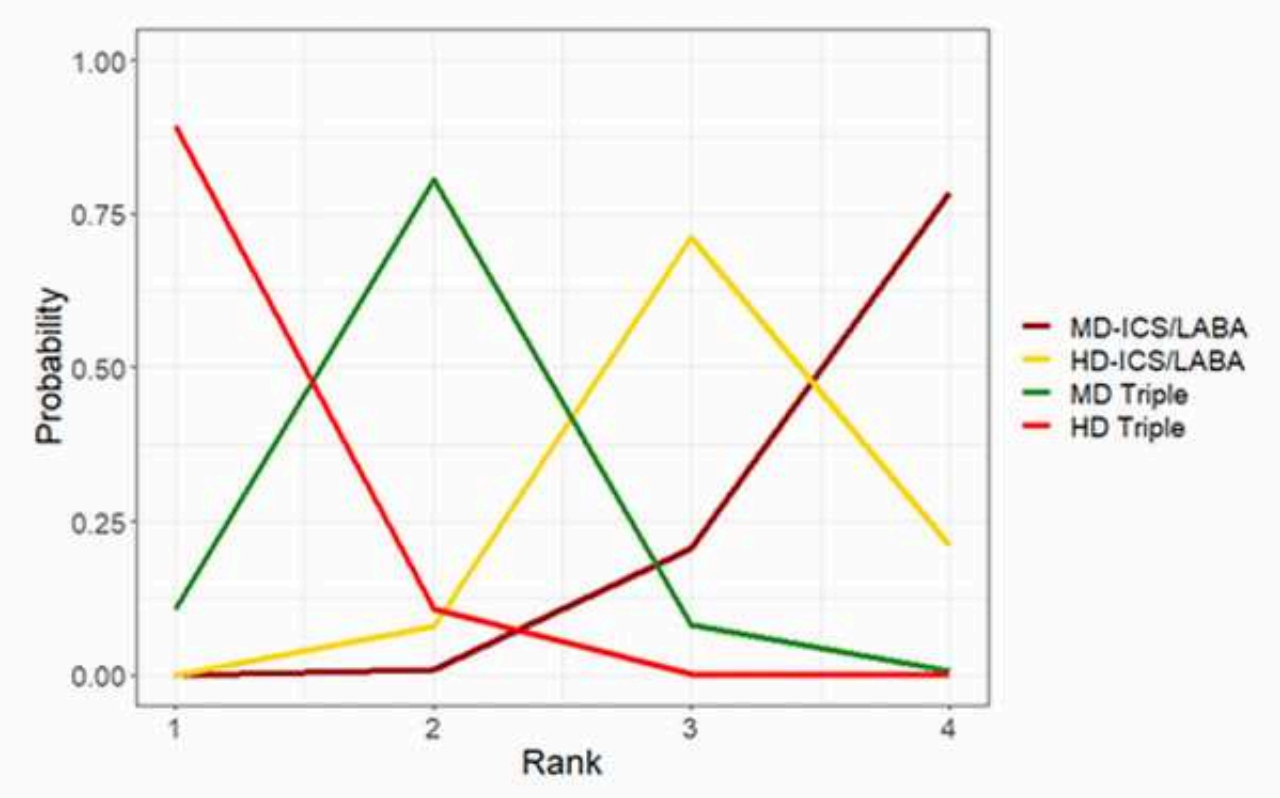
Hazard ratios for moderate-severe exacerbations are presented in Figure 31. The HRs for the comparison of all treatment groups against each other are reported in Table 10. There is evidence to suggest that MD Triple and HD Triple reduce the hazards of moderate-severe exacerbations compared to MD-ICS/LABA (HR 0.80 [95% CrI 0.66 to 0.97] and 0.70 [0.56 to 0.87], respectively) and HD Triple reduces the hazards of moderate-severe exacerbations compared to HD-ICS/LABA (HR 0.76 [95% CrI 0.65 to 0.88]). This is consistent with the results for the overall NMA (Table 10).

Figure 31. Forest plot of hazard ratios for moderate to severe exacerbations for high-risk individuals. Hazard ratio less than one favours the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 32, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 11. HD Triple ranked marginally better than MD Triple, both of which ranked better than the other treatments (median rank 1 [95% CrI 1 to 2] and 2 [1 to 3], respectively), but overall, treatment ranks are very uncertain, with very wide credible intervals.

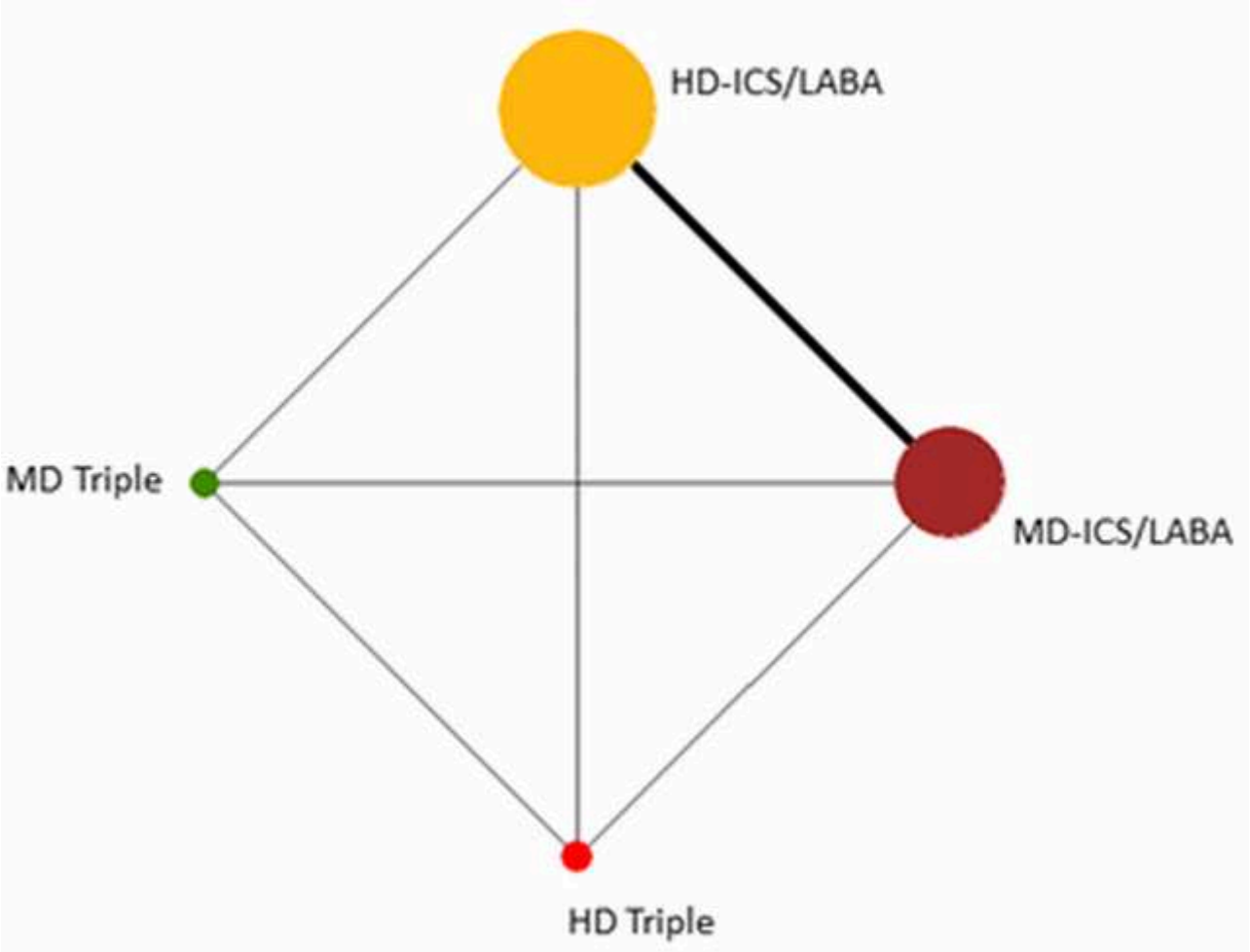
Figure 32. Rank plots for modearate to severe exacerbations for high-risk individuals. (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



1.2.1.2.2 Low-risk subgroup

For this outcome, 5 trials (4436 participants) comparing four treatments provided evidence as dichotomous data. A network diagram for the studies included in the NMA is presented as Figure 33. A summary of the studies included in the analysis is presented in Appendix 5.

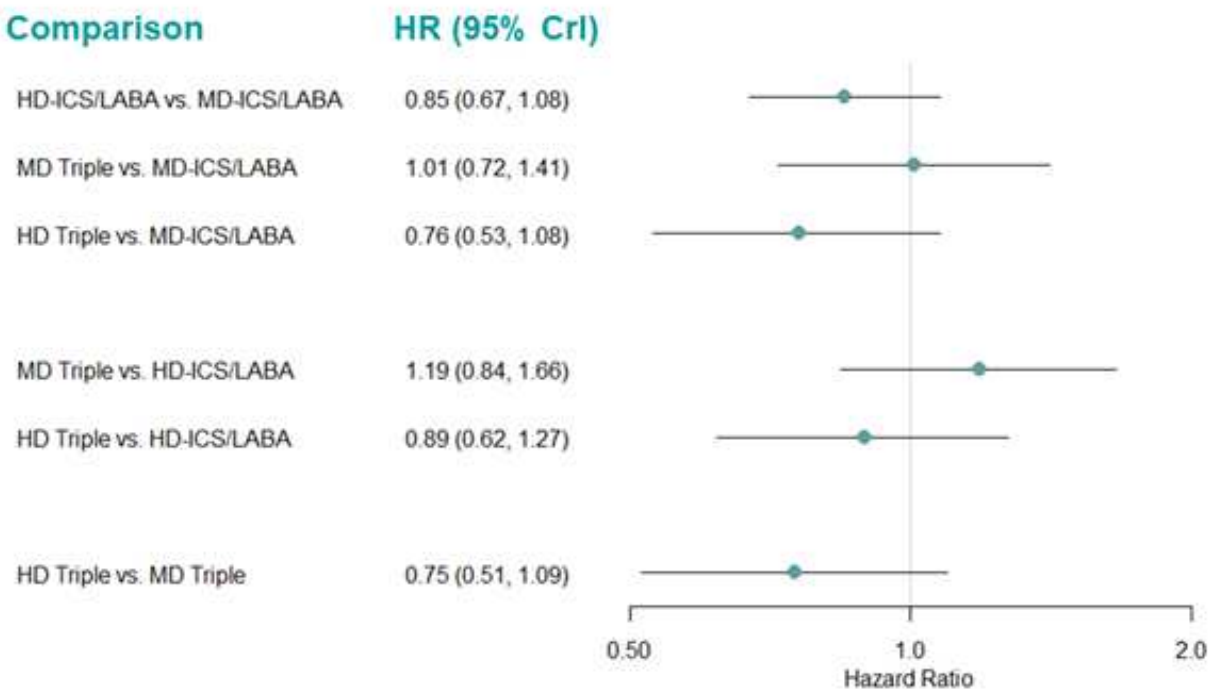
Figure 33. Network diagram for moderate to severe exacerbations for low-risk individuals. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Model fit parameters for the fixed-effect- and random-effects models are reported in Appendix 3. Both fixed-effect- and random-effects models fit the data well. There was moderate between-study heterogeneity in the random-effects model with a wide credible interval. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. A node-splitting analysis was not performed because there is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

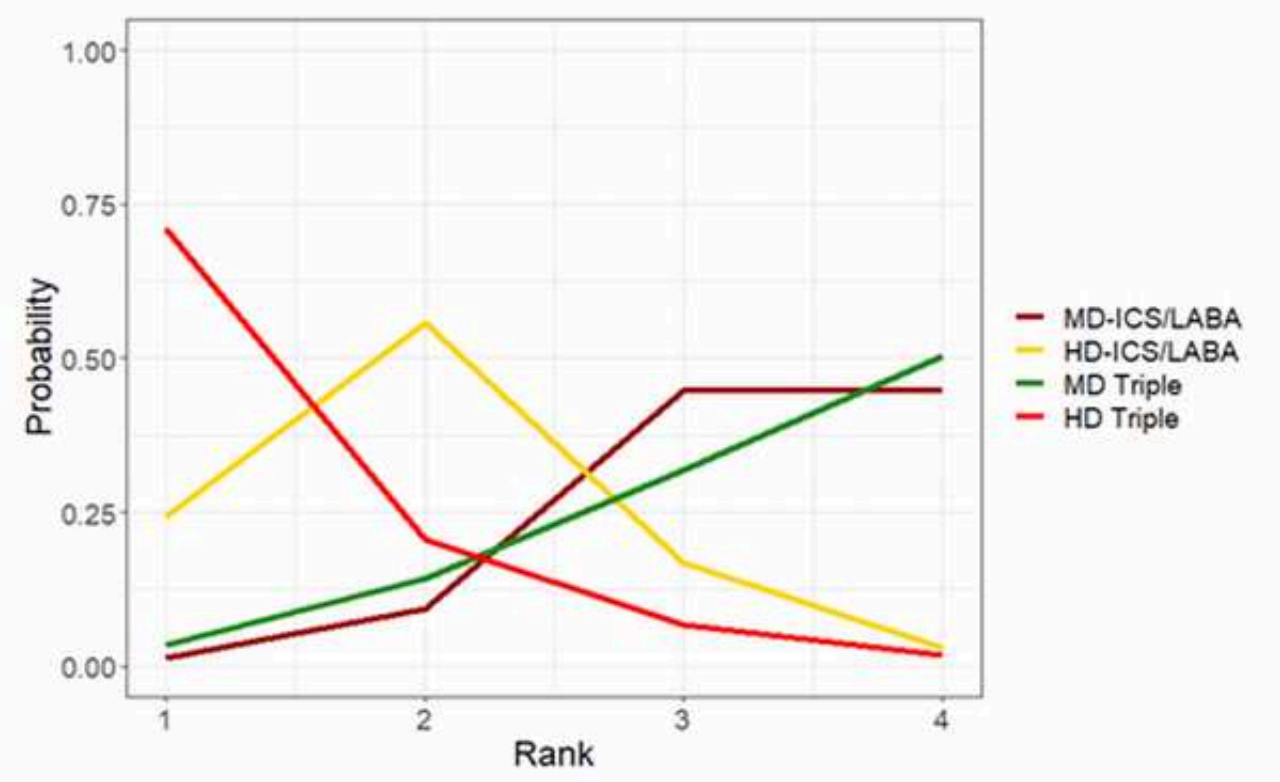
Hazard ratios for moderate-severe exacerbations in low-risk individuals are presented in Figure 34. The HRs for the comparison of all treatment groups against each other are reported in Table 10. There is insufficient evidence to suggest that there is a change in hazards of moderate-severe exacerbations for any of the treatment comparisons.

Figure 34. Forest plot of hazard ratios for moderate to severe exacerbations for low-risk individuals. Hazard ratio less than one favours the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots are presented in Figure 35, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 11. HD Triple ranks higher than the other treatments, but the wide credible intervals demonstrate the uncertainty in treatment rankings (median rank 1 [95% CrI 1 to 3]).

Figure 35. Rank plots for modearate to severe exacerbations for low-risk individuals. (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

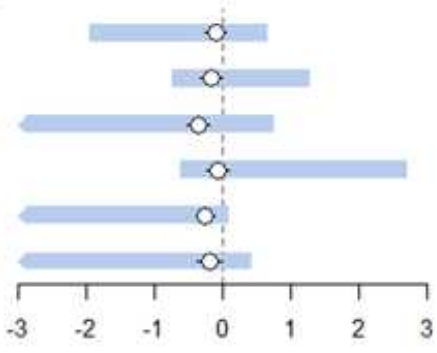


1.2.1.3 Threshold analysis

The forest plot for the threshold analysis is presented in Figure 36 and the thresholds and new optimum treatments are presented in Table 12.

Figure 36. Forest plot for threshold analysis for moderate to severe exacerbations for grouped treatments (fixed effect model). Treatment Codes: 1=MD-ICS/LABA, 2= HD-ICS/LABA, 3=MD Triple, 4= HD Triple. The optimum treatment for this analysis was HD Triple. HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; NT: no threshold (no amount of change in this direction would change the recommendation).

Contrast	log-HR	95% Credible Interval	Invariant Interval	
2 vs. 1	-0.11	(-0.26, 0.04)	2 (-1.95, 0.66)	1
3 vs. 1	-0.18	(-0.34, -0.01)	3 (-0.73, 1.29)	1
4 vs. 1	-0.37	(-0.54, -0.19)	– (NT, 0.76)	3
3 vs. 2	-0.07	(-0.24, 0.10)	3 (-0.62, 2.70)	2
4 vs. 2	-0.26	(-0.39, -0.12)	– (NT, 0.08)	2
4 vs. 3	-0.19	(-0.38, -0.00)	– (NT, 0.41)	3



log-HR — 95% Credible Interval — Invariant Interval

Base-case optimal treatment set is 4.

No credible intervals extended beyond the limits of the invariant intervals for any comparison, therefore the recommended treatment is not sensitive to the uncertainty in the data. The recommended treatment did seem to be sensitive to moderate potential bias in the negative direction for MD Triple versus MD-ICS/LABA, MD Triple vs. HD-ICS/LABA, which would make MD Triple the recommended treatment. This is consistent with the ranks discussed in Section 1.2.1.2, where MD Triple is ranked the next best treatment after HD Triple.

A change in the positive direction in the HD Triple versus HD-ICS/LABA comparison could also change the preferred treatment to HD-ICS/LABA. However, all these thresholds (Table 12) are relatively high and changes do not seem to be very plausible.

1.2.1.4 Pairwise meta-analysis

Results from the pairwise meta-analysis are qualitatively similar to those of the NMA (Analysis 1.2; Summary of findings 2). There is no qualitative difference between direct and NMA estimates (Table 9). There is little evidence to suggest HD-ICS/LABA reduces moderate to severe exacerbations compared to MD-ICS/LABA (6 trials, 5452 participants, RR 0.93 [95% CI 0.82 to 1.05]; I^2 =0% [high certainty]).

HD TRIPLE likely results in a slight reduction in moderate to severe exacerbations compared to MD TRIPLE (3 trials, 3470 participants, RR 0.85 [95% CI 0.72 to 1.01]; I^2 = 0%; ARR 23 fewer per 1000 patients [moderate certainty]).

Triple therapy (ICS/LABA/LAMA) reduces moderate to severe exacerbations compared to dual (ICS/LABA) therapy when analysed combining all MD- and HD-ICS formulations in each combination therapy (5 trials, 8173 participants; RR 0.85 [95% CI 0.78 to 0.92]; I^2 =0% [high certainty]). There was no difference in the results between fixed-effect and random-effects models.

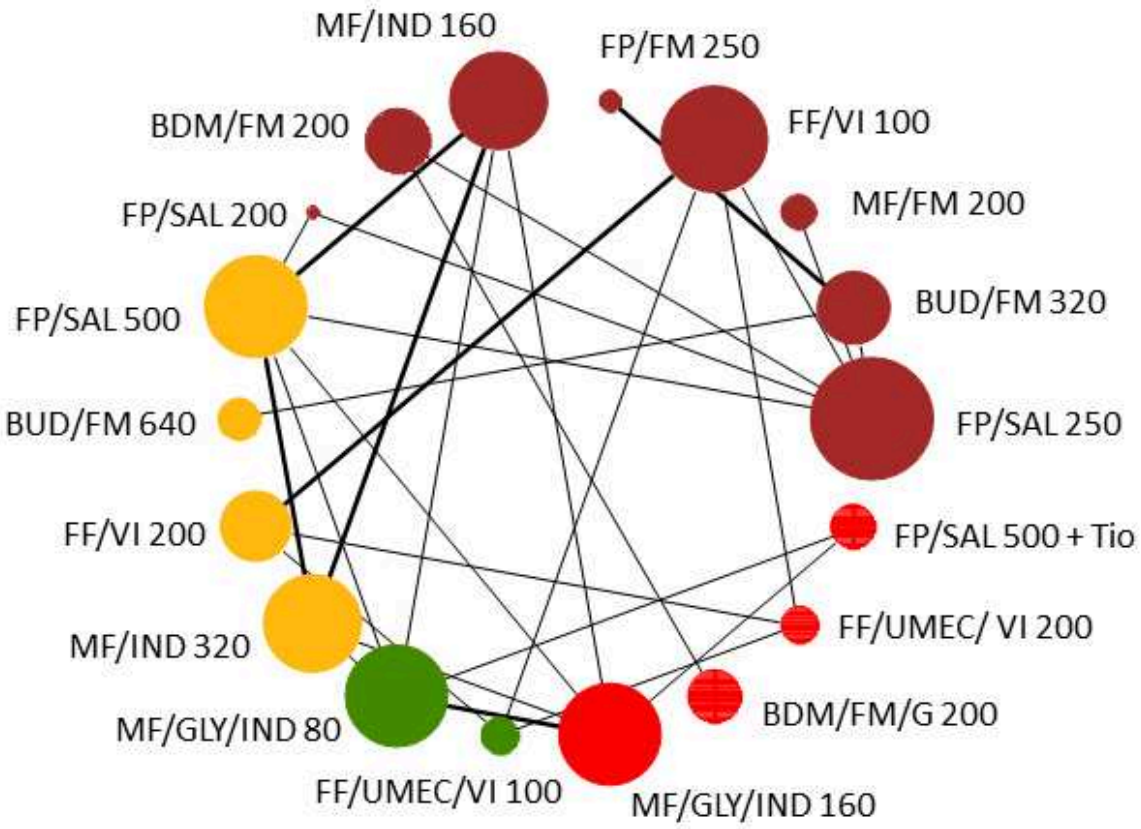
In the subgroup analyses, the evidence suggests HD TRIPLE reduces moderate to severe exacerbations compared to MD TRIPLE slightly in the high risk subgroup (RR 0.89 [95% CI 0.73 to 1.09]; ARR 15 fewer per 1000 patients; [moderate certainty] and moderately in the low risk subgroup (RR 0.79 [95% CI 0.57 to 1.08]; ARR 37 fewer per 1000 patients; [low certainty] Analysis 7.6).

Triple therapy (ICS/LABA/LAMA) reduces moderate to severe exacerbations compared to dual therapy (ICS/LABA) only in the high-risk subgroup (RR 0.84 [95% CI 0.77 to 0.92]; ARR 42 fewer per 1000 patients; [high certainty]) but not in the low-risk subgroup (RR 0.96 [95% CI 0.77 to 1.20]; [moderate certainty] Analysis 7.7).

1.2.2 Individual treatments

For this outcome, 14 trials (13,127 participants) provided evidence as dichotomous data across 18 individual treatments. There were no studies that provided evidence as logHR data. A network diagram for the studies included in the NMA is presented in Figure 37. A summary of the studies included in the analysis is presented in Appendix 6. We added a continuity correction of 0.5 to the zero count events to help improve model convergence due to the sparsity of the evidence in Mansfield 2017.

Figure 37. Network diagram for moderate to severe exacerbations for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. BDP: beclomethasone dipropionate, BUD:budesonide, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, UMEC: umeclidinium, VI:vilanterol



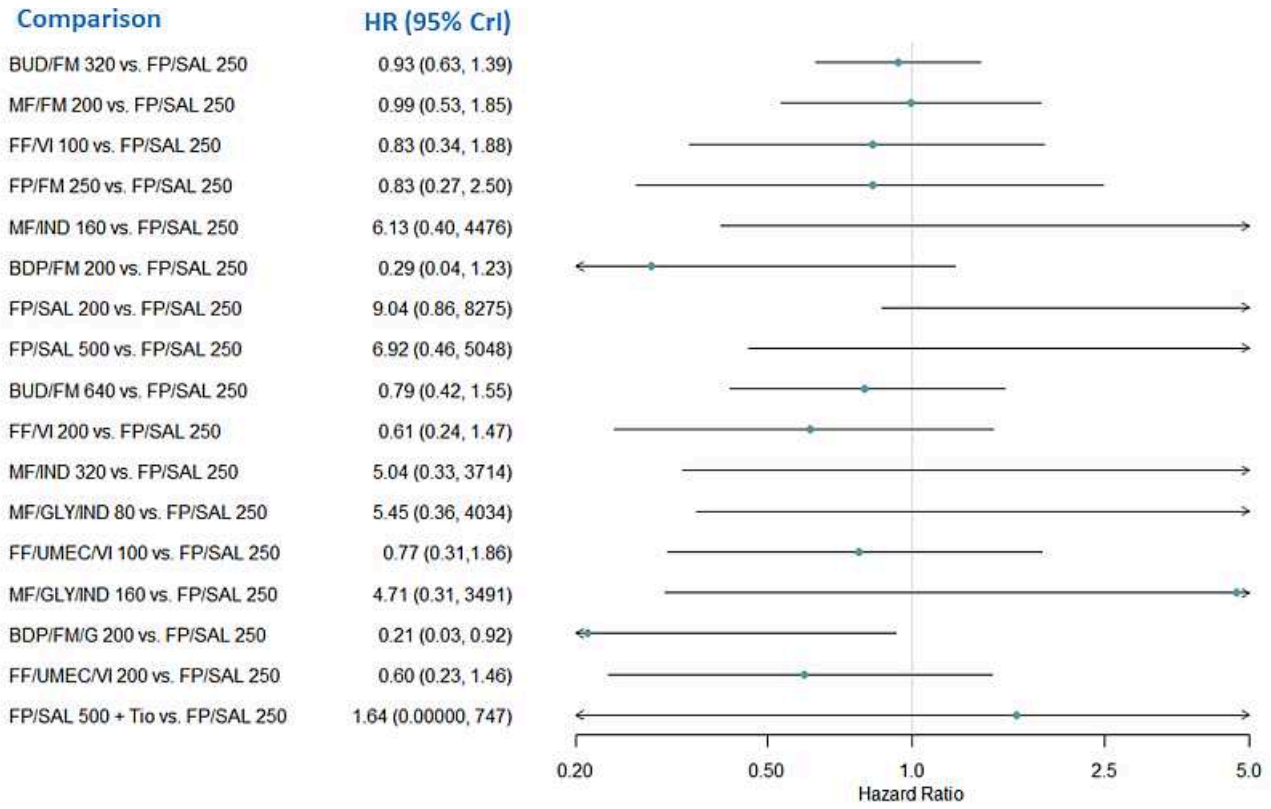
1.2.2. 1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low, but the credible interval was wide. As the DIC for the fixed-effect model was lower than for the random-effects model, the fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 1.2.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

1.2.2.2 NMA results

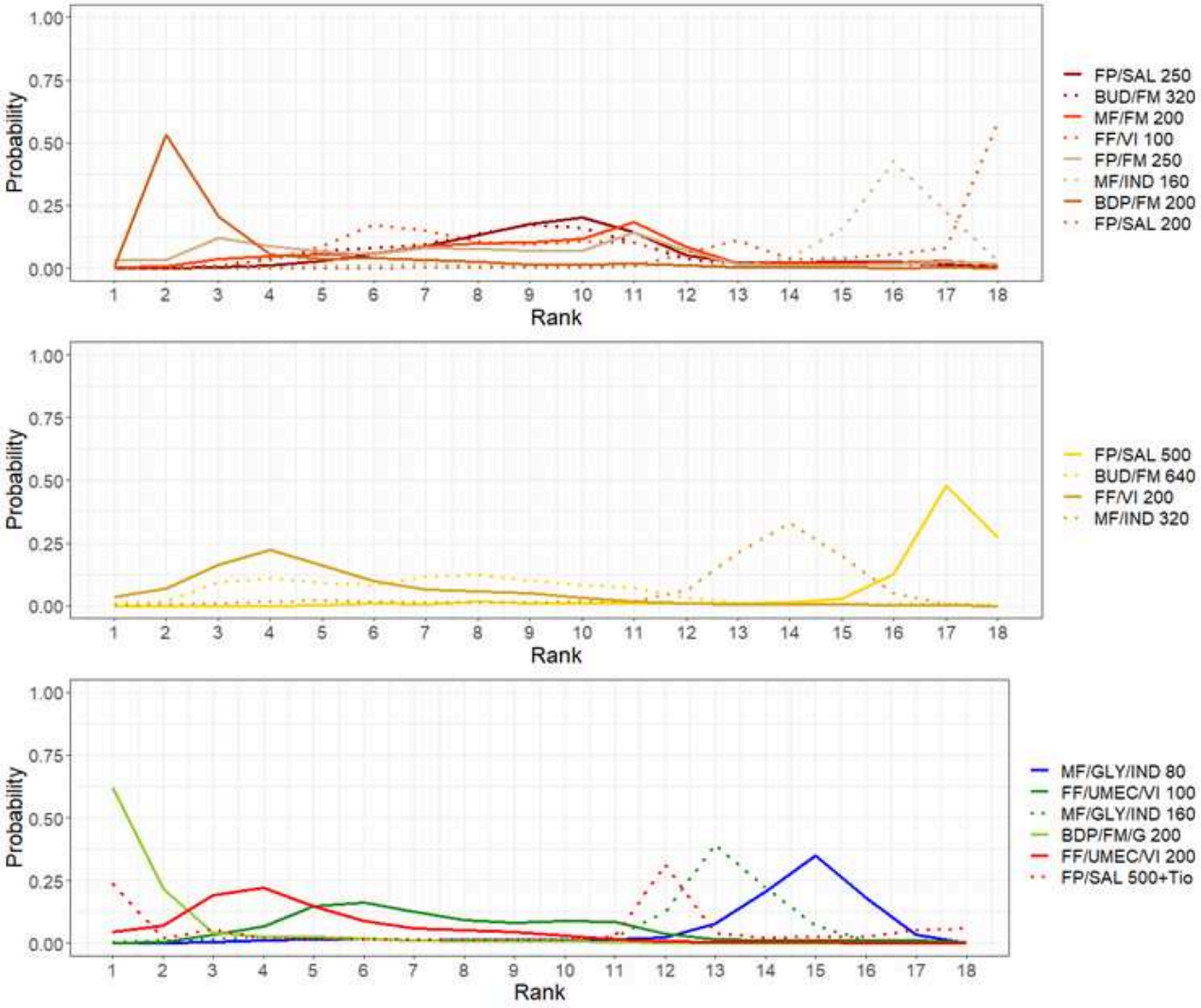
Hazard ratios for moderate-severe exacerbations in individual treatments, compared to FP/SAL 250/50 µg (MD-ICS/LABA) are presented in Figure 38. The HRs for the comparison of all treatment groups against each other are reported in Table 13. The impact of the sparse evidence available for each comparison can be seen in the number of comparisons for which the HRs are extremely uncertain (highlighted in yellow in Table 13).

Figure 38. Forest plot of hazard ratios relative to FP/SAL 250 for moderate to severe exacerbations for individual treatments. Hazard Ratios greater than one favor the comparator treatment over FP/SAL 250. BUD:budesonide, CrI:Credible Interval; FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, HR: hazard ratio; IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



The rank plots for individual treatments are presented in Figure 39, and the mean and median ranks with their corresponding 95% CrIs are presented in Table 14. Beclomethasone dipropionate/formoterol/glycopyrronium (BDP/FM/GLY) 200/12/20 µg (MD Triple) has the highest probability of being the best treatment, but overall, treatment ranks are very uncertain, and most treatments have probabilities less than 50% for all ranks.

Figure 39. Rank plots for individual treatments for moderate to severe exacerbations (fixed effect model) Line colors denote the treatment group. BUD:budesonide, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



2. Secondary, continuous outcomes

2.1 Asthma Control Questionnaire (ACQ) score

2.1.1 Change from baseline at three months

2.1.1.1 Grouped treatments

For this outcome, 4 trials (4529 participants) comparing four treatment groups were included in the NMA (Figure 3). A summary of the studies included in the analysis is presented in Appendix 7.

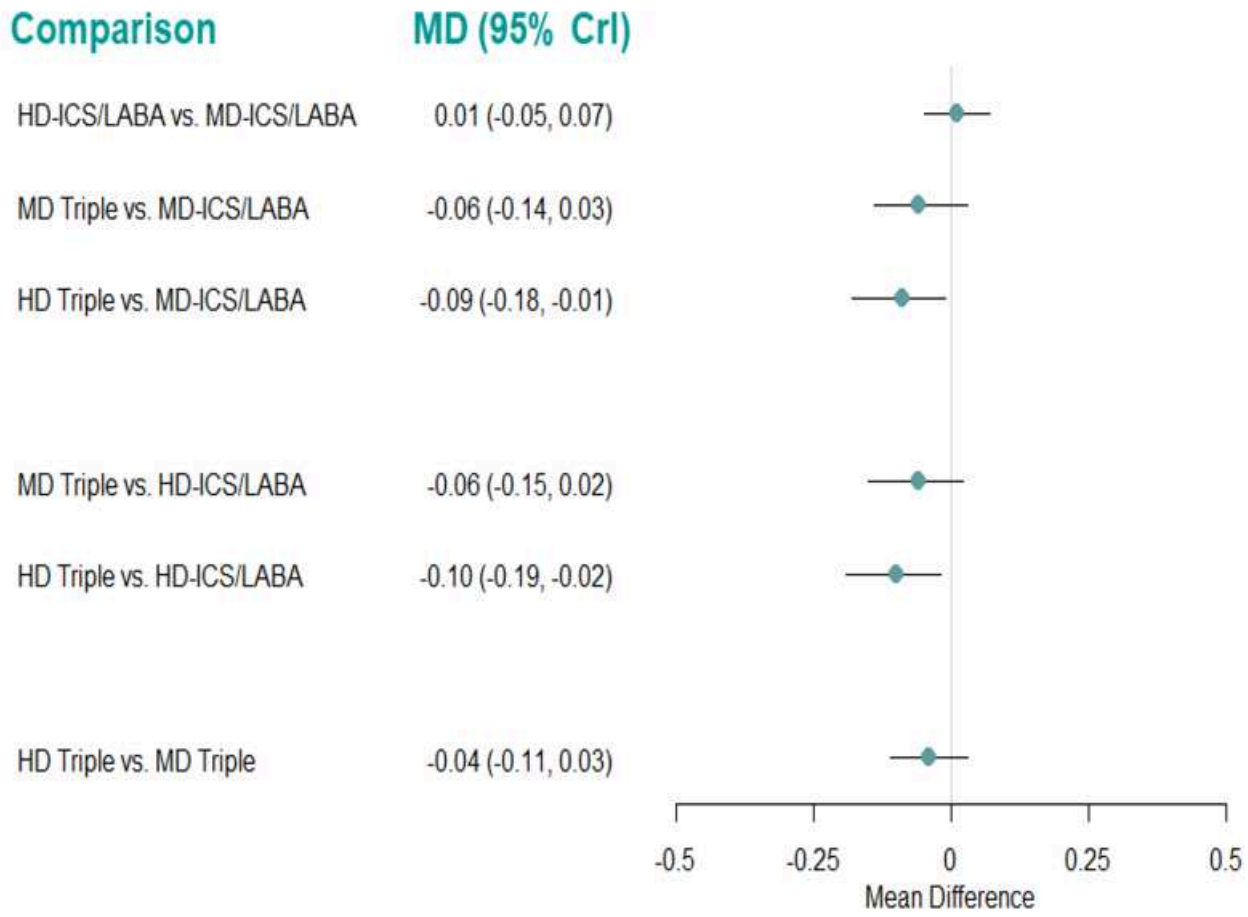
2.1.1.1.1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.1.1.1.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

2.1.1.1.2 NMA results

Mean differences in CFB in ACQ scores at three months are presented in Figure 40. The mean differences in CFB in ACQ scores at three months comparing all treatment groups against each other are reported in Table 15.

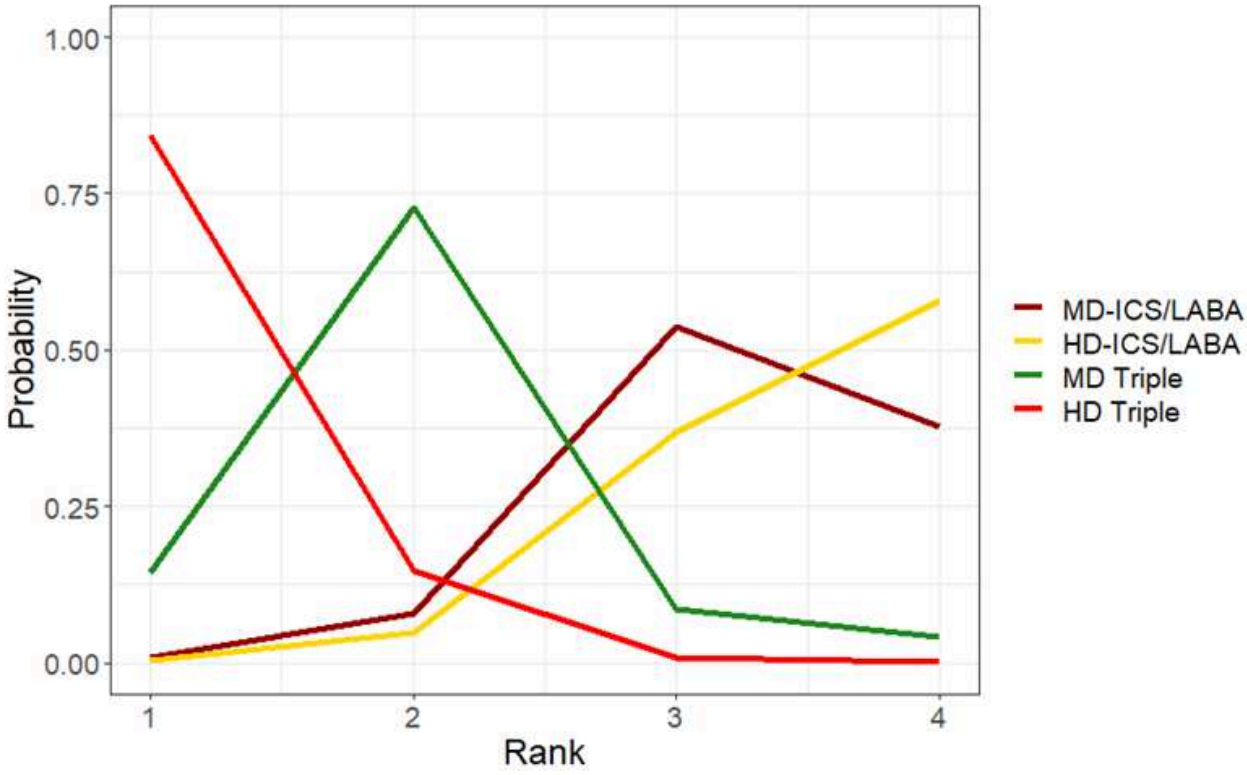
Figure 40. Forest plot of relative effects for the change from baseline ACQ score at 3 months using the fixed effect model. Mean differences less than zero favor the first named treatment. CrI:Credible Interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: mean difference; MD: medium dose.



There is evidence to suggest that HD Triple reduces the ACQ score at three months compared to HD-ICS/LABA (mean difference -0.09 [95% CrI -0.18 to -0.01]). However, this difference does not satisfy the minimal clinically important difference (MCID) of 0.5 (Juniper 2005). An NMA summary of findings is presented in Summary of findings 4

The rank plots for grouped treatments are presented in Figure 41, and the mean and median ranks are presented in Table 16. HD Triple ranks higher than the other treatments (median rank 1 [95% CrI 1 to 2]). All other treatment ranks display wide credible intervals, reflecting high uncertainty in treatment rankings.

Figure 41. Rank plots for grouped treatments for change from baseline in ACQ scores at 3 months (fixed effect model). HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose



2.1.2 Change from baseline at six months

2.1.2.1 Grouped treatments

For this outcome, 6 trials (7957 participants) comparing four treatment groups were included in the NMA (Figure 4). A summary of the studies included in the analysis is presented in Appendix 8.

2.1.2.1.1 Model selection and inconsistency checking

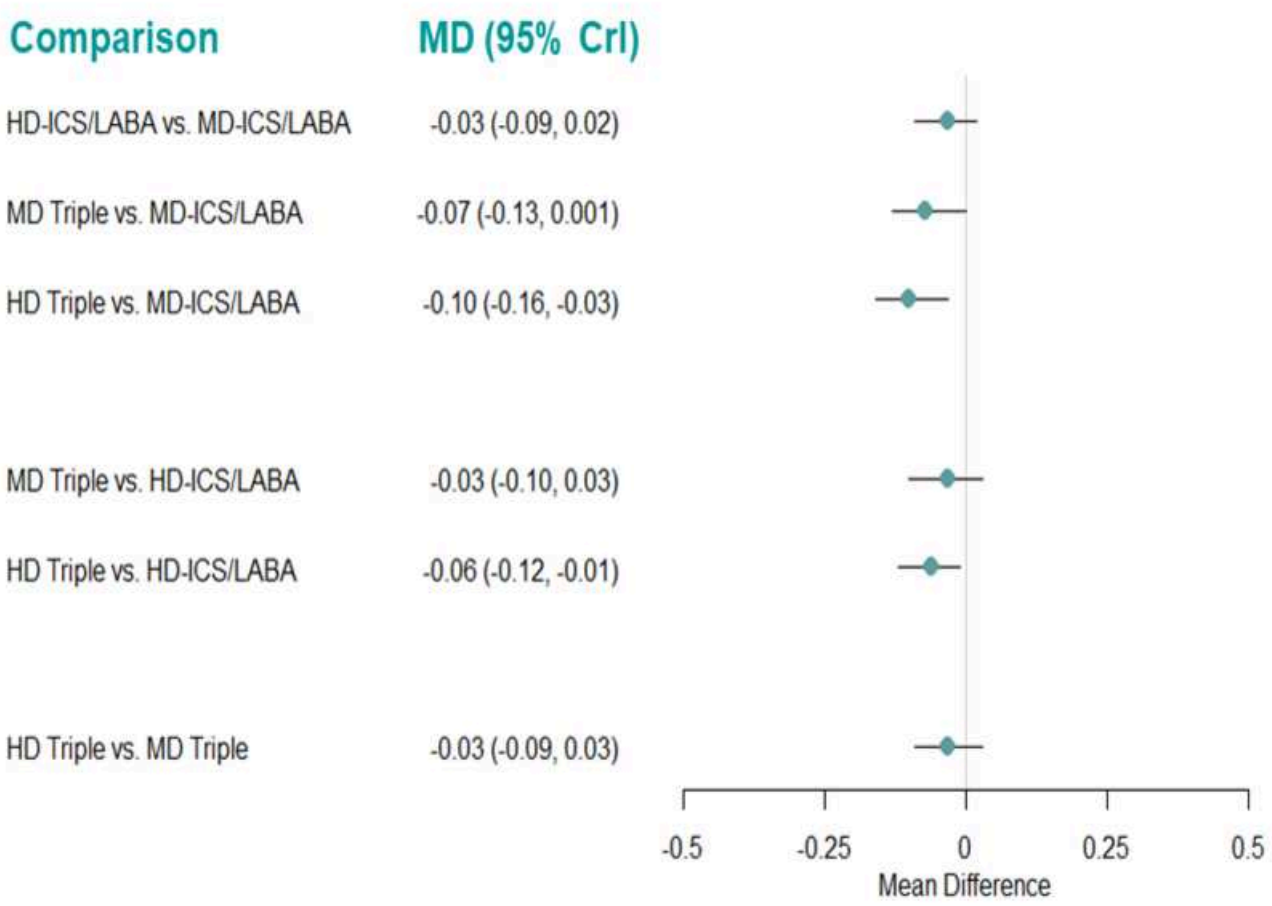
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 17. There was no evidence to suggest any inconsistency in the model.

2.1.2.1.2 NMA results

The mean difference in CFB in ACQ scores at six months are presented in Figure 42. The mean difference in CFB in ACQ scores at six months comparing all treatment groups against each other are reported in Table 18.

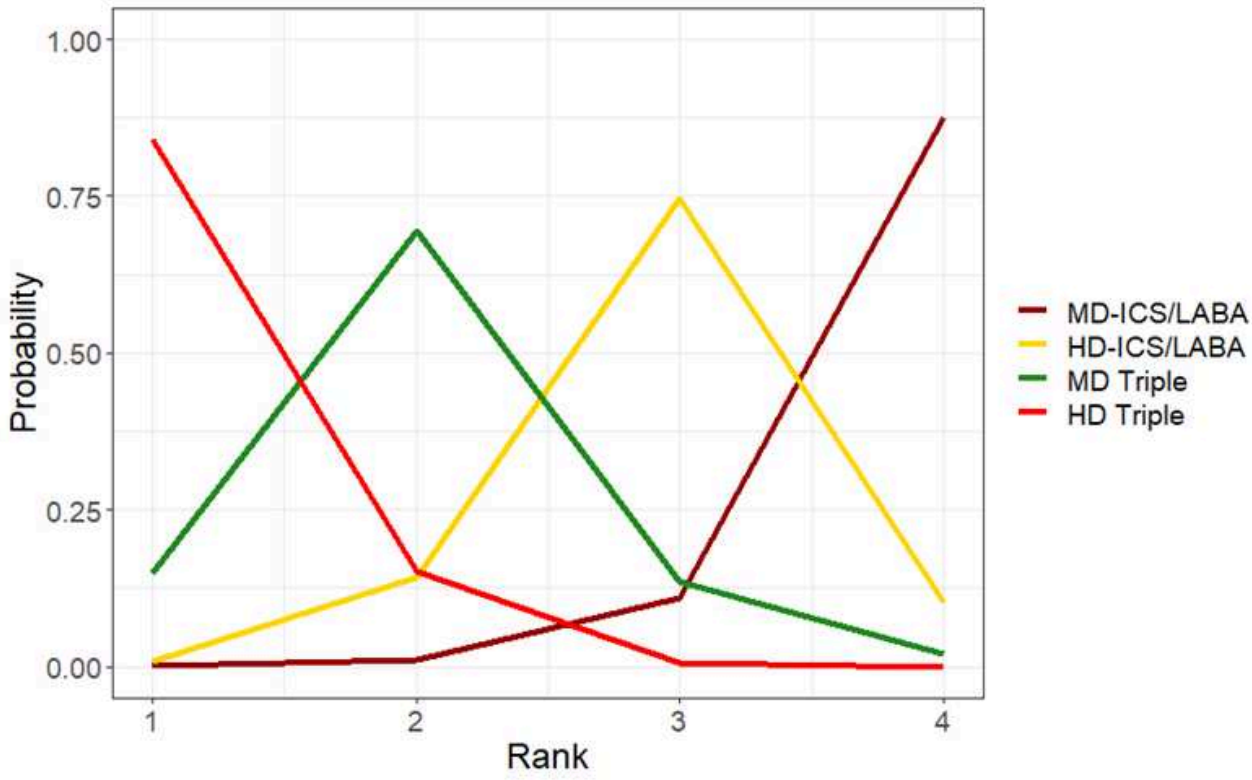
Figure 42. Forest plot of relative effects for the change from baseline in ACQ score at 6 months using fixed- and random-effects models. Mean differences less than zero favor the first named treatment. CrI:Credible Interval; FE: fixed effect; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: mean difference; MD: medium dose; RE: random effects.



There is evidence to suggest that HD Triple reduces the ACQ score at six months compared to MD-ICS/LABA and HD-ICS/LABA (mean difference -0.10 [95% CrI -0.16 to -0.03] and -0.06 [-0.12 to -0.01], respectively). However, these differences do not satisfy the MCID of 0.5 (Juniper 2005). An NMA summary of findings is presented in Summary of findings 5

The rank plots for grouped treatments are presented in Figure 43, and the mean and median ranks are presented in Table 19. HD Triple ranks higher than the other three grouped treatments (median rank 1 [95% CrI 1 to 2]).

Figure 43. Rank plots for grouped treatments for change from baseline in ACQ scores at 6 months for the fixed effect (A) and random effects (B) models. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



2.1.3 Change from baseline at 12 months

2.1.3.1 Grouped treatments

For this outcome, 5 trials (5440 participants) comparing 4 treatment groups were included in the NMA (Figure 5). A summary of the studies included in the analysis is presented in Appendix 9.

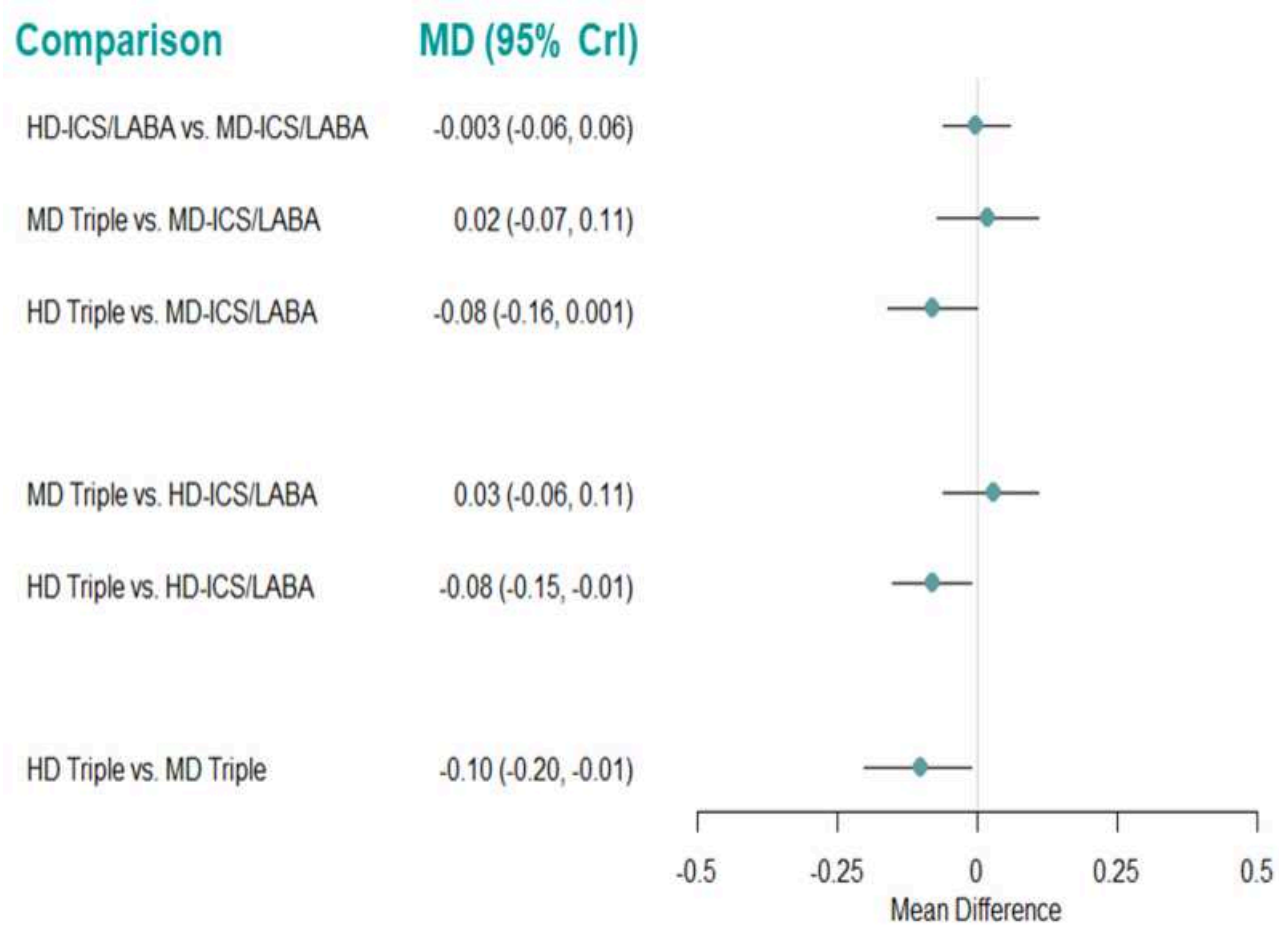
2.1.3.1.1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.1.3.1.2. A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 20. There was no evidence to suggest inconsistency in the network.

2.1.3.1.2 NMA results

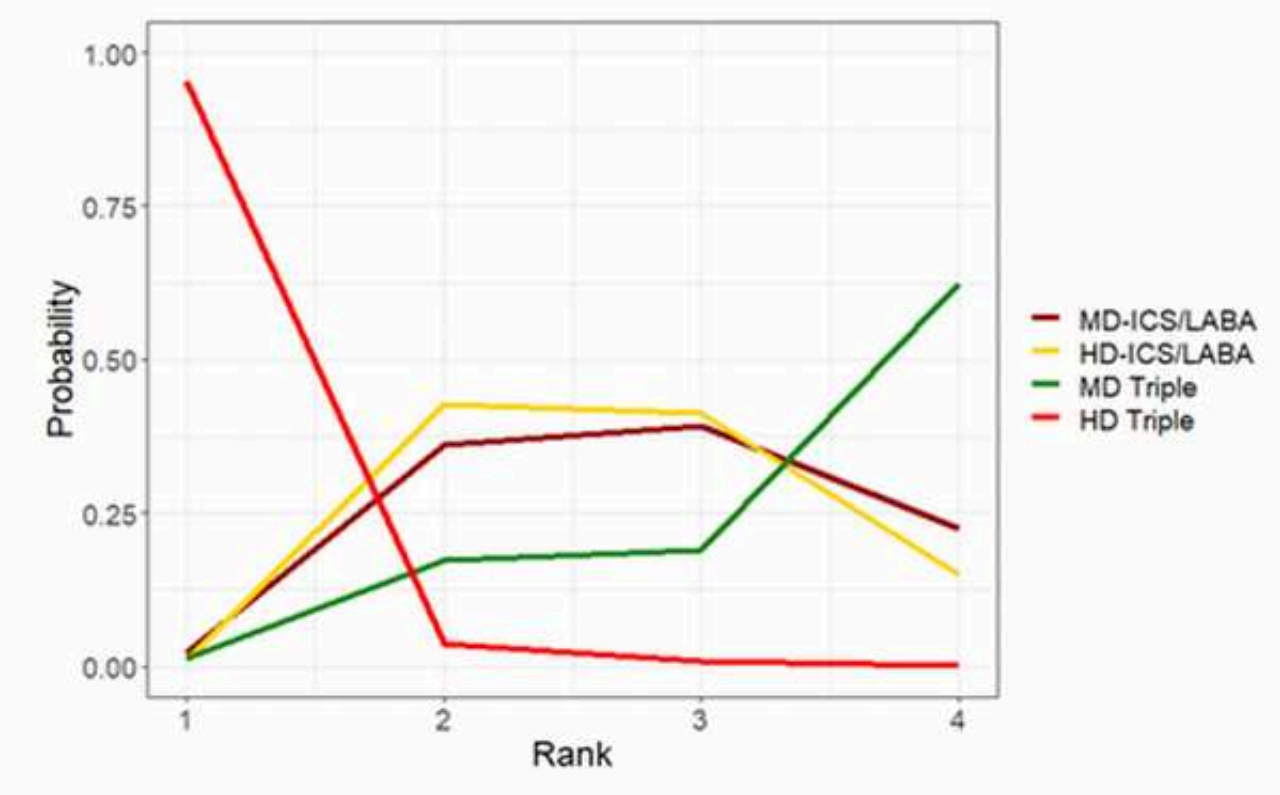
Mean differences in CFB in ACQ scores at 12 months are presented in Figure 44. The mean differences in CFB in ACQ scores at 12 months comparing all treatment groups against each other are reported in Table 21. There is evidence to suggest that there is a change in ACQ scores at 12 months for HD Triple compared to HD-ICS/LABA and MD Triple (mean difference -0.08 [95% CrI -0.15 to -0.01] and -0.10 [-0.20 to -0.01], respectively). However, none of these differences reach the MCID of 0.5 (Juniper 2005). An NMA summary of findings is presented in Summary of findings 6.

Figure 44. Forest plot of mean differences for change from baseline in ACQ scores at 12 months using the fixed effect model. Mean differences less than zero favor the first named treatment. CrI: Credible Interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: mean difference; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 45, and the mean ranks are presented in Table 22. HD Triple ranks higher than the other treatments (median rank 1 [95%CrI 1 to 2]). All other treatment ranks display wide credible intervals, reflecting high uncertainty in treatment rankings.

Figure 45. Rank plots for grouped treatments for change from baseline in ACQ scores at 12 months (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



2.1.4 Pairwise meta-analysis

2.1.4.1 Change from baseline in ACQ scores at three, six, and 12 months

There is insufficient evidence to suggest that there is a clinically meaningful change in ACQ scores (MCID 0.5) at three, six, and 12 months for any of the treatment comparisons (Analysis 2.1, Analysis 2.2, and Analysis 2.3). The results were unchanged when Lee 2020,which is considered at high risk of bias due to high attrition rates, was removed in CFB in ACQ scores at 12 months. The certainty of evidence ranges from low to moderate (Summary of findings 7). There was no difference in the results between fixed-effect and random-effects models. Above results are qualitatively similar to those of the NMA.

2.2 Asthma Quality of Life Questionnaire (AQLQ) score

2.2.1 Change from baseline at six months

2.2.1.1 Grouped treatments

For this outcome, 4 trials (3556 participants) comparing four treatment groups were included in the NMA (Figure 6). A summary of the studies included in the analysis is presented in Appendix 10.

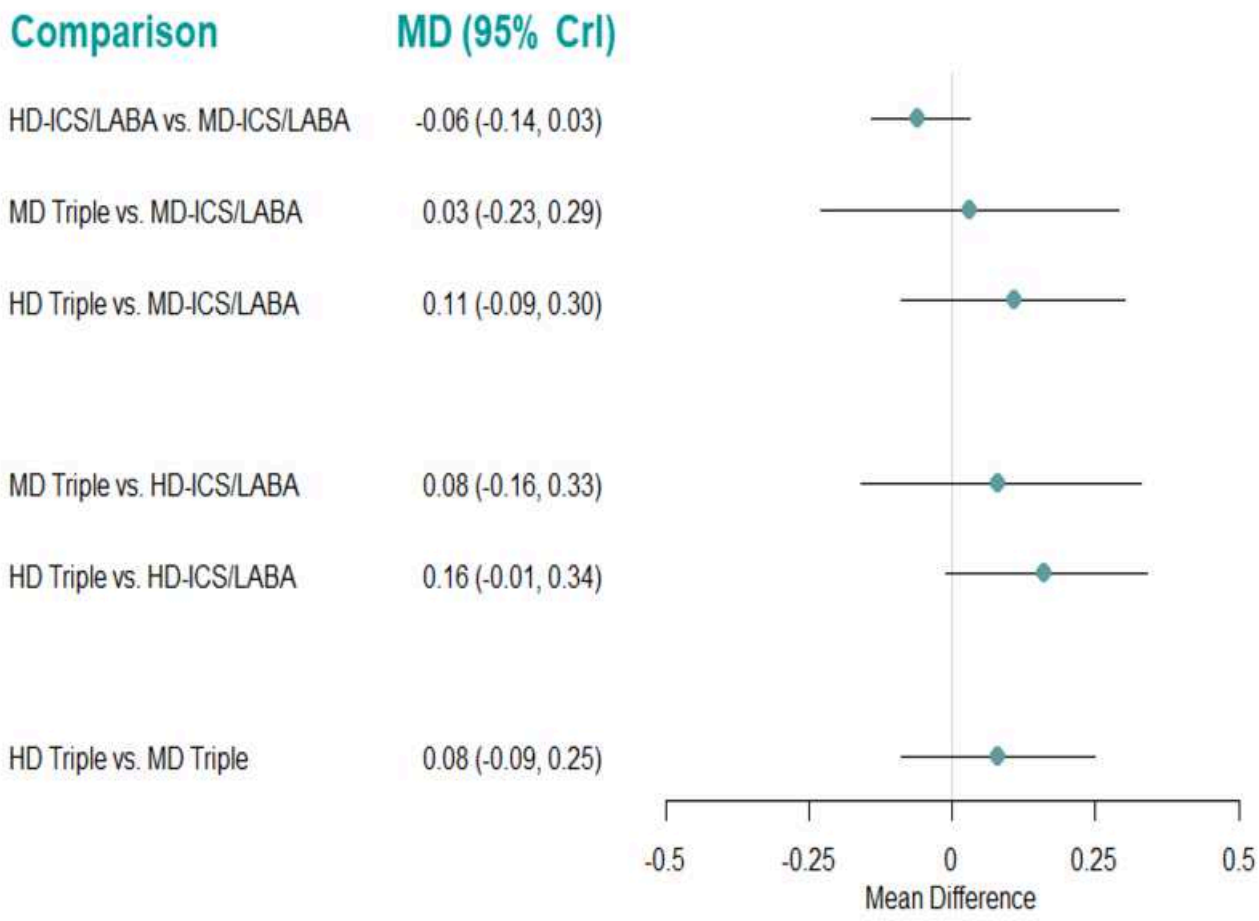
2.2.1.1.1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect- and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect- and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.2.1.1.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

2.2.1.1.2 NMA results

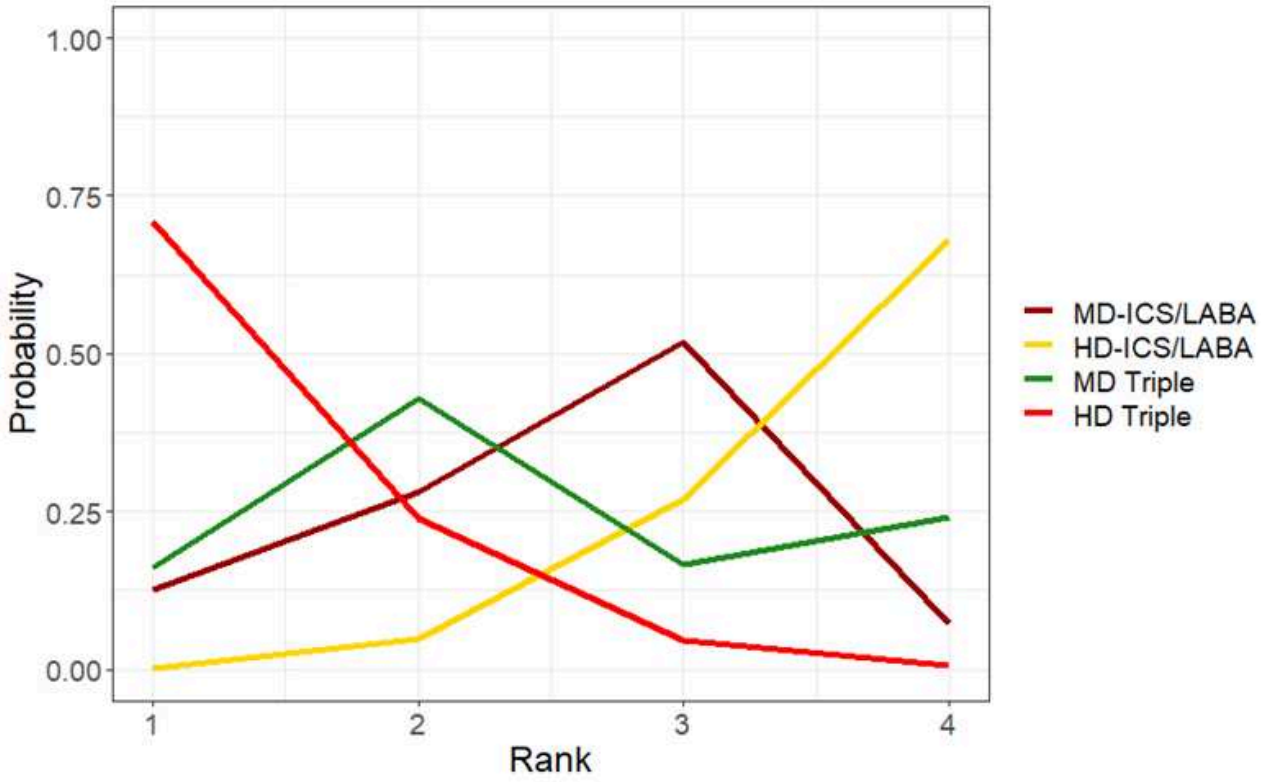
Mean differences in CFB in AQLQ scores at six months are presented in Figure 46. The mean differences in CFB in AQLQ scores at six months comparing all treatment groups against each other are reported in Table 23. There is insufficient evidence to suggest that there is a change in AQLQ scores at six months for any of the treatment comparisons. An NMA summary of findings is presented in Summary of findings 8.

Figure 46. Forest plot of mean differences for change from baseline in AQLQ scores at 6 months using the fixed effect model. Mean differences less than zero favor the first named treatment. CrI: Credible Interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: mean difference; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 47, and the mean and median ranks are presented in Table 24. HD Triple ranks the highest of all the grouped treatments (median rank 1 [95% CrI 1 to 3]). All other treatment ranks display wide credible intervals, reflecting high uncertainty in treatment rankings.

Figure 47. Rank plots for grouped treatments for change from baseline in AQLQ scores at 6 months (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



2.2.2 Change from baseline at 12 months

2.2.2.1 Grouped treatments

For this outcome, 4 trials (4809 participants) comparing four treatment groups were included in the NMA (Figure 7). A summary of the studies included in the analysis is presented in Appendix 11.

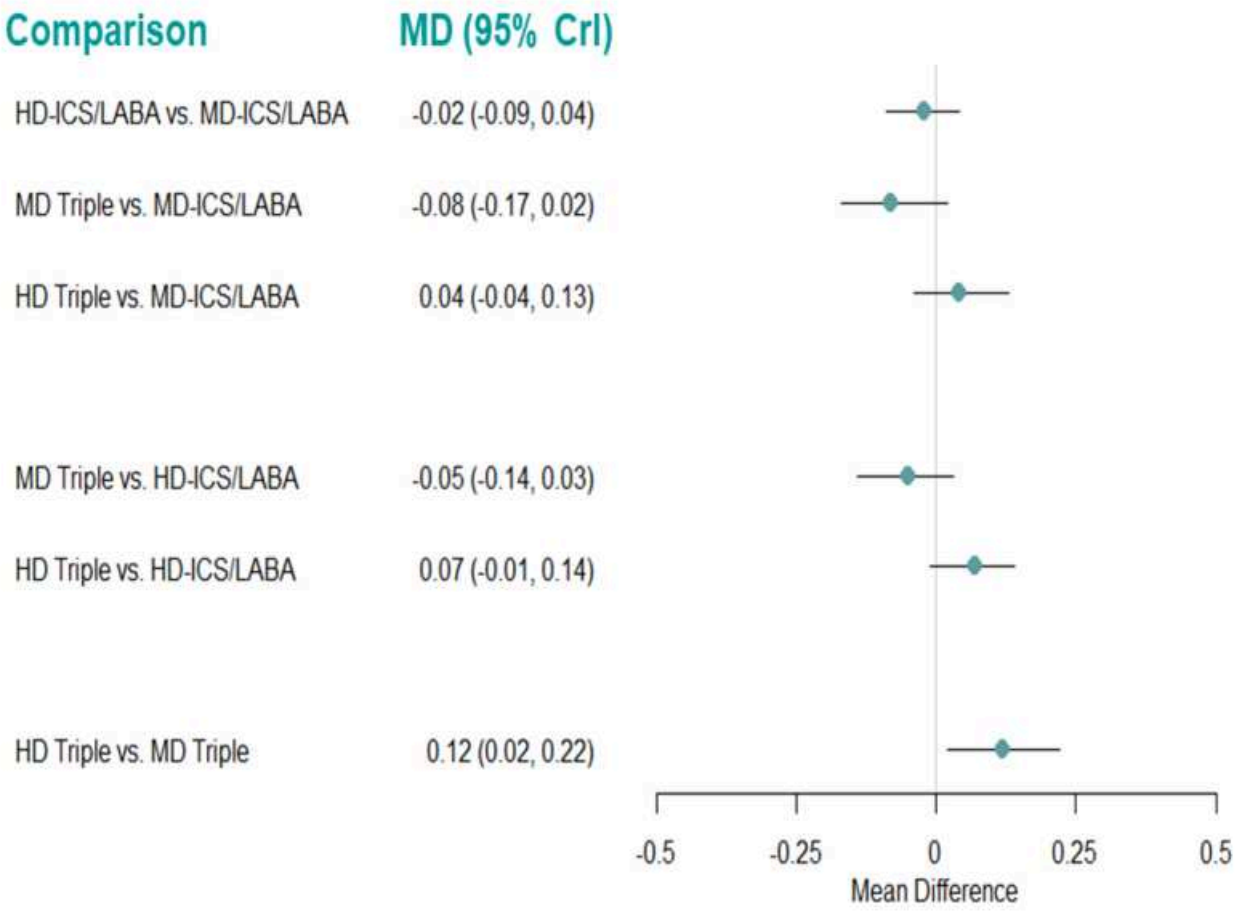
2.2.2.1.1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 2.2.2.1.2. A node-splitting model was fit to assess inconsistency in the model. The results of node-splitting are presented in Table 25. There was no evidence to suggest inconsistency in the network.

2.2.2.1.2 NMA results

Mean differences in CFB in AQLQ scores at 12 months are presented in Figure 48. The mean differences in CFB in AQLQ scores at 12 months comparing all treatment groups against each other are reported in Table 26.

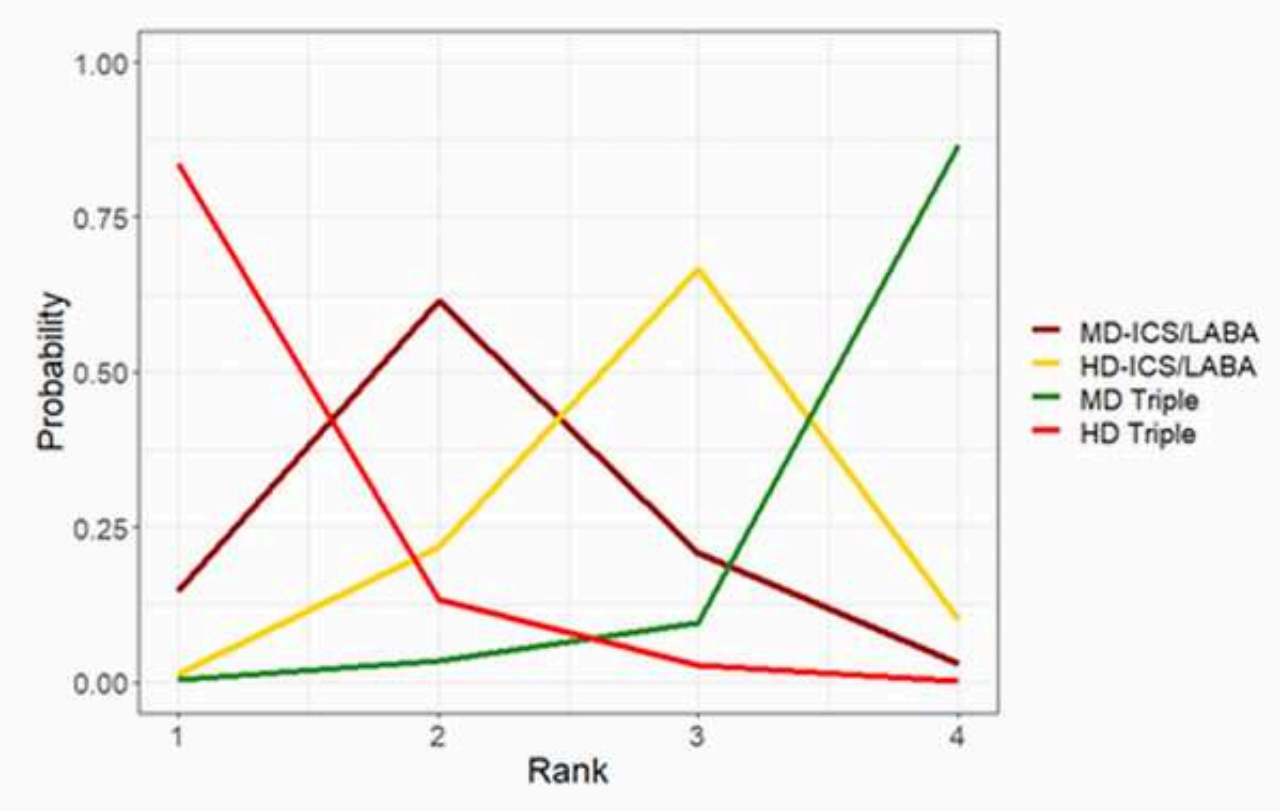
Figure 48. Forest plot of mean differences for change from baseline in AQLQ scores at 12 months using the fixed effect model. Mean differences less than zero favor the first named treatment. CrI: Credible Interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: mean difference; MD: medium dose.



There is evidence to suggest that there is a change in AQLQ scores at 12 months for HD Triple compared to MD Triple (MD 0.12 [95% CrI 0.02 to 0.22]). However, this difference does not reach the MCID of 0.5 (Juniper 1994). An NMA summary of findings is presented in Summary of findings 9.

The rank plots for grouped treatments are presented in Figure 49, and the mean and median ranks are presented in Table 27. HD Triple ranks the highest of all the grouped treatments (median rank 1 [95% CrI 1 to 3]), but credible intervals for treatment ranks are wide.

Figure 49. Rank plots for grouped treatments for change from baseline in AQLQ scores at 12 months (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



2.2.3 Pairwise meta-analysis

2.2.3. 1 change from baseline in AQLQ scores at six and 12 months

There is insufficient evidence to suggest that there is a clinically meaningful change in AQLQ scores (MCID 0.5) at six or 12 months for any of the treatment comparisons (Analysis 3.1 and Analysis 3.2). The certainty of evidence ranges from low to moderate (Summary of findings 10). There was no difference in the results between fixed-effect and random-effects models. Above results are similar to those of the NMA.

3. Secondary, dichotomous outcomes

3.1 Asthma Control Questionnaire (ACQ) responders

3.1.1 ACQ responders at six months.

3.1.1.1 Grouped treatments

For this outcome, 7 trials (10,453 participants) comparing four treatment groups were included in the NMA (Figure 8). A summary of the studies included in the analysis is presented in Appendix 12.

3.1.1.1.1 Model selection and inconsistency checking

The Turner prior comparing pharmacological interventions for subjective outcomes, i.e. a Log-Normal (-2.93, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

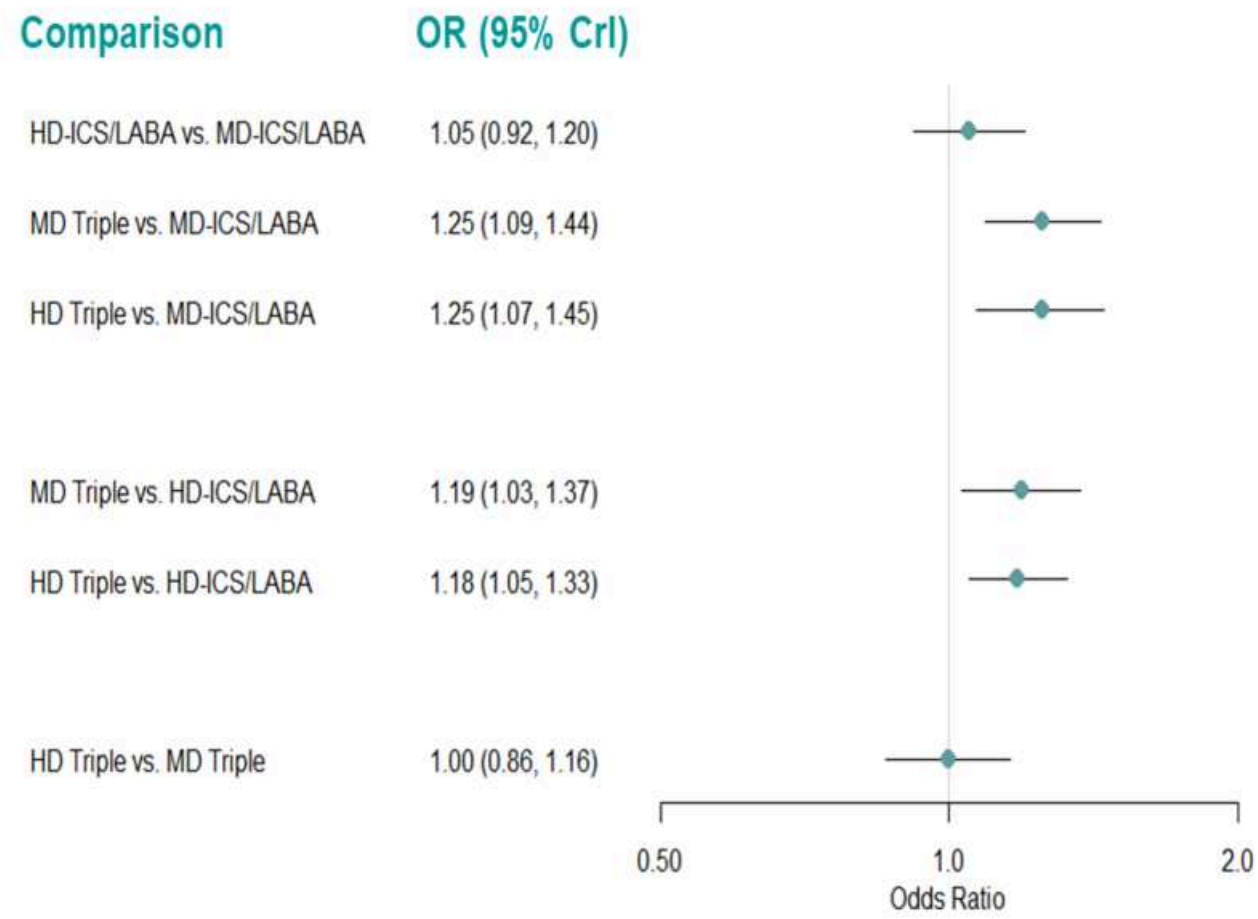
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.1.1.1.2.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 28. There was no evidence to suggest inconsistency in the network.

3.1.1.1.2 NMA results

The odds ratios of ACQ responders at six months are presented in Figure 50. The odds ratios of ACQ responders at six months comparing all treatment groups against each other are reported in Table 29.

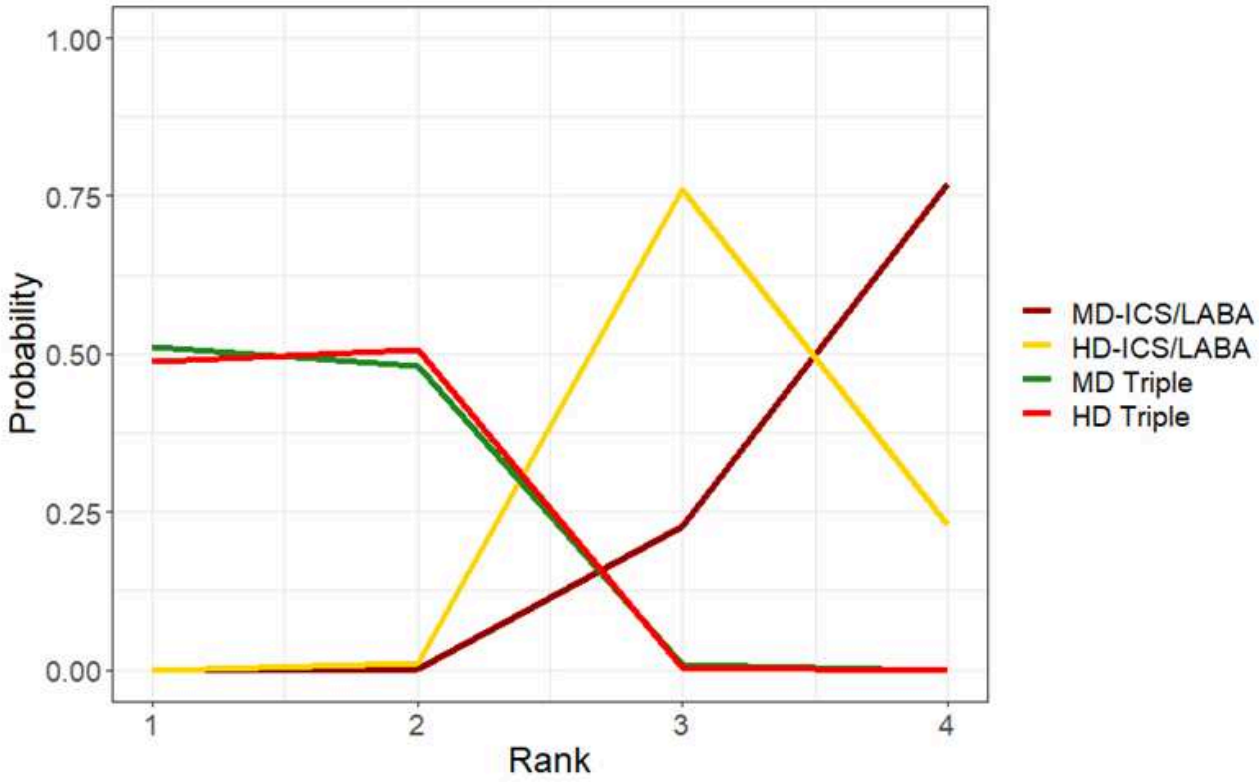
Figure 50. Forest plot of odds ratios relative for ACQ responders at 6 months for grouped treatments. Odds ratio greater than one favors the first named treatment. CrI: Credible Interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



There is evidence to suggest that MD Triple and HD Triple increase the odds of patient response compared to MD-ICS/LABA (OR 1.25 [95% CrI 1.09 to 1.44] and 1.25 [1.07 to 1.45]) and HD-ICS/LABA (OR 1.19 [95% CrI 1.03 to 1.37] and 1.18 [1.05 to 1.33]). An NMA summary of findings is presented in Summary of findings 11.

The rank plots for grouped treatments are presented in Figure 51, and the mean and median ranks are presented in Table 30. MD Triple and HD Triple rank higher than the other treatments (median rank 1 [95% CrI 1 to 2] and 2 [1 to 2], respectively). However, it is difficult to differentiate between MD Triple and HD Triple, and MD-ICS/LABA and HD-ICS/LABA in terms of treatment ranks.

Figure 51. Rank plots for grouped treatments for ACQ responders at 6 months (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



3.1.1.1.3 Pairwise meta-analysis

Results of pairwise meta-analysis are presented in Analysis 4.1 and Summary of findings 13). The evidence suggests that HD and MD Triple increase ACQ responders at six months compared to MD-ICS/LABA (RR 1.11 [95% CI 0.91 to 1.35]; absolute benefit increase (ABI) 69 more per 1000 patients; [very low certainty] and RR 1.09 [95% CI 0.99 to 1.19]; ABI 52 more per 1000 patients; [low certainty], respectively).

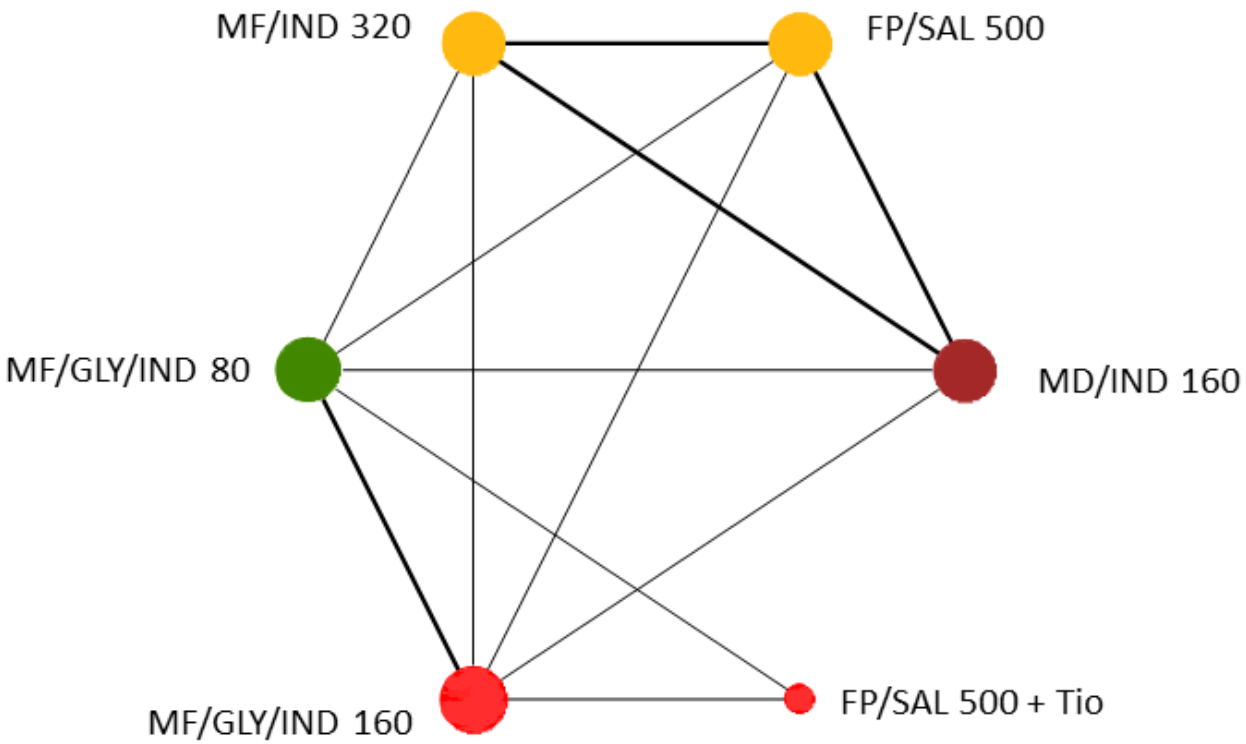
There is evidence to suggest that triple therapy (ICS/LABA/LAMA) increases ACQ responders at six months compared to dual therapy (ICS/LABA) (RR1.09 [95% CI 1.02 to 1.15]; ABI 54 more per 1000 patients; [low certainty]).

The results were unchanged when van Zyl-Smit 2020, which is considered at high risk of bias due to high attrition rates, was removed. There was no difference in the results between fixed-effect and random-effects models.

3.1.1.2 Individual treatments

For this outcome, 3 trials (5380 participants) comparing six distinct treatments were included in the NMA (Figure 52). A summary of the studies included is presented in Appendix 13. Three studies (Kerstjens 2012, Lee 2020, and Virchow 2019a) that were identified were excluded from this analysis, as they were disconnected from the main network shown in Figure 52.

Figure 52. Network diagram for ACQ responders at 6 months for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium.



3.1.1.2.1 Model selection and inconsistency checking

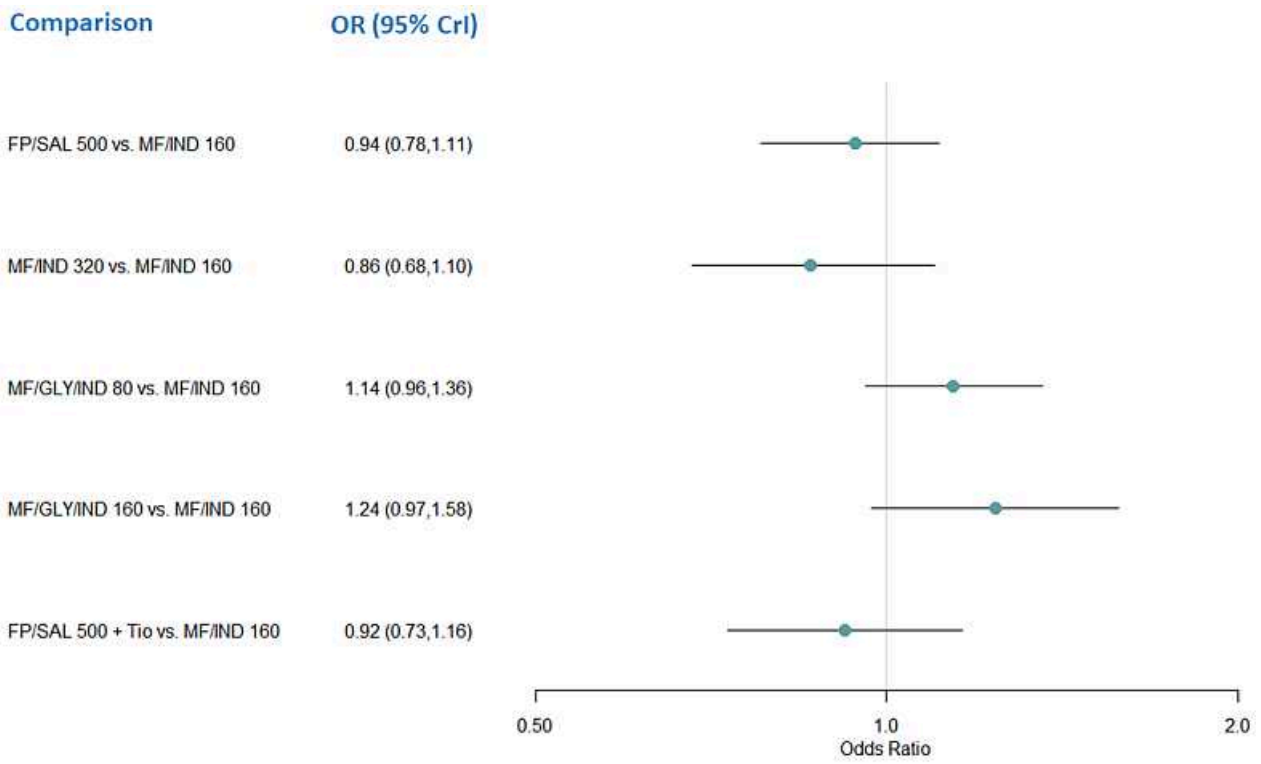
The Turner prior comparing pharmacological interventions for subjective outcomes, i.e. a Log-Normal (-2.93, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.1.1.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.1.1.2.2 NMA results

The odds ratios of ACQ responders at six months, compared to mometasone furoate/indacaterol (MF/IND)160/150 µg (MD-ICS/LABA), are presented in Figure 53. The odds ratios of ACQ responders at six months comparing all treatment groups against each other are reported in Table 31.

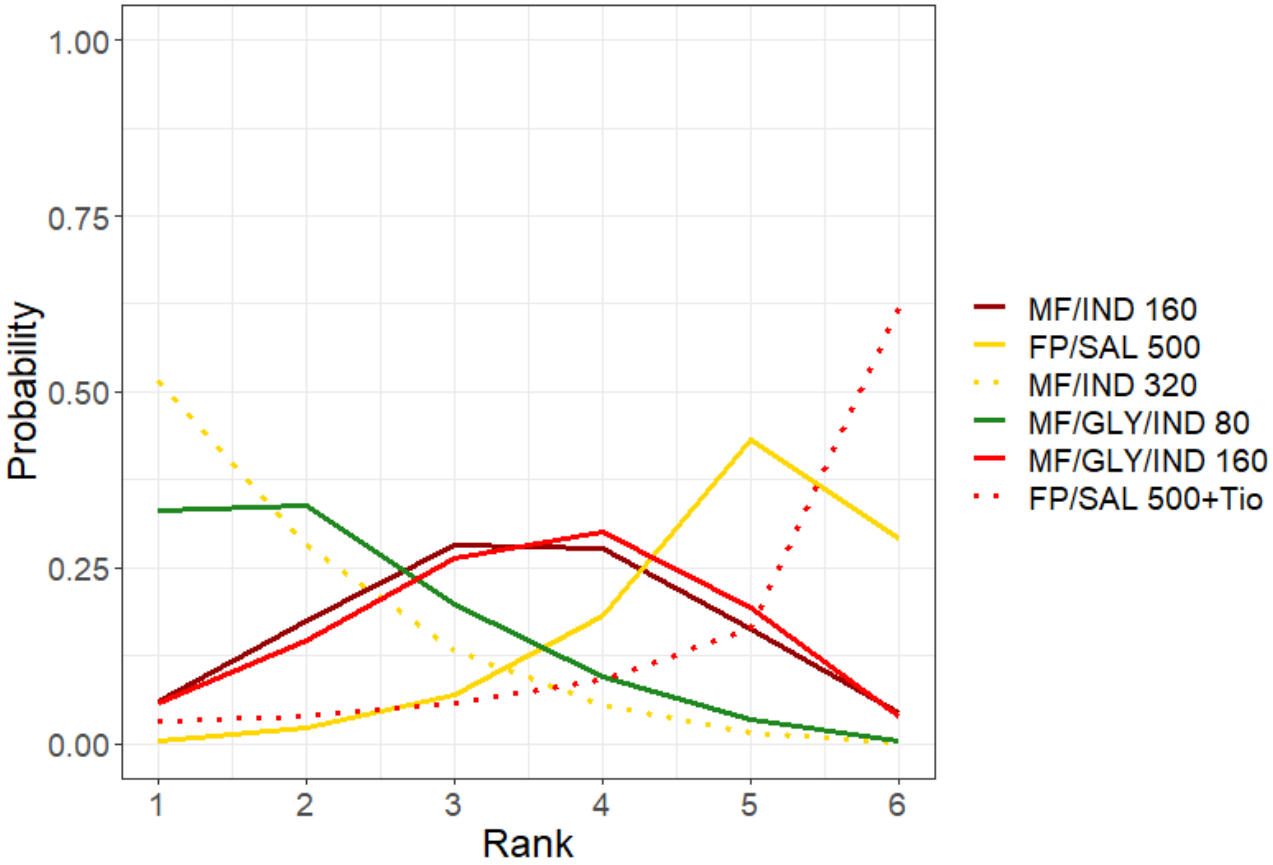
Figure 53. Forest plot of odds ratios relative to MF/IND160 for ACQ responders at 6 months for individual treatments. Odds ratio greater than one favors the comparator treatment over MF/IND 160. CrI: credible interval, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium.



There is no evidence to suggest that there is a change in odds of ACQ responders at six months for any individual treatments compared to MF/IND 160/150 µg (MD-ICS/LABA), but there was evidence to suggest that LD and MD triple therapies with mometasone furoate/glycopyrronium/indacaterol (80/50/150 µg and160/50/150 µg) and FP/SAL 500/50 µg plus tiotropium 5 µg (HD Triple) increase the odds of ACQ responders compared to FP/SAL 500/50 µg (HD-ICS/LABA).

The rank plots for individual treatments are presented in Figure 54, and the mean and median ranks are presented in Table 32. MF/IND 320/150 µg (HD-ICS/LABA) has the highest probability of being better than the other individual treatments (median rank 1 [95% CrI,1 to 4]).

Figure 54. Rank plots for individual treatments for ACQ responders at 6 months (fixed effect model) Line colors denote the treatment group. FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium.



3.1.2 Asthma control questionnaire (ACQ) responders at 12 months.

3.1.2.1 Grouped treatments

For this outcome, 5 trials (7391 participants) comparing four treatment groups were included in the NMA (Figure 9). A summary of the studies included in the analysis is presented in Appendix 14.

3.1.2.1.1 Model selection and inconsistency checking

For this subjective outcome comparing pharmacological interventions, a Log-Normal (-2.93, 1.58^2) prior distribution was used for the between-study heterogeneity (Turner 2015).

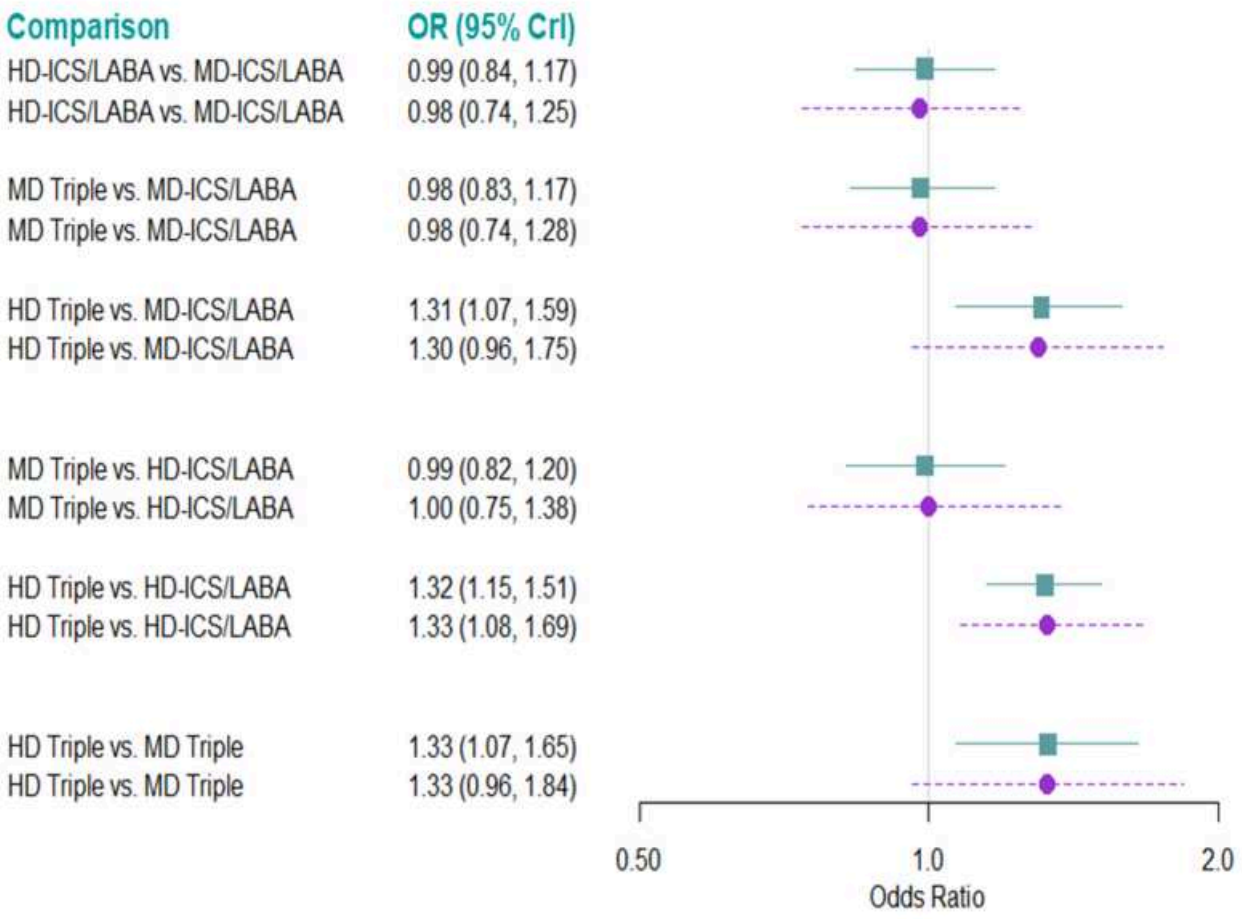
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. While the random-effects model appears to fit the data well, the total residual deviance for the fixed-effect model is a little high. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen, however due to the poor fit of this model, results for the random-effects model are presented along with the results for the fixed-effect model in Section 3.1.2.1.2.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 33. There was no evidence to suggest inconsistency in the network.

3.1.2.1.2 NMA results

The odds ratios of ACQ responders at 12 months are presented in Figure 55. The odds ratios of ACQ responders at 12 months comparing all treatment groups against each other are reported in Table 34.

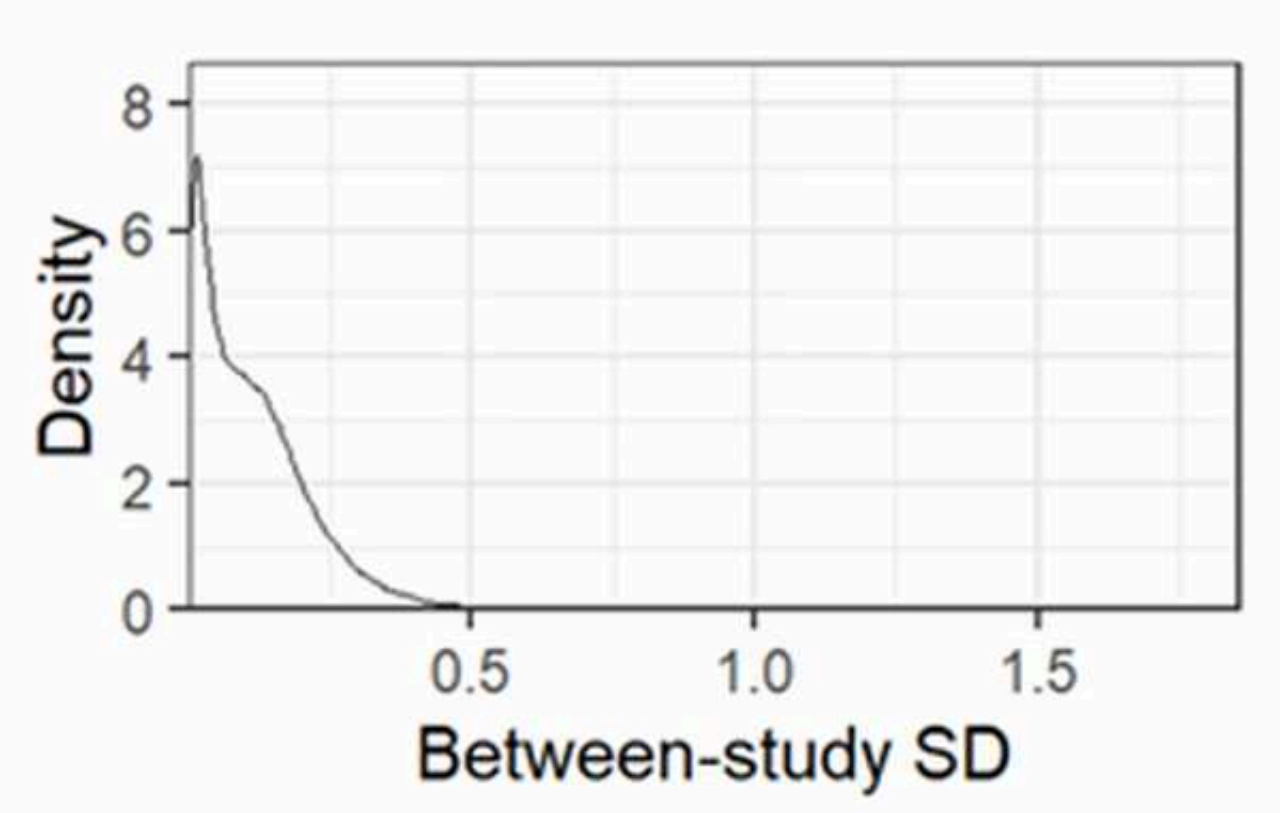
Figure 55. Forest plot of odds ratios relative to MD-ICS/LABA for ACQ responders at 12 months for grouped treatments (fixed- and random-effectsmodel). Odds ratio greater than one favors the comparator treatment over MD-ICS/LABA. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



Results for the fixed-effect and random-effects models are largely consistent in terms of odds ratios; in both models HD Triple increases the odds of ACQ response at 12 months compared to HD-ICS/LABA (OR 1.32 [95%CrI 1.15 to 1.51] and 1.33 [1.08 to 1.69] for the fixed-effect and random-effects models, respectively). In the fixed-effect model, HD Triple increases the odds of ACQ response compared to MD-ICS/LABA and MD Triple (OR 1.31 [95% CrI 1.07 to 1.59] and 1.33 [1.07 to 1.65], respectively). The credible intervals for these comparisons for the random-effects model include the "null" effect. An NMA summary of findings is presented in Summary of findings 12.

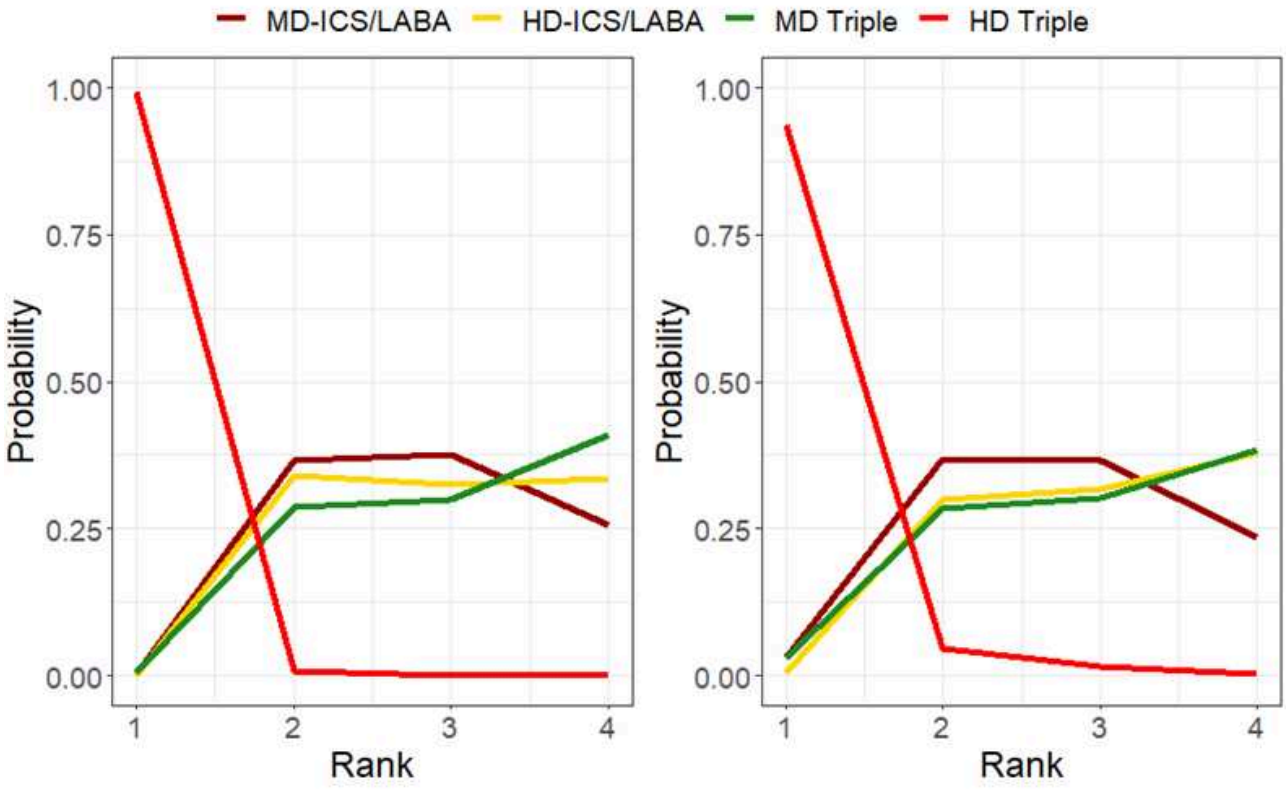
The density plot for the between-study heterogeneity is presented in Figure 56. Its high peak close to zero is consistent with the fixed-effect model, although higher values cannot be discarded.

Figure 56. Density plot for the between-study standard deviation (SD) for the random effects model for ACQ Responders at 12 months for grouped interventions



The rank plots for grouped treatments are presented in Figure 57, and the mean and median ranks are presented in Table 35. HD Triple ranks higher than the other grouped treatments (median rank 1 [95% CrI 1 to 1] for the fixed-effect model, median rank 1 [95% CrI 1 to 2] for the random-effects model).

Figure 57. Rank plots for grouped treatments for ACQ responders at 12 months for the fixed effect (A) and random effects (B) model. HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



3.1.2.1.3 Pairwise meta-analysis

Results of pairwise meta-analysis are presented in Analysis 4.2 and Summary of findings 13. There is moderate evidence that HD Triple increases ACQ responders at 12 months compared to MD Triple (RR 1.08 [95% CI 1.01 to 1.16]; ABI 58 more per 1000 patients and HD Triple compared to MD-ICS/LABA (RR 1.08 [95% CI 1.01 to 1.16]; ABI 58 more per 1000 patients).

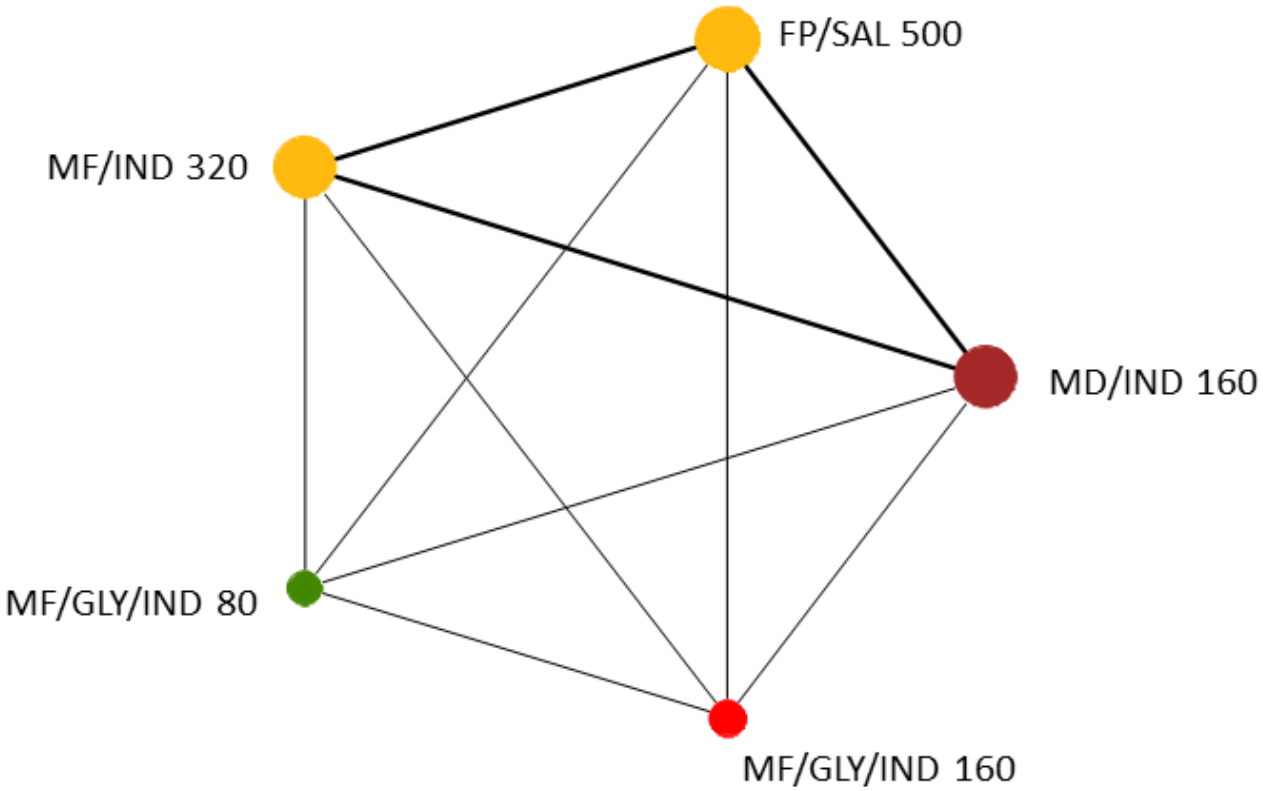
The evidence suggests triple therapy (ICS/LABA/LAMA) increases ACQ responders at 12 months compared to dual therapy (ICS/LABA) (RR 1.05 [95% CI 1.02 to 1.09]; I^2 = 75%) when analysed using the fixed-effect model. However, the confidence intervals included the null effect when Kerstjens 2012 was removed or the random-effects model was used. Therefore, it is very uncertain if triple therapy (ICS/LABA/LAMA) increases ACQ responders at 12 months compared to dual therapy (ICS/LABA).

The results were unchanged when van Zyl-Smit 2020, which is considered at high risk of bias due to high attrition rates, was removed. The use of fixed-effect or random-effect analysis did not change the results except for triple versus dual therapy as mentioned above and HD Triple vs. HD-ICS/LABA in which the confidence intervals included the "null" effect with the random-effects analysis.

3.1.2.2 Individual treatments

For this outcome, 2 trials (3906 participants) comparing five distinct treatments were included in the NMA (Figure 58). A summary of the studies included is presented in Appendix 15. Two studies (Kerstjens 2012, and Virchow 2019) that were identified were excluded from this analysis, as they were disconnected from the main network shown in Figure 58.

Figure 58. Network diagram for ACQ responders at 12 months for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol.



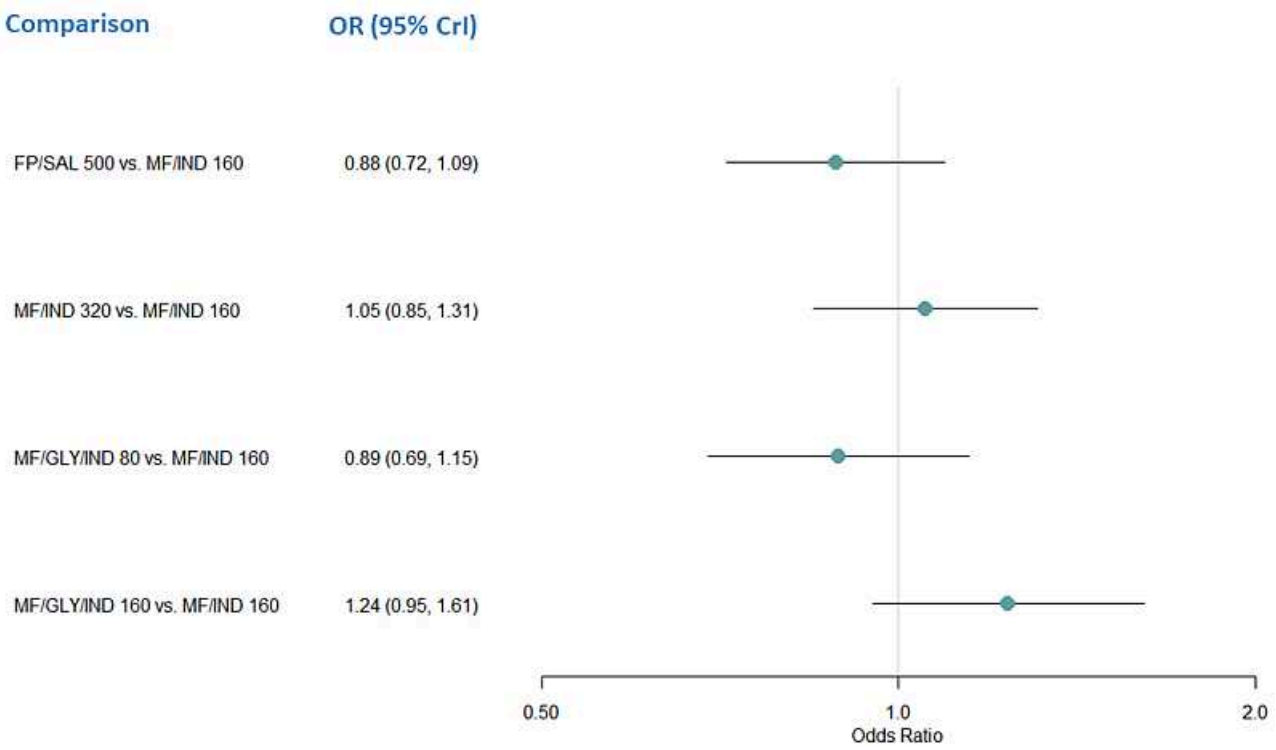
3.1.2.2.1 Model selection and inconsistency checking

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.1.2.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.1.2.2.2 NMA results

The odds ratios of ACQ responders at 12 months, compared to MF/IND 160/150 (MD-ICS/LABA), are presented in Figure 59. The odds ratios of ACQ responders at 12 months comparing all treatment groups against each other are reported in Table 36.

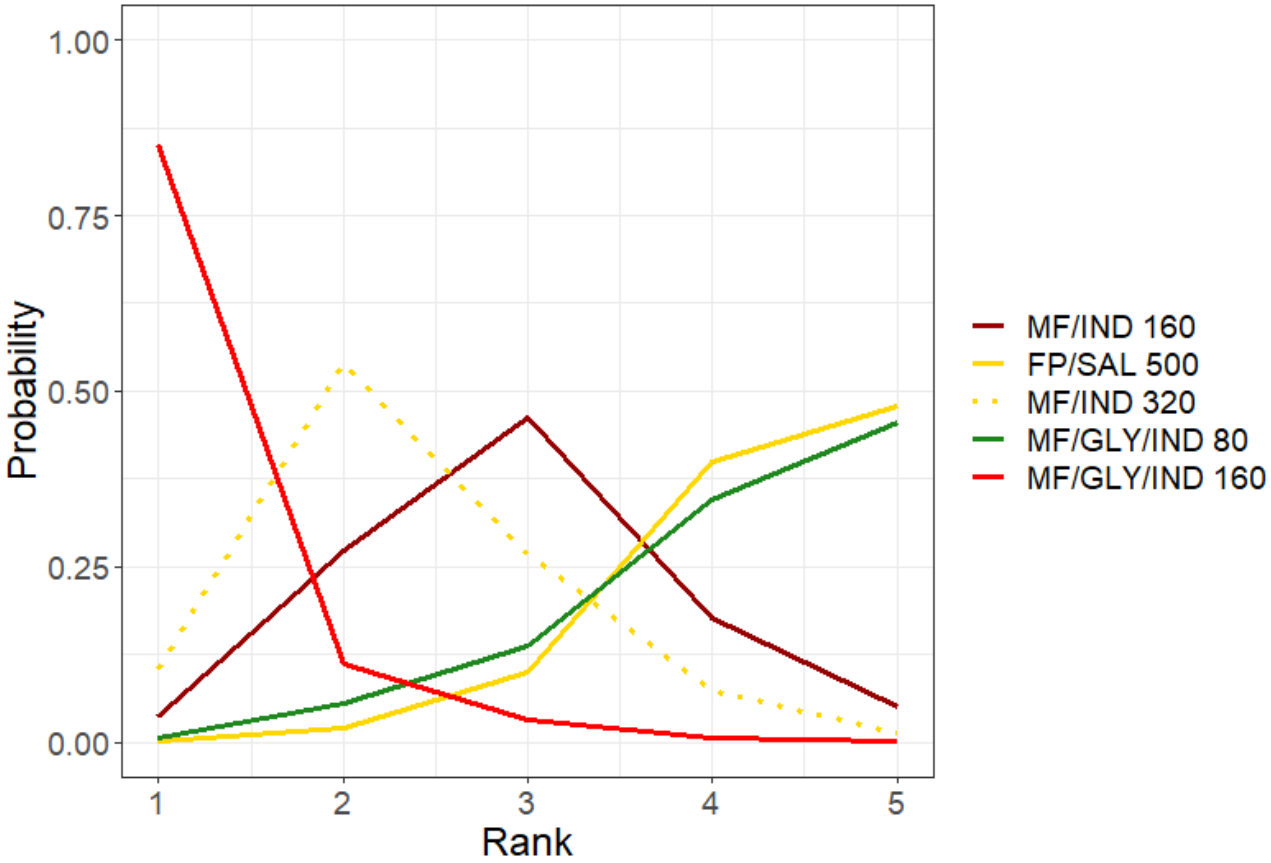
Figure 59. Forest plot of odds ratios relative to MF/IND160 for ACQ responders at 12 months for individual treatments (fixed effect model) Odds Ratio greater than one favors the comparator treatment over MF/IND 160.CrI: credible interval, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol.



There is no evidence to suggest that there is a change in odds of ACQ responders at 12 months for any individual treatments compared to MF/IND 160/150 µg (MD-ICS/LABA). However, there is evidence to suggest that MF/GLY/IND 160/50/150 µg (MD Triple) increases the odds of ACQ responders at 12 months compared to MF/GLY/IND 80/50/150 µg (LD Triple) (OR 1.39 [95% CrI 1.05 to 1.84]) and MF/GLY/IND 160/50/150 µg (MD Triple) increases the odds of ACQ responders at 12 months compared to FP/SAL 500/50 µg (HD-ICS/LABA) (OR 1.40 [95% CrI 1.08 to 1.82]).

The rank plots for individual treatments are presented in Figure 60, and the mean and median ranks are presented in Table 37. MF/GLY/IND 160/50/150 µg (MD Triple) has the highest probability of being the best treatment (median rank 1 [95% CrI 1 to 3]), but credible intervals for treatment ranks are very wide.

Figure 60. Rank plots for individual treatments for ACQ responders at 12 months (fixed effect model) Line colors denote the treatment group. FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol.



3.2 Serious adverse events (SAEs)

3.2.1 All-cause SAEs

3.2.1.1 Grouped treatments

For this outcome, 13 trials (14,476 participants) comparing four treatment groups were included in the NMA (Figure 10). A summary of the studies included in the analysis is presented in Appendix 16.

3.2.1.1.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

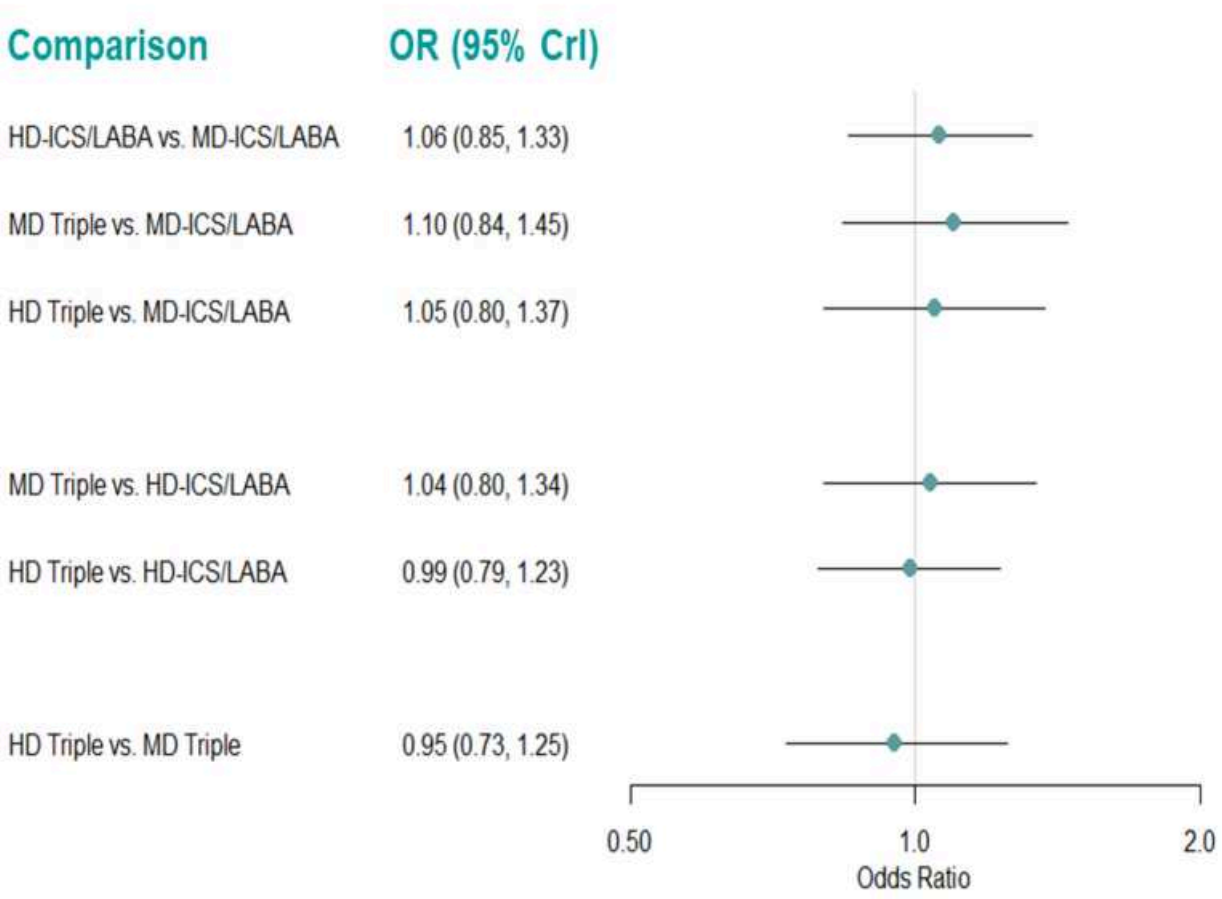
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.2.1.1.2.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 38. There was no evidence to suggest inconsistency in the network.

3.2.1.1.2 NMA results

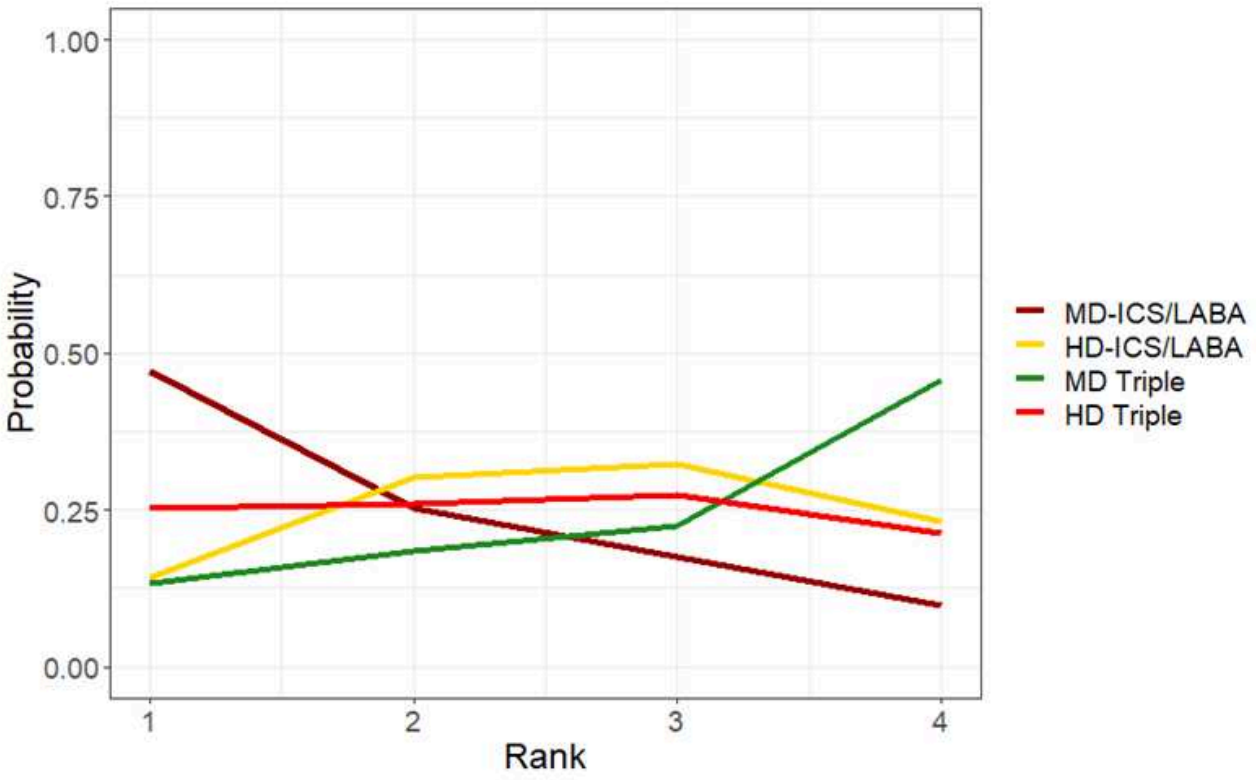
The odds ratios of all-cause SAEs are presented in Figure 61. The odds ratios of all-cause SAEs comparing all treatment groups against each other are reported in Table 39. There is no evidence to suggest there is a change in odds of all-cause SAEs for any of the treatment comparisons. An NMA summary of findings is presented in Summary of findings 14.

Figure 61. Forest plots of odds ratios for all-cause SAEs for grouped treatments (fixed effect model). Odds ratio less than one favors the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



The rank plots for grouped treatments are presented in Figure 62, and the mean and median ranks are presented in Table 40. Treatment ranks are very uncertain, - none of the treatments have over 50% probability of ranking in any of the four possible positions, and all treatments have the same, very wide, 95% CrIs.

Figure 62. Rank plots for grouped treatments for all-cause SAEs (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



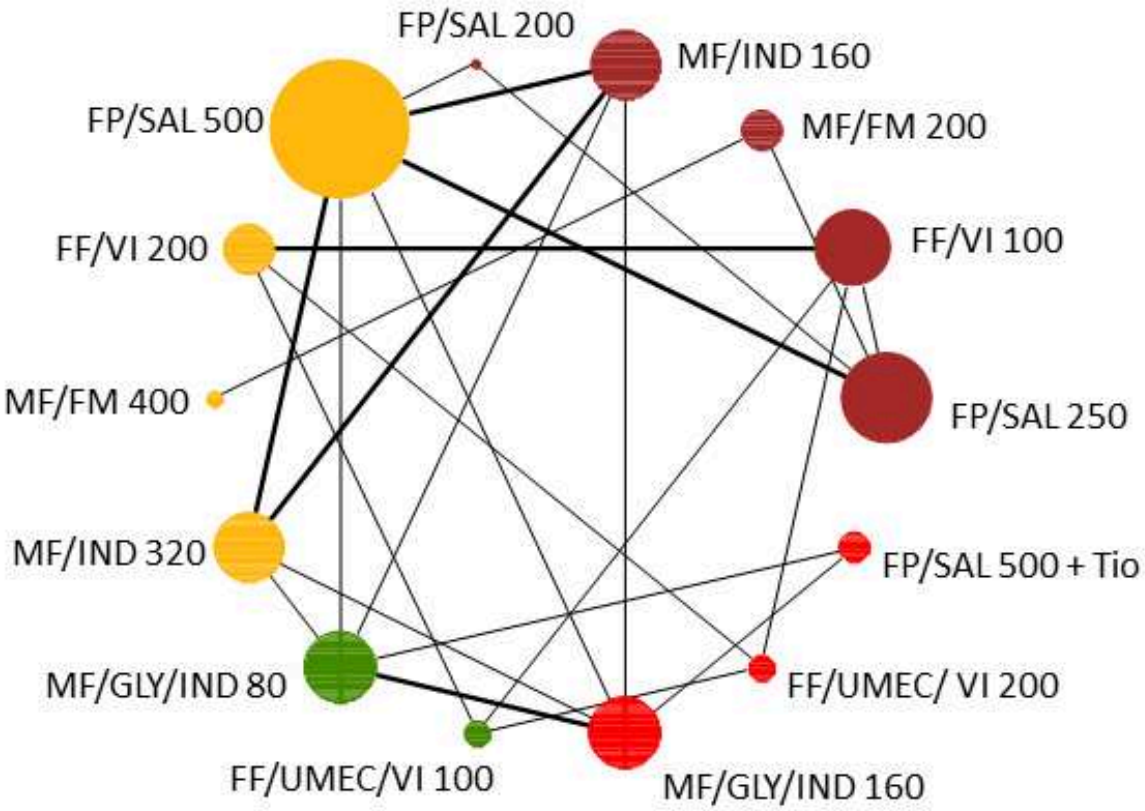
3.2.1.1.3 Pairwise meta-analysis

The evidence suggests there is no or little difference in all-cause SAEs for any of the treatment comparisons [moderate to high certainty] (Analysis 5.1, Summary of findings 15). There was no difference in the results between fixed- and random-effects analyses.

3.2.1.2 Individual treatments

For this outcome, 10 trials (11,936 participants) comparing 14 distinct treatments were included in the NMA (Figure 63). A summary of the studies included is presented in Appendix 17. Seven studies (Bodzenta-Lukaszyk 2012, Cukier 2013, Kerstjens 2012a, Kerstjens 2012b, Peters 2008, Virchow 2019a, and Virchow 2019b) that were identified were excluded from this analysis as they were disconnected from the main network shown in Figure 63.

Figure 63. Network diagram for all-cause SAEs for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



3.2.1.2.1 Model selection and inconsistency checking

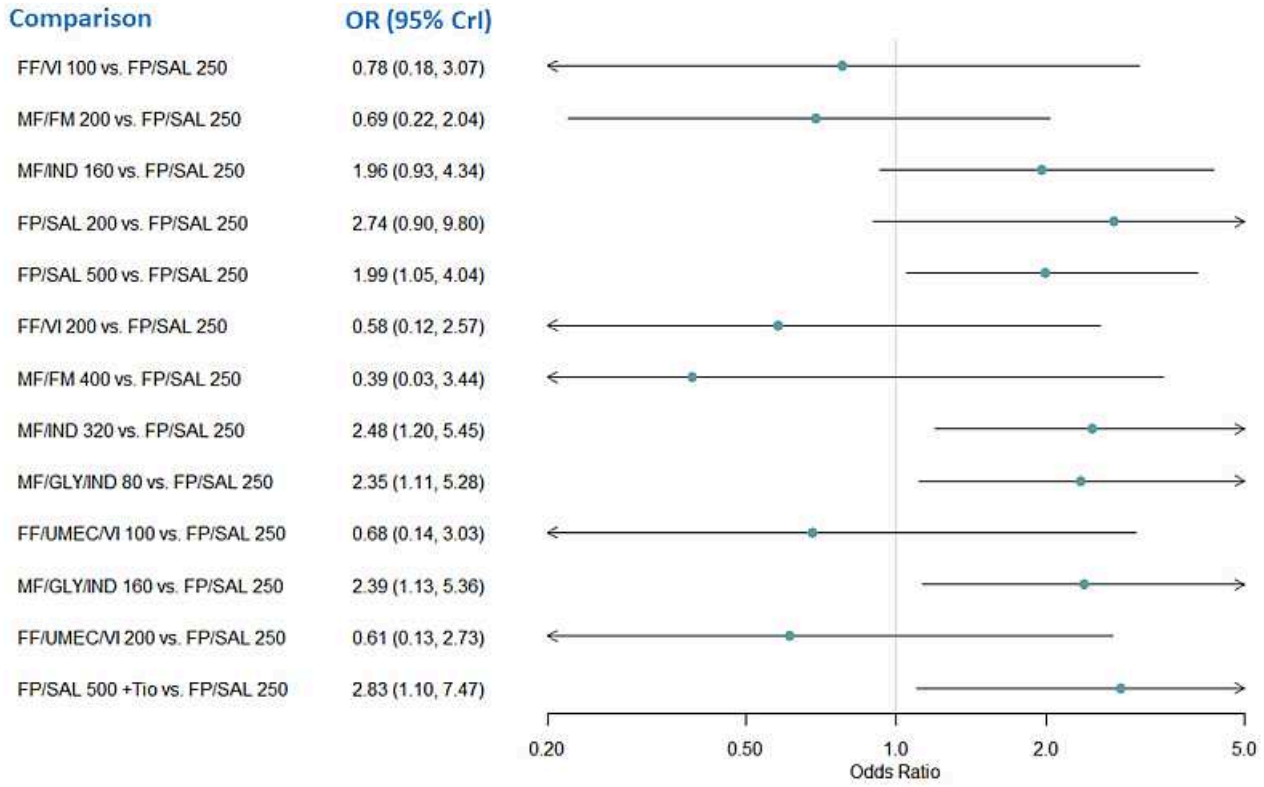
The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.2.1.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.2.1.2.2 NMA results

The odds ratios of all-cause SAEs, compared to FP/SAL 250/50 µg (MD-ICS/LABA), are presented in Figure 64. The odds ratios of all-cause AEs comparing all treatment groups against each other are reported in Table 41.

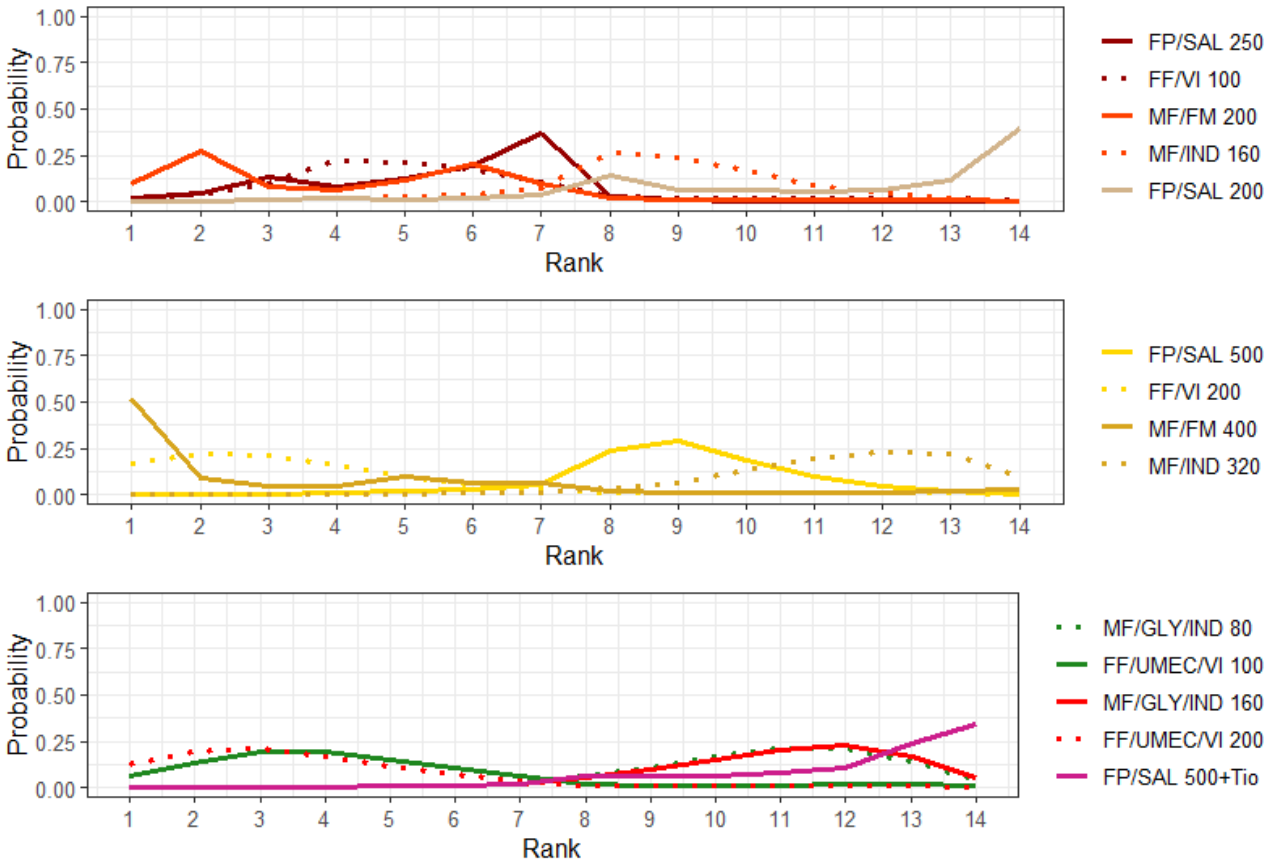
Figure 64. Forest plot of odds ratios relative to FP/SAL 250 for all-cause SAEs for individual treatments. Odds ratio less than one favors the comparator treatment over FP/SAL 250. CrI:credible interval, FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



FP/SAL 500/50 µg (HD-ICS/LABA), MF/IND 320/150 µg (HD-ICS/LABA), MF/GLY/IND 80/50/150 µg (LD Triple), MF/GLY/IND 160/50/150 µg (MD Triple), and FP/SAL 500/50 µg + Tio 5 µg (HD Triple) increase the odds of all-cause SAEs compared to FP/SAL 250/50 µg (MD-ICS/LABA). There is a lot of uncertainty in the estimates of odds ratios, and many of the comparisons have wide credible intervals.

The rank plots for individual treatments are presented in Figure 65, and the mean and median ranks are presented in Table 42. Although MF/FM 400/10 µg (HD-ICS/LABA) has the highest probability of being the best treatment, the probability that it is the best treatment is only a little over 50%. Overall, treatment ranks are very uncertain, and all the other treatments have under 50% probability for any of the 14 other possible ranks.

Figure 65. Rank plots for individual treatments for all-cause SAEs (fixed effect model). Line colors denote the treatment group. FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



3.2.2 Asthma-related SAEs

3.2.2.1 Grouped treatments

For this outcome, 11 trials (13,209 participants) comparing 4 treatment groups were included in the NMA (Figure 11). A summary of the studies included in the analysis is presented in Appendix 18.

3.2.2.1.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

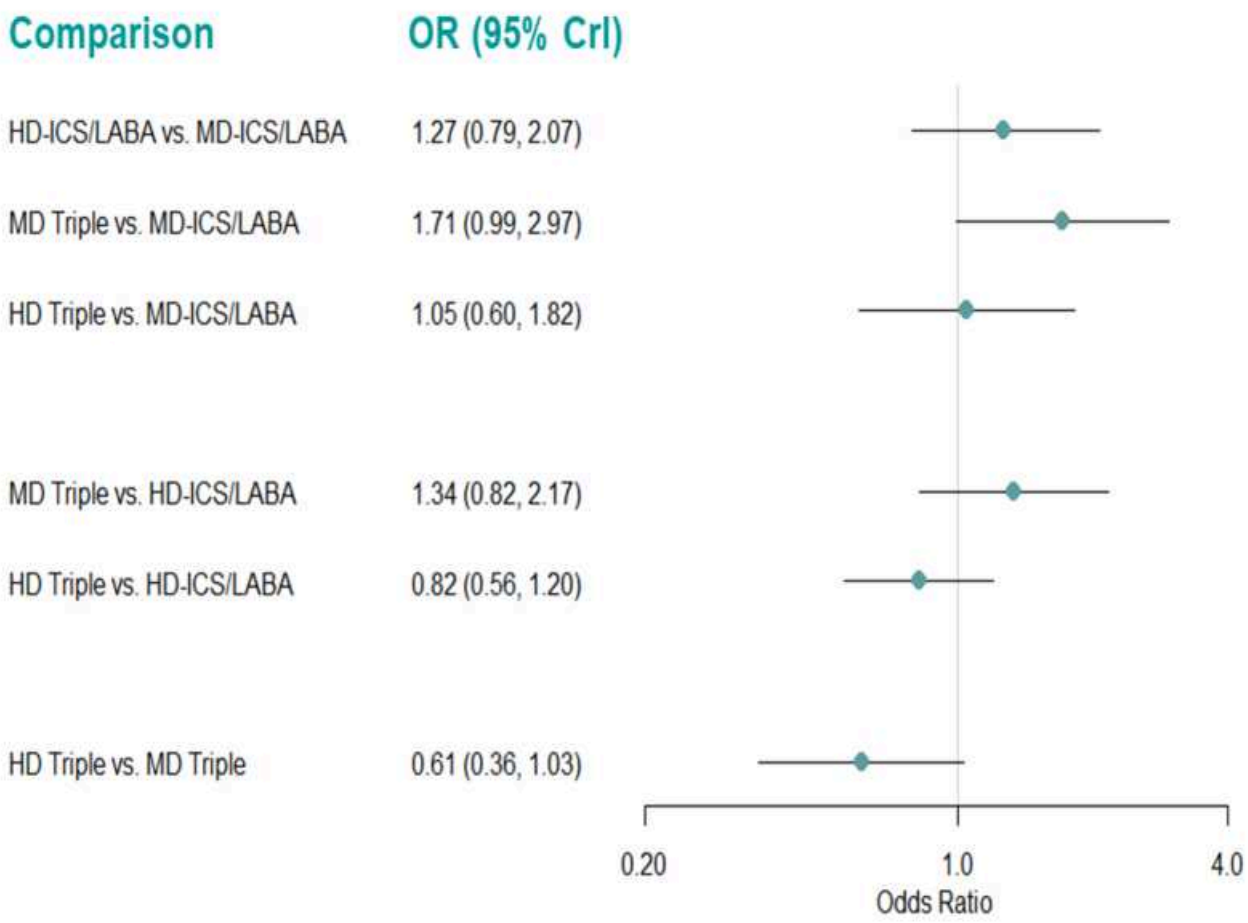
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.2.1.1.2.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 43. There was no evidence to suggest inconsistency in the network.

3.2.2.1.2 NMA results

The odds ratios of asthma-related SAEs are presented in Figure 66. The odds ratios of asthma-related SAEs comparing all treatment groups against each other are reported in Table 44.

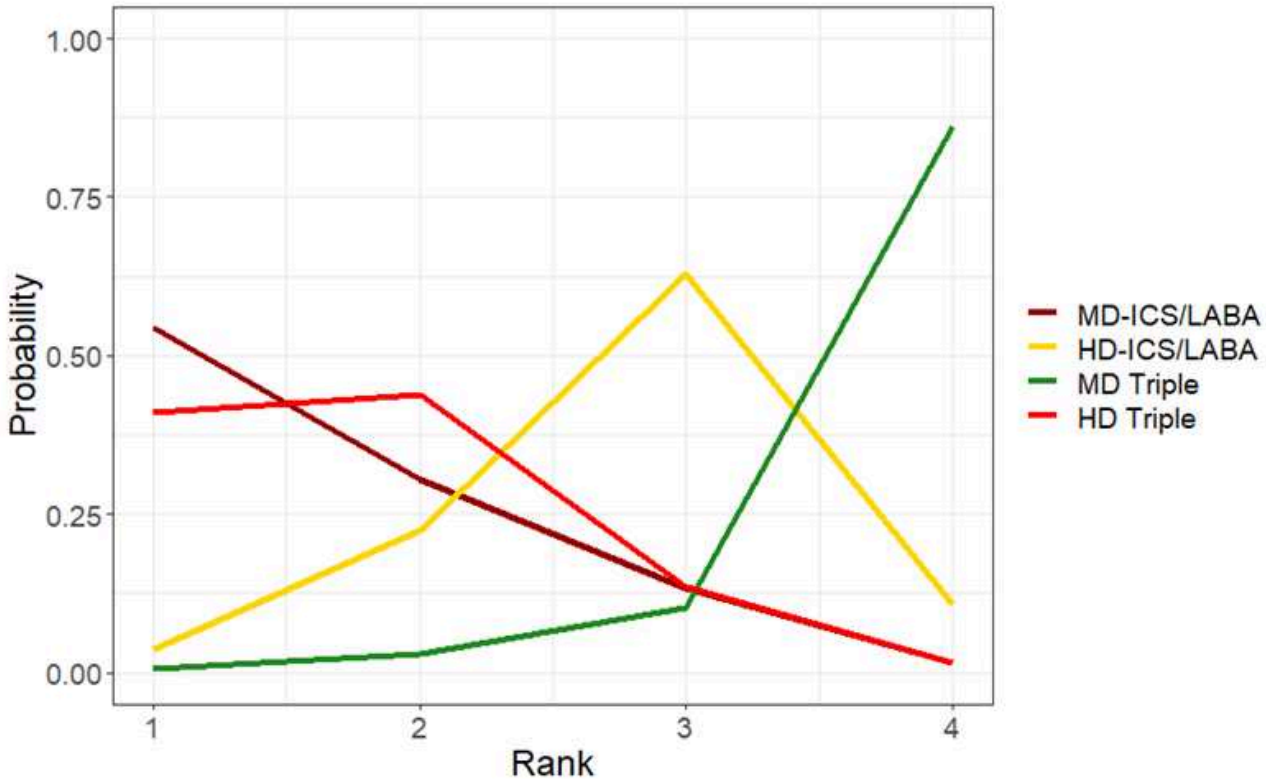
Figure 66. Forest plots of odds ratios relative for asthma-related SAEs for grouped treatments (fixed effect model). Odds ratio (OR) less than one favors the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



There is insufficient evidence to suggest a difference in odds of asthma-related SAEs for any treatment comparisons. An NMA summary of findings is presented in Summary of findings 16.

The rank plots for grouped treatments are presented in Figure 67, and the mean and median ranks are presented in Table 45. MD-ICS/LABA ranks higher than the other grouped treatments (median rank 1 [95% CrI 1 to 3] and MD Triple has a high probability of being the worst group for this outcome (median rank 4 [95% CrI 2 to 4]).

Figure 67. Rank plots for grouped treatments for asthma-related SAEs (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



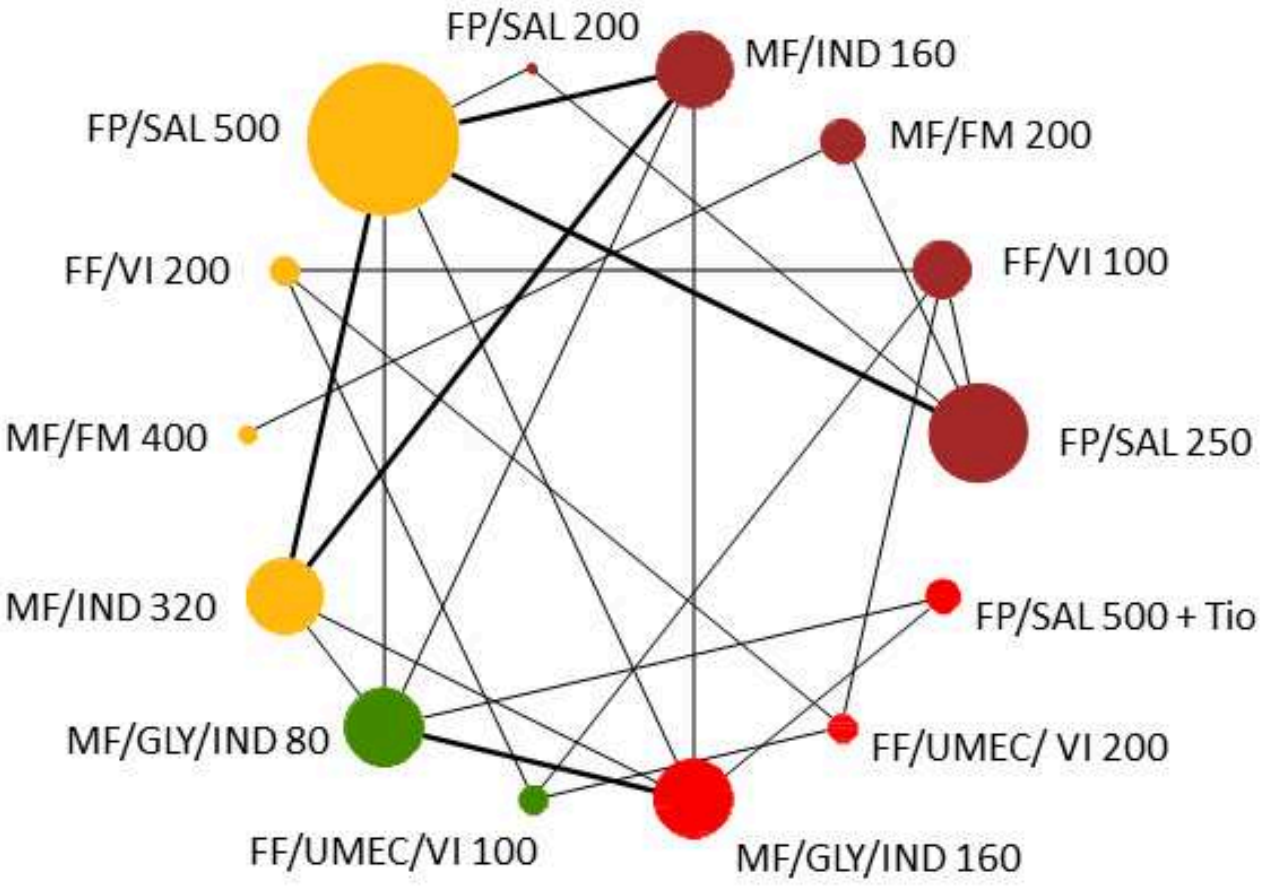
3.2.2.1.3 Pairwise meta-analysis

The evidence suggests there is no or little difference in asthma-related SAEs for any of the treatment comparisons [moderate to high certainty] (Analysis 5.2, Summary of findings 15). There was no difference in the results between fixed-effect and random-effects models.

3.2.2.2 Individual treatments

For this outcome, 9 trials (11,246 participants) comparing 14 distinct treatments were included in the NMA (Figure 68). A summary of the studies included is presented in Appendix 19. Four studies (Kerstjens 2012a, Kerstjens 2012b, Virchow 2019a, and Virchow 2019b) that were identified were excluded from this analysis as they were disconnected from the main network shown in Figure 68.

Figure 68. Network diagram for asthma-related SAEs for individual interventions. Node colors denote the treatment group. The size of the nodes and the thickness of edges depend on the number of people randomised and the number of trials conducted. FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



As the data are sparse, with few studies per comparison which have very few events in each treatment arm, the results for this analysis are very uncertain.

One of the arms (for the treatment MF/FM 200) in Weinstein 2010 reported no events. The second arm (for the treatment MF/FM 400) for this study reported only one event. The zero cell caused problems with model convergence, attributable to the fact that this is the only study that contributes MF/FM 400 to the network. We added a continuity correction of 0.5 to the zero count events to help improve model convergence due to the sparsity of the evidence in this study. When fitting this model in OpenBUGS (version 3.2.3), a less-vague prior of Normal (0, 0.01) was also used for the relative treatment effects to make the model more stable.

3.2.2.2.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

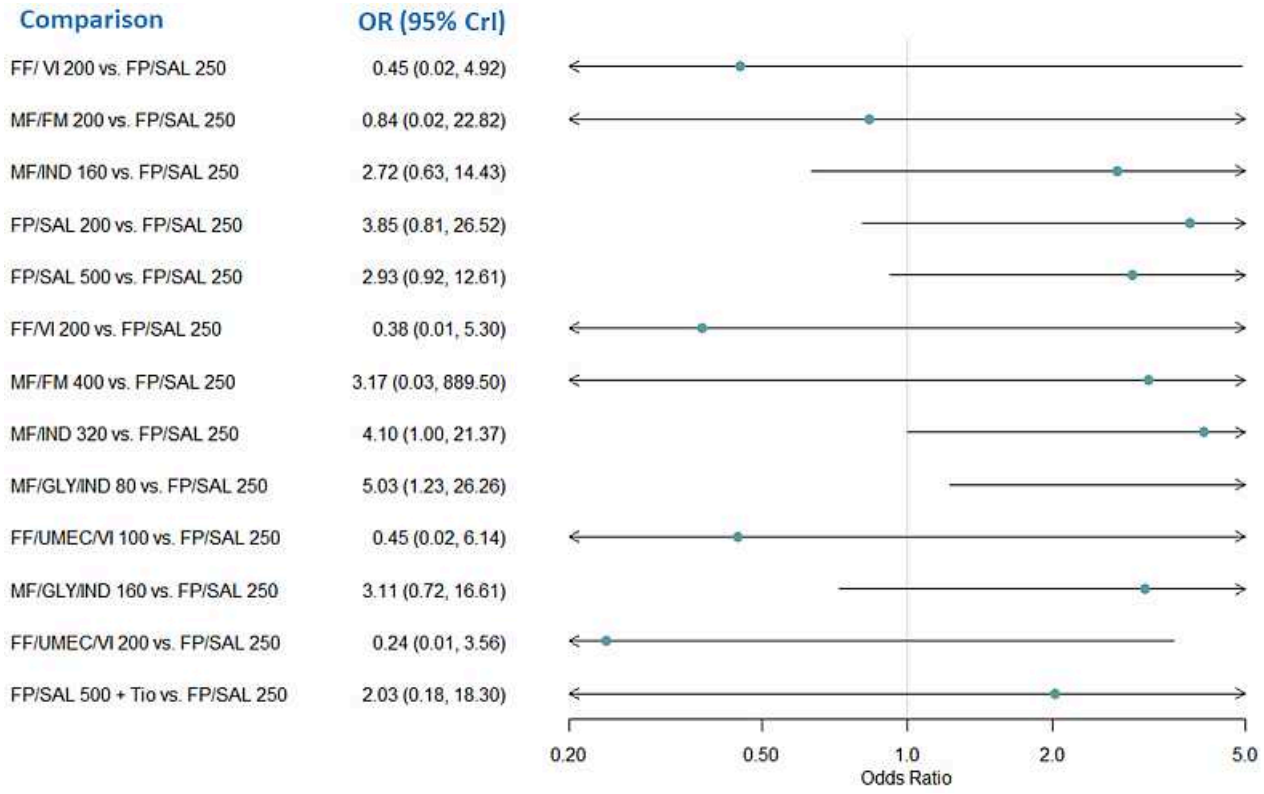
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low, with a wide credible interval. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.2.2.2.2.

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.2.2.2.2 NMA results

The odds ratios of asthma-related SAEs, compared to MF/IND160/150 µg (MD-ICS/LABA), are presented in Figure 69. The odds ratios of asthma-related SAEs comparing all treatment groups against each other are reported in Table 46. There is evidence to suggest that MF/IND 320/150 µg (HD-ICS/LABA) and MF/GLY/IND 80/50/150 µg (LD Triple) increase the odds of asthma-related SAEs compared to FP/SAL 250/50 µg (MD-ICS/LABA) (OR 4.1 [95% CrI 1.003 to 21.4] and 5.0 [1.2 to 26.3] respectively).

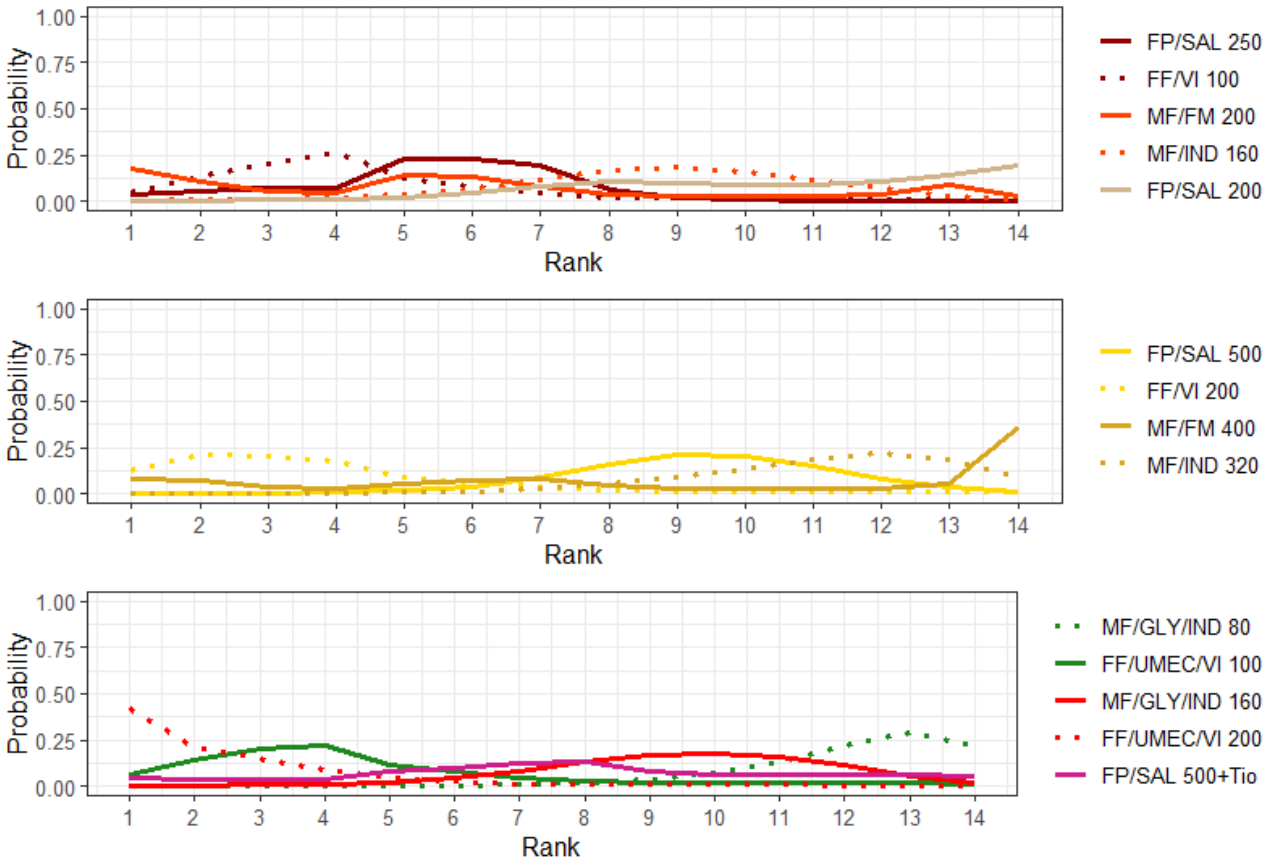
Figure 69. Forest plot of odds ratios for asthma-related SAEs relative to FP/SAL 250 for individual treatments. Odds ratio less than one favors the comparator treatment over FP/SAL 250. FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



The impact of the zero-cell in Weinstein 2010 identified in Section 3.2.2.2 can be observed in Figure 69, where the credible interval estimated for MF/FM 400/10 µg is wide enough that the OR could be considered not estimable. The upper credible limit for most of the other comparisons was also quite large.

The rank plots for individual treatments are presented in Figure 70, and the mean and median ranks are presented in Table 47. It is very unclear which intervention is the best, as treatment ranks are very uncertain, none of the treatments have over 50% probability for any of the 14 possible ranks. The uncertainty in ranks is further highlighted by the large overlap in their credible intervals.

Figure 70. Rank plots for individual treatments for asthma-related SAEs (fixed effect model) Line colors denote the treatment group. FF:fluticasone furoate, FM:formoterol, FP:fluticasone propionate, GLY: glycopyrronium, IND:indacaterol, MF:mometasone furoate, SAL:salmeterol, Tio:tiotropium, UMEC: umeclidinium, VI:vilanterol.



3.3 Adverse events (AEs)

3.3.1 All-cause AEs

3.3.1.1 Grouped treatments

For this outcome, 12 trials (12,915 participants) comparing 4 treatment groups were included in the NMA (Figure 12). A summary of the studies included in the analysis is presented in Appendix 20.

3.3.1.1.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

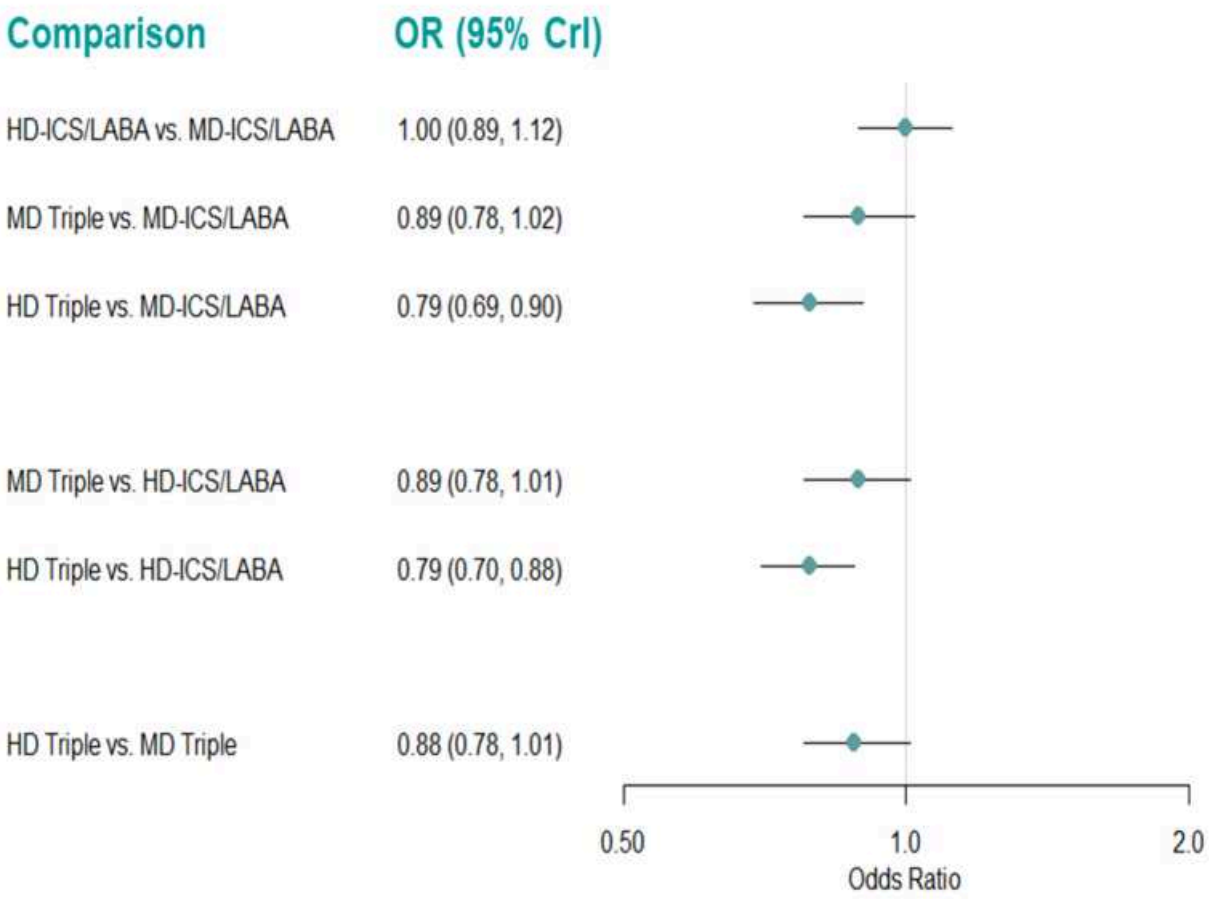
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.3.1.1.2.

A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 48. There is no evidence to suggest inconsistency in the network.

3.3.1.1.2 NMA results

The odds ratios of all-cause AEs are presented in Figure 71. The odds ratios of all-cause AEs comparing all treatment groups against each other are reported in Table 49.

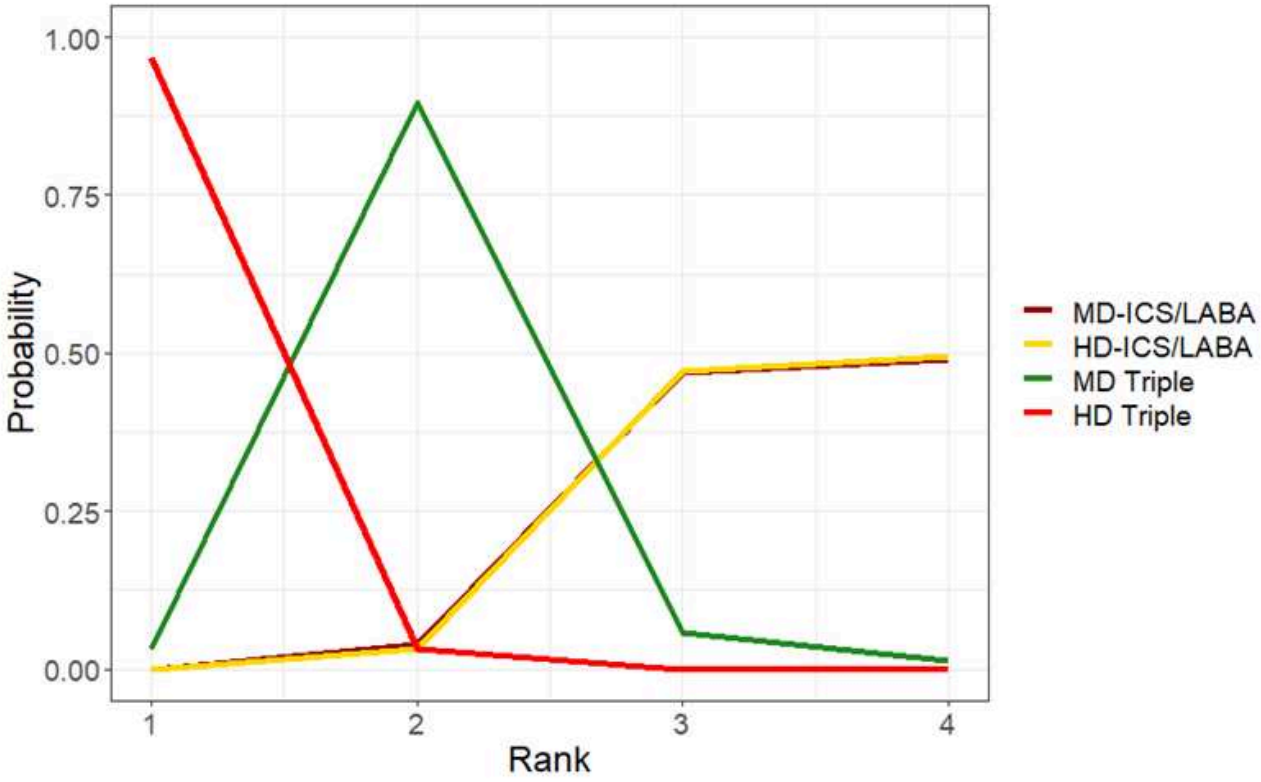
Figure 71. Forest plots of odds ratios for all-cause AEs for grouped treatments (fixed effect model). Odds ratio less than one favors the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



There is evidence to suggest that treatment with HD Triple reduces the odds of all-cause AEs compared to MD-ICS/LABA and HD-ICS/LABA (OR 0.79 [95% CrI 0.69 to 0.90] and 0.79 [0.70 to 0.88], respectively). An NMA summary of findings is presented in Summary of findings 17.

The rank plots for grouped treatments are presented in Figure 72, and the mean and median ranks are presented in Table 50. HD Triple has the highest probability of being better than the other grouped treatments (median rank 1 [95% CrI 1 to 2]).

Figure 72. Rank plots for grouped treatments for all-cause AEs (fixed effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



3.3.1.1.3 Pairwise meta-analysis

The evidence suggests HD and MD Triple result in a reduction in all-cause AEs compared to MD-ICS/LABA (RR 0.96 [95% CI 0.91 to 1.00]; ARR 42 fewer per 1000 patients; [moderate certainty] and RR 0.92 [95% CI 0.85 to 1.00]; ARR 25 fewer per 1000 patients; [moderate certainty], respectively).

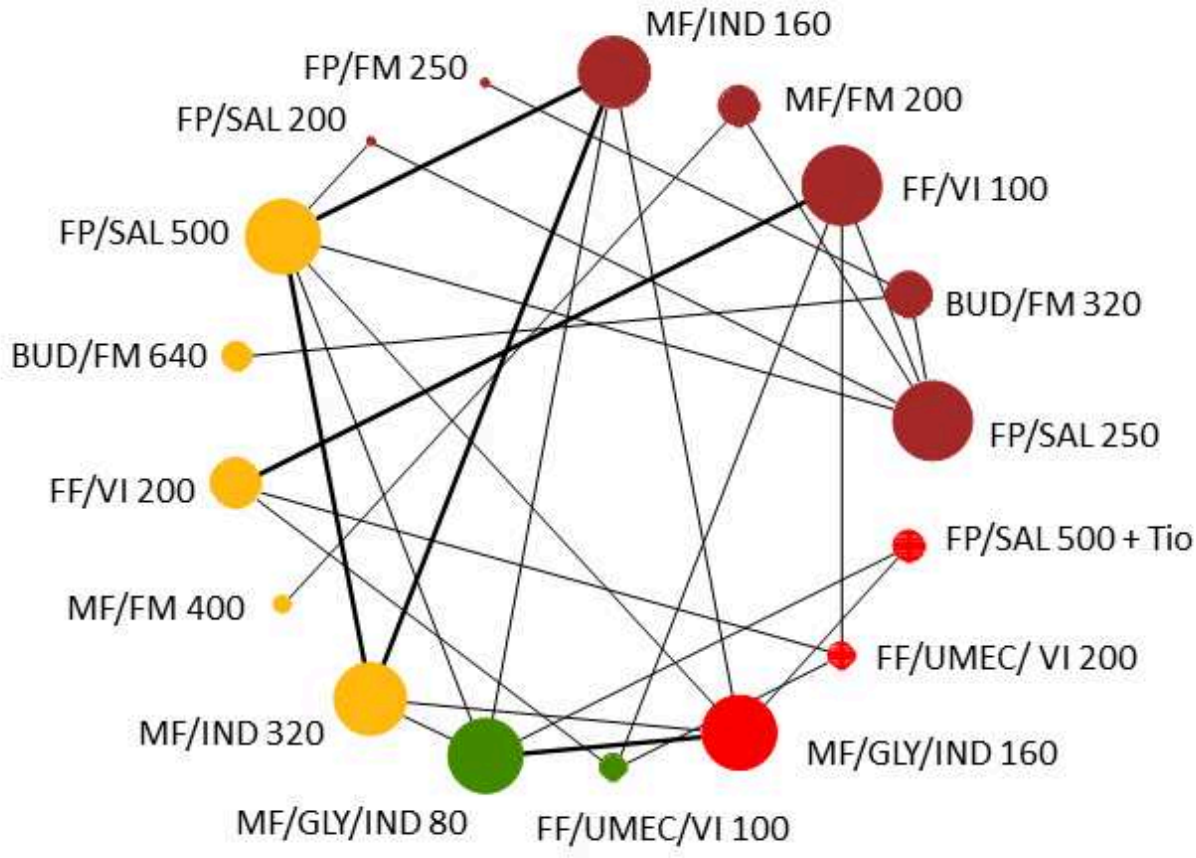
Triple therapy (ICS/LABA/LAMA) results in a reduction in all-cause AEs compared to dual therapy (ICS/LABA) (RR 0.93 [95% CI 0.90 to 0.96]; ARR 44 fewer per 1000 patients; [high certainty]) and HD Triple likely results in a slight reduction in all-cause AEs compared to MD Triple (RR 0.95 [95% CI 0.90 to 1.02]; ARR 26 fewer per 1000 patients; [moderate certainty]) (Analysis 5.3, Summary of findings 15).

There was no difference in the results between fixed-effect and random-effects models.

3.3.1.2 Individual treatments

For this outcome, 12 trials (12,009 participants) comparing 17 distinct treatments were included in the NMA (Figure 73). A summary of the studies included is presented in Appendix 21. Four studies (Kerstjens 2012a; Kerstjens 2012b; Virchow 2019a; Virchow 2019b) that were identified were excluded from this analysis as they were disconnected from the main network shown in Figure 73.

Figure 73. Network diagram for all-cause AEs for individual interventions. Node colors denote the treatment group. BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



3.3.1.2.1 Model selection and inconsistency checking

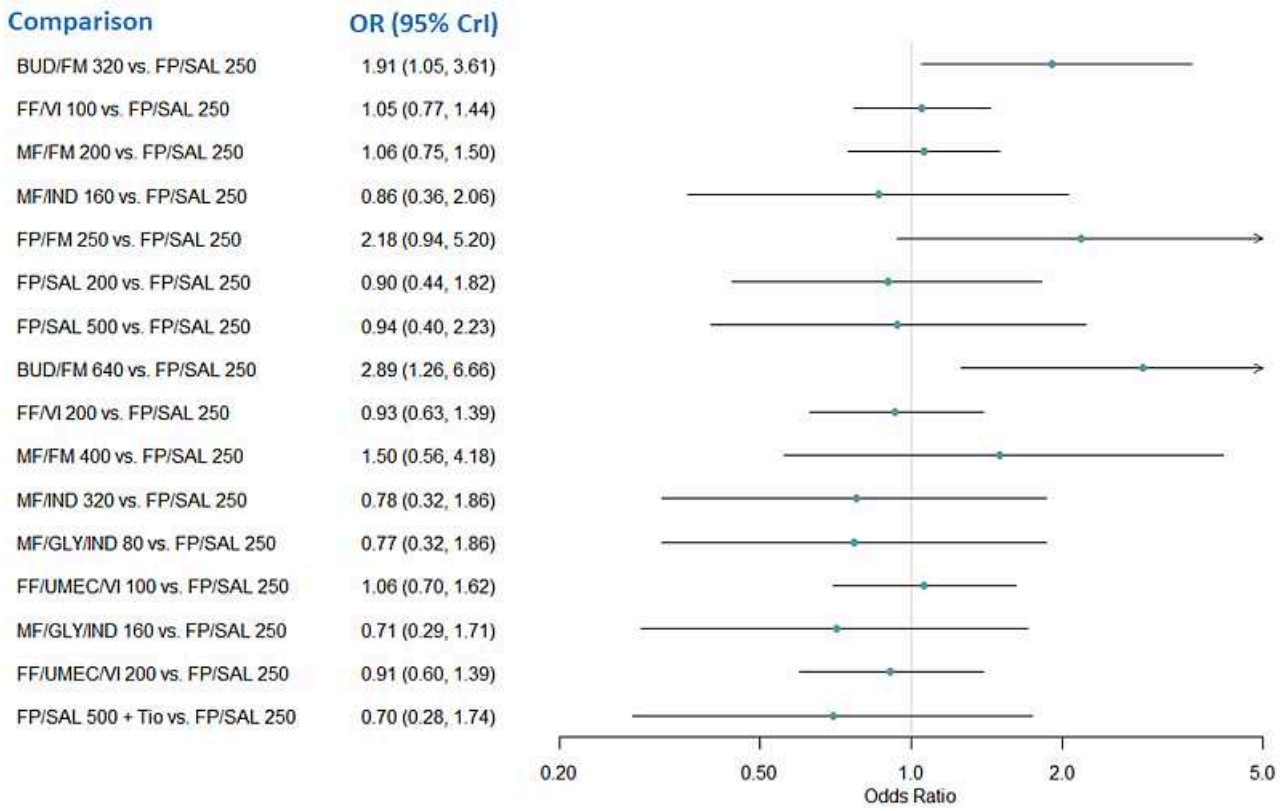
The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.3.1.2.2. There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.3.1.2.2 NMA results

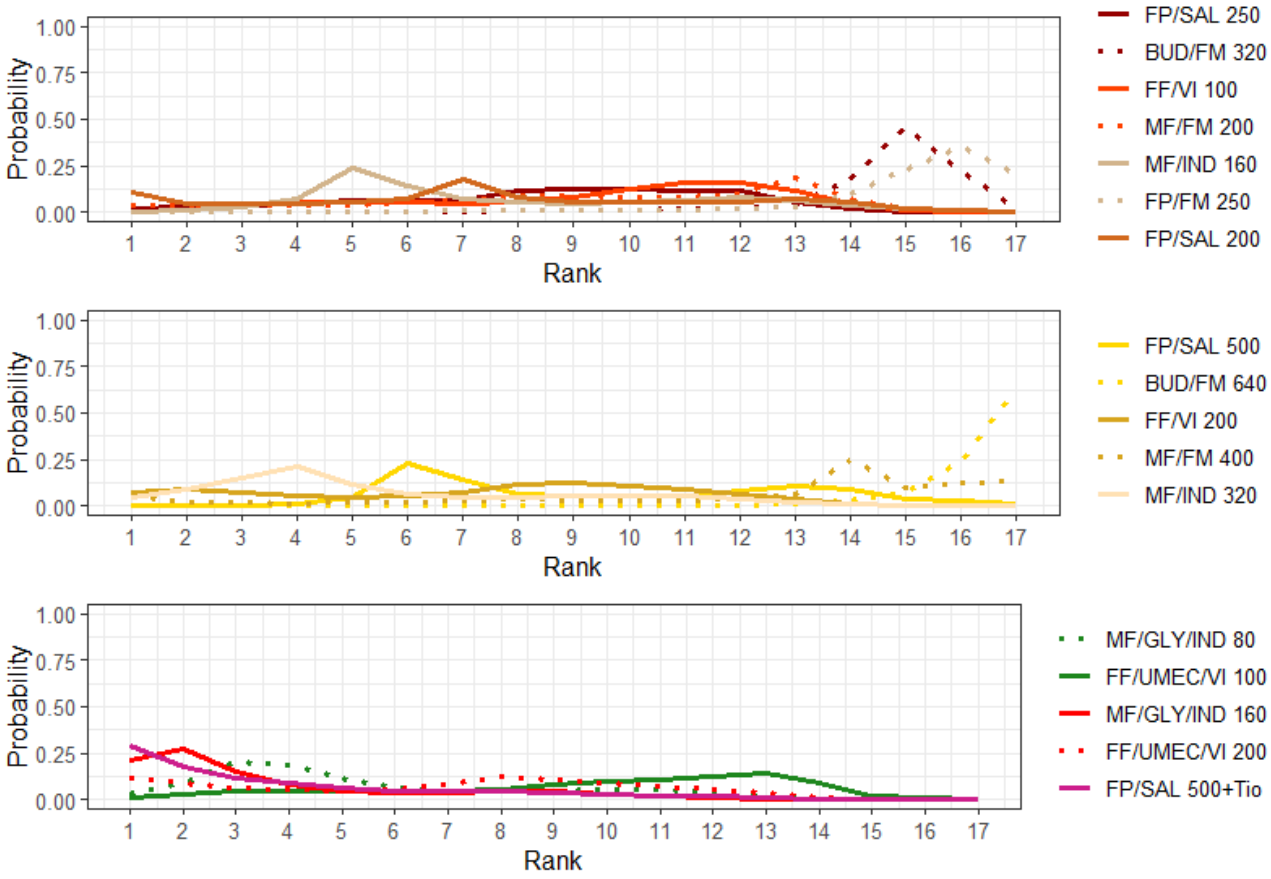
The odds ratios of all-cause AEs, compared to FP/SAL 250/50 µg (MD-ICS/LABA), are presented in Figure 74. The odds ratios of all-cause AEs comparing all treatment groups against each other are reported in Table 51. Treatment with budesonide/formoterol (BUD/FM) 320/10 µg (MD-ICS/LABA) and BUD/FM 640/10 µg (HD-ICS/LABA) increase the odds of all-cause AEs compared to FP/SAL 250/50 µg (MD-ICS/LABA) (OR 1.9 [1.05 to 3.6] and 2.9 [1.3 to 6.7] respectively). Other comparisons which do not include the "null" treatment effect are highlighted in bold font in Table 51.

Figure 74. Forest plot of odds ratios relative to FP/SAL 250 for all-cause AEs for individual treatments. Odds ratio less than one favors the comparator treatment. BUD: budesonide, CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, OR: odds ratio, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



The rank plots for individual treatments are presented in Figure 75, and the mean ranks are presented in Table 52. It is very unclear which intervention is the best, as the treatment ranks are very uncertain. Except BUD/FM 640/10 µg (HD-ICS/LABA) which has a probability of approximately 60% of being the lowest ranked treatment (median rank 17 [95% CrI 12 to 17]), none of the other treatments have even 50% probability for any of the possible ranks.

Figure 75. Rank plots for individual treatments for all-cause AEs (fixed-effect model). Line colors denote the treatment group. BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



3.3.2 Dropouts due to AEs

3.3.2.1 Grouped treatments

For this outcome, 12 trials (12,951 participants) comparing 4 treatment groups were included in the NMA (Figure 13). A summary of the studies included in the analysis is presented in Appendix 22.

3.3.2.1.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.3.2.1.2.

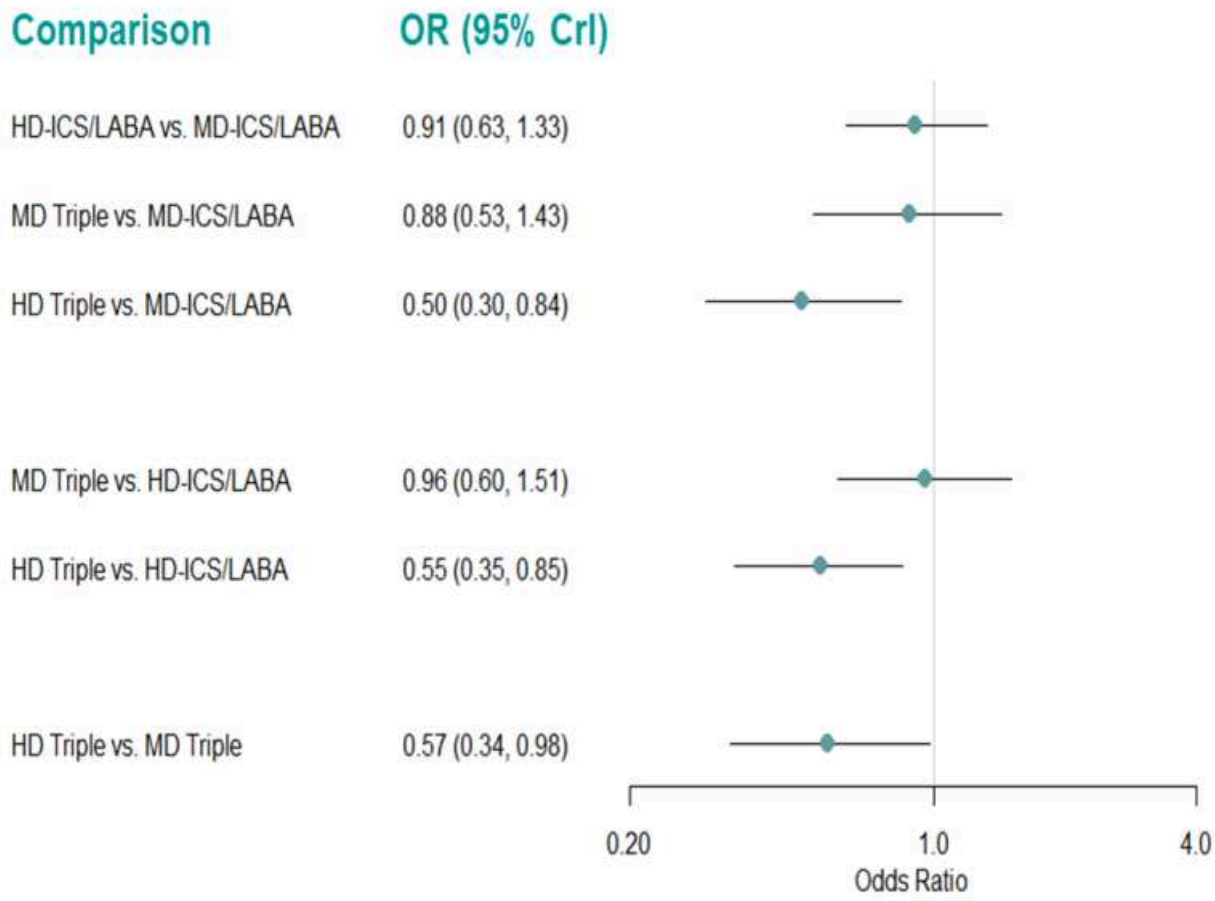
A node-splitting model was fit to assess inconsistency. The results of node-splitting are presented in Table 53. There was evidence of inconsistency for the comparisons of HD-ICS/LABA with MD-ICS/LABA and HD Triple with MD Triple, which are directly linked to multiple loops in the network. Therefore, results for dropouts due to AEs for this comparison should be interpreted with caution.

3.3.2.1.2 NMA results

As discussed in 3.3.2.1.1, all results in this section should be regarded with caution due to the inconsistency in the model.

The odds ratios of dropouts due to AEs are presented in Figure 76. The odds ratios of dropouts due to AEs comparing all treatment groups against each other are reported in Table 54.

Figure 76. Forest plots of odds ratios for drop-outs due to AEs for grouped treatments (fixed-effect model). Odds ratio less than one favors the first named treatment. CrI: credible interval, HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

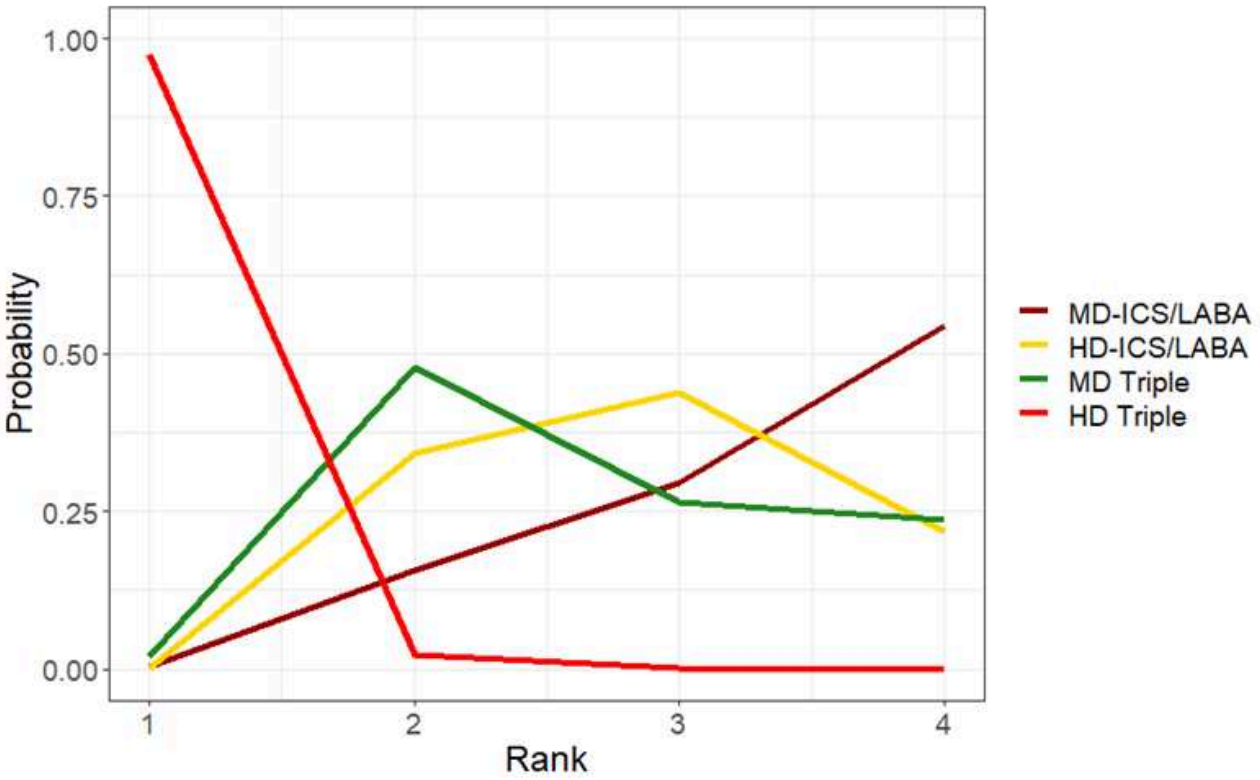


There is evidence to suggest that treatment with HD Triple reduces the odds of dropouts due to AE compared to MD ICS/LABA, HD ICS/LABA, and MD Triple (OR 0.50 [95% CrI 0.30 to 0.84], 0.55 [0.35 to 0.85], and 0.57 [0.34 to 0.98], respectively).

An NMA summary of findings is presented in Summary of findings 18. Certainty of evidence and the interpretation of findings for HD-ICS/LABA vs. MD-ICS/LABA is based on the direct evidence which is rated as high certainty and contributes greater than indirect evidence in the NMA (Schünemann 2020).

The rank plots for grouped treatments are presented in Figure 77, and the mean and median ranks are presented in Table 55. HD Triple ranks higher than the other treatments (median rank 1 [95% CrI 1 to 2]).

Figure 77. Rank plots for grouped treatments for dropouts due to AEs (fixed-effect model) HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.



3.3.2.1.3 Pairwise meta-analysis

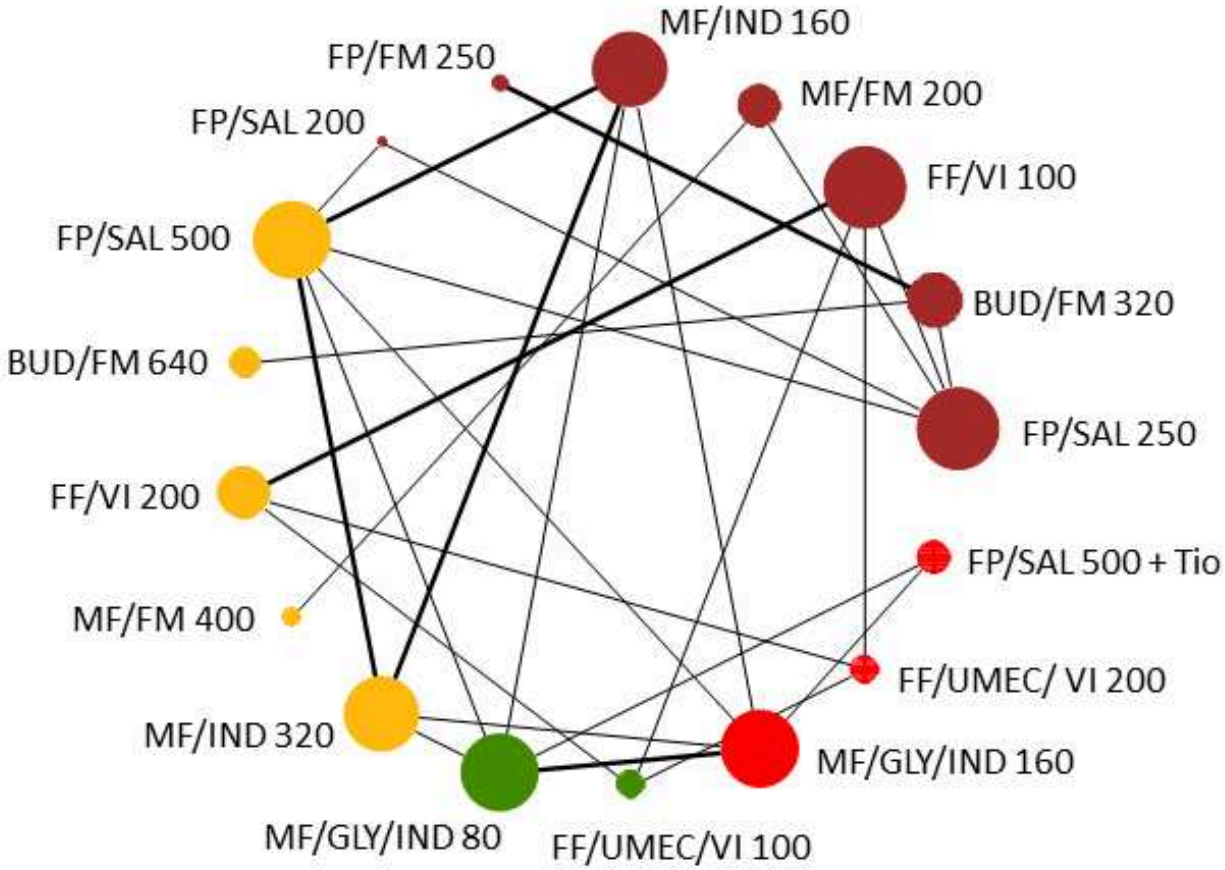
The evidence suggests HD triple results in a slight reduction in dropouts due to AE compared to HD-ICS/LABA and MD-ICS/LABA (RR 0.60 [95% CI 0.38 to 0.95]; ARR 9 fewer 1000 patients; [high certainty]) and RR 0.47 [95% CI 0.19 to 1.18]; ARR 15 fewer per 1000 patients; [high certainty], respectively) while MD triple does not. Triple therapy likely results in a slight reduction in dropouts due to AE compared to dual therapy (RR 0.59 [95% CI 0.33 to 1.03]; ARR 9 fewer per 1000 patients [moderate certainty]; Analysis 5.4, Summary of findings 15).

While triple vs. dual therapy and HD Triple vs. MD-ICS/LABA do not include the "null" effect for the fixed-effect model (RR 0.71 [95% CI 0.51 to 0.98]; I2= 43% and RR 0.52 [95% CI 0.29 to 0.94]; I2=35%, respectively), they do for the random-effects model.

3.3.2.2 Individual treatments

For this outcome, 13 trials (12,230 participants) comparing 17 distinct treatments were included in the NMA (Figure 78). A summary of the studies included is presented in Appendix 23. Four studies (Kerstjens 2012a, Kerstjens 2012b, Virchow 2019a, and Virchow 2019b) that were identified were excluded from this analysis as they were disconnected from the main network shown in Figure 78.

Figure 78. Network diagram for dropouts due to AEs for individual interventions. Node colors denote the treatment group. BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



As the data are sparse, with few studies per comparison which have very few events in each treatment arm, the results for this analysis are very uncertain.

Two three-arm studies, Mansfield 2017 and van Zyl-Smit 2020 reported no events. In Mansfield 2017, one arm (i.e., FP/SAL 200) reported zero events, and two arms (MF/IND 160 and MF/IND 320) reported zero events in van Zyl-Smit 2020. The zero cells caused problem with model convergence, so we added a continuity correction of 0.5 to the two studies. When fitting this model in OpenBUGS (version 3.2.3), a less-vague prior distribution (Normal (0, 0.01)) was used for the relative treatment effects, to make the model more stable.

3.3.2.2.1 Model selection and inconsistency checking

The Turner prior for adverse event outcomes comparing pharmacological interventions, i.e. a Log-Normal (-2.10, 1.58^2) prior distribution, was used for the between-study heterogeneity (Turner 2015).

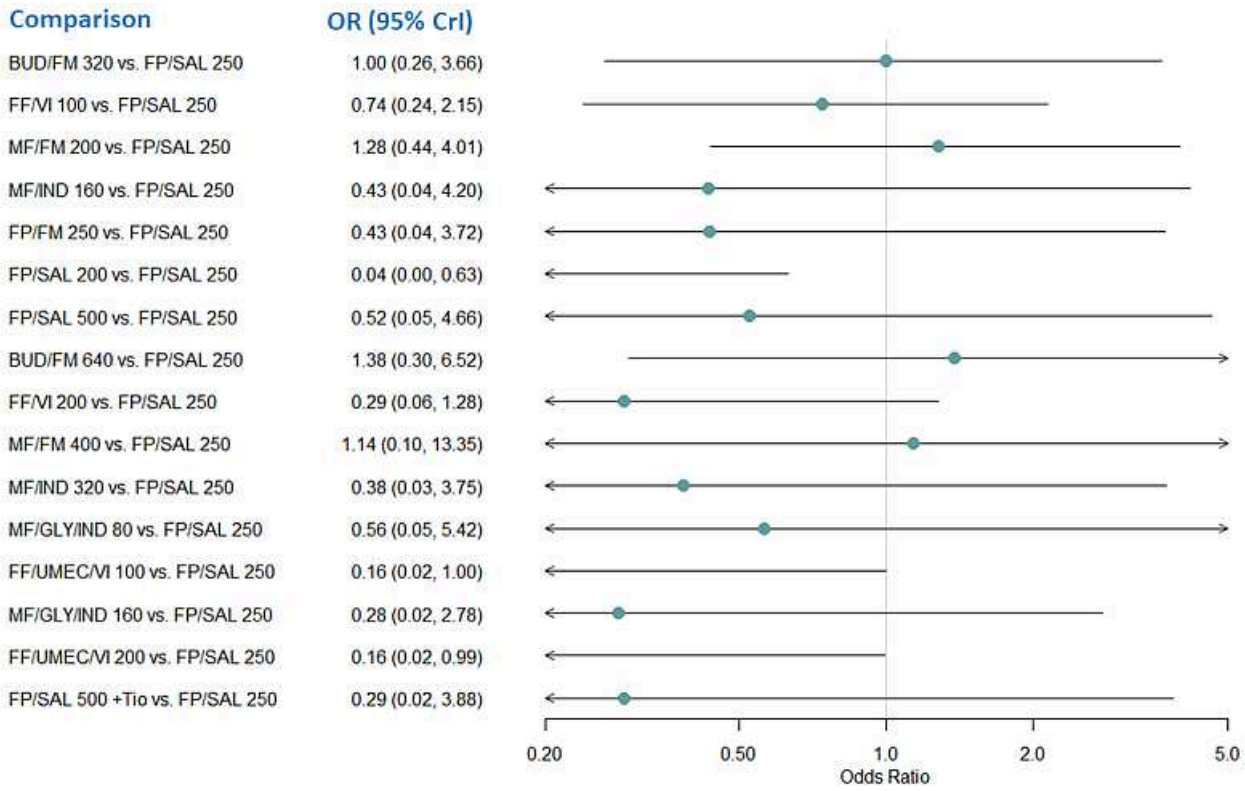
Model fit parameters for the fixed-effect and random-effects models are reported in Appendix 3. Both fixed-effect and random-effects models fit the data well. The between-study heterogeneity was low, with a wider credible interval. As the difference in DICs between the fixed-effect and random-effects models was less than 3, the simpler fixed-effect model was chosen. Results for the fixed-effect model are presented in Section 3.3.2.2.2.

There is no potential for inconsistency in this network as there is no independent, indirect evidence for any of the comparisons.

3.3.2.2.2 NMA results

The odds ratios of dropouts due to AEs, compared to FP/SAL 250/50 µg (MD-ICS/LABA), are presented in Figure 79. The odds ratios of dropouts due to AEs comparing all treatment groups against each other are reported in Table 56. There is no evidence to suggest that there is a change in odds for dropouts due to AEs for any of the individual treatments compared to FP/SAL 250/50 µg. Other comparisons which do not include the "null" treatment effect are highlighted in bold font in Table 56.

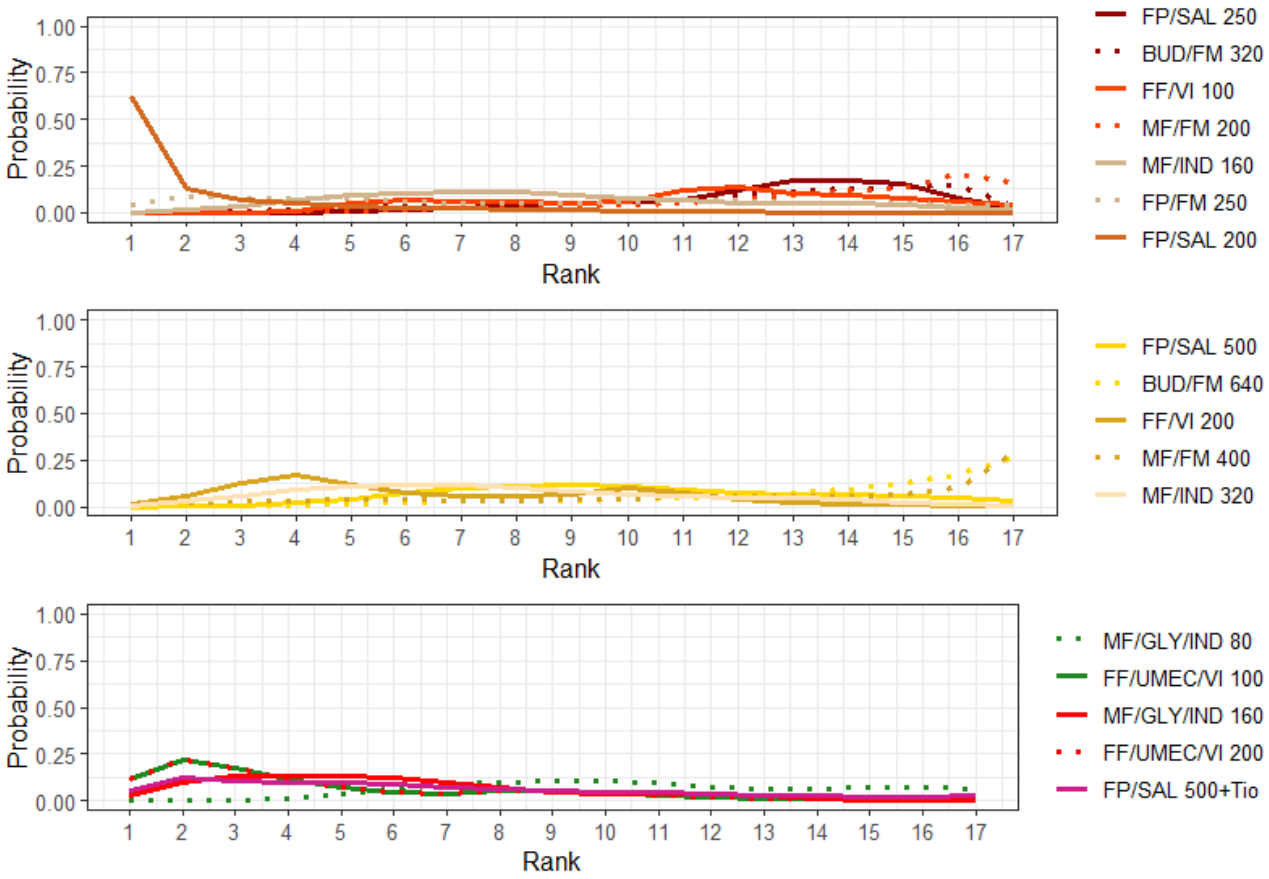
Figure 79. Forest plot of odds ratios for dropouts due to AEs relative to FP/SAL 250 for dropouts due to AEs for individual treatments. Odds ratio less than one favors the comparator treatment. BUD: budesonide, CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate,OR: odds ratio, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



While the ORs and their corresponding 95% CrIs comparing all treatments to FP/SAL 250/50 µg were reasonable, the ORs for some comparisons (shown in Table 56) had very wide credible intervals that effectively meant that the ORs were extremely uncertain due to the scarcity of data to make the comparisons.

The rank plots for individual treatments are presented in Figure 80, and the mean ranks are presented in Table 57. It was very unclear which treatment was best, as treatment ranks are very uncertain. Except FP/SAL 200/12.5 µg (MD-ICS/LABA), all the treatments had probabilities much lower than 50% for each of the possible treatment ranks. While FP/SAL 200/12.5 µg has the highest probability (over 50%) of being the best treatment (median rank 1 [95% CrI 1 to 10]), all evidence for this treatment is obtained from a single study (Mansfield 2017), where no events were observed in the FP/SAL 200/12.5 µg treatment arm and the 95% CrI is very wide. The ranking results therefore should be interpreted with caution.

Figure 80. Rank plots for individual treatments for dropouts due to AEs (fixed-effect model). Line colors denote the treatment group. BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.



DISCUSSION

Summary of main results

We included 17,161 adolescents and adults with uncontrolled asthma who were eligible or had been treated with medium-dose inhaled corticosteroids long-acting beta2-agonist (MD-ICS/LABA) from 17 studies (median duration 26 weeks; mean age 49.1 years; male 40%; white 81%; mean forced expiratory volume in 1 second (FEV1) 1.9 litres and 61% predicted). The quality of included studies was generally good except for some outcomes in a few studies due to high attrition rates (Figure 15).

Medium-dose (MD) and high-dose (HD) triple therapies reduce steroid-requiring (moderate to severe) asthma exacerbations (Hazard ratio (HR) 0.84 [95% Credible interval (CrI)0.71 to 0.99] and 0.69 [0.58 to 0.82], respectively [high certainty]), but not asthma-related hospitalisations, compared to MD-ICS/LABA. High-dose triple therapy likely reduces steroid-requiring asthma exacerbations compared to MD triple therapy (HR 0.83 [95% CrI 0.69 to 0.996], [moderate certainty]). Subgroup analyses suggest the reduction in steroid-requiring exacerbations associated with triple therapies may be only for those with a history of asthma exacerbations in the previous year, but not for those without.

High-dose triple therapy, but not MD-triple, results in a reduction in all-cause adverse events (AEs) and likely reduces dropouts due to AEs compared to MD-ICS/LABA (OR 0.79 [95% CrI 0.69 to 0.90], [high certainty] and 0.50 [95% CrI 0.30 to 0.84], [moderate certainty], respectively). Triple therapy results in little to no difference in all-cause or asthma-related serious adverse events(SAEs) compared to dual therapy [high certainty].

The impact of triple therapy compared to dual therapy is less clear on symptom and quality of life scores. The network meta-analyses (NMA) evidence suggests HD triple increases the odds of Asthma Control Questionnaire (ACQ) responder at six and 12 months (odds ratio (OR) 1.25, 95% CrI 1.07 to 1.45), [ow certainty and 1.08 (95%CrI 1.02 to 1.14), moderate certainty, respectively compared to MD-ICS/LABA and MD Triple also does at six months (OR 1.25 [95%CrI 1.09 to 1.44], low certainty), but not at 12 months (OR 0.99 [95% CrI 0.94 to 1.05], [moderate certainty]). However, theNMAs suggest no clinically important difference in symptoms or quality of life comparing HD or MD Triple to MD-ICS/LABA considering the minimal clinically important differences (MCIDs) [very low to moderate certainty].

The evidence suggests HD-ICS/LABA is unlikely to result in any significant benefit or harm compared to MD-ICS/LABA.

The evidence that any specific formulation would be better than the others within the same group in any outcomes is uncertain due to the scarcity of data and resulting imprecision of estimates.

Overall completeness and applicability of evidence

The evidence suggests little or no difference in the safety outcomes comparing HD-ICS/LABA to MD-ICS/LABA. However, long-term side effects of higher ICS doses need to be addressed in phase 4 or observational studies as the maximum study duration of the included studies was 12 months, and available evidence suggests medium- and high- ICS doses are associated with increased risk of clinically important systemic side effects compared to low-ICS doses. (Beasley 2019).

Our results may not be applicable to active smokers as they were excluded in the included studies and cigarette smoking is known to impair the efficacy of ICS treatment (Shimoda 2016).

Clinical trials for triple combination therapies included in this review did not include adolescents. The efficacy and safety of LAMAs for adolescents have not been established except for tiotropium soft mist inhaler. Although the efficacy and safety of tiotropium soft mist inhaler as add-on to ICS, with or without another maintenance therapy, such as LABA, in the adolescent is similar to those in the adult (Hamelmann 2017), the results regarding triple combination therapies in this review may or may not be applicable to the adolescent.

A post hoc analysis in Lee 2020 showed HD-ICS containing groups had greater improvements in both FEV1 and annualised rates of moderate to severe exacerbations in participants with higher blood eosinophils and fractional exhaled nitric oxide at baseline than did MD-ICS containing groups. A previous meta-analysis showed that treatment tailored using type 2 biomarkers resulted in fewer asthma exacerbations compared with traditional management but did not impact final daily ICS doses (Petsky 2018). Although, this review suggests HD-ICS containing combinations provide no additional benefits compared with MD-ICS combinations in the population studied, the optimal approach to ICS dosing in participants with the biomarker-high phenotype remains to be established with further studies.

Quality of the evidence

The quality of included studies was generally good except for some outcomes in a few studies due to high attrition rates (i.e., change from baseline (CFB) in ACQ scores at 12 months in Lee 2020 and ACQ responders at 6 and 12 months in van Zyl-Smit 2020, Figure 15). The certainty of evidence varied from very low to high which is presented in the interpretation of findings and summary of findings tables.

Potential biases in the review process

The proportions of participants who had a history of asthma exacerbation in the previous year were 33% and 60% in MD- and HD-ICS/LABA groups, respectively and those in the triple therapy groups were much higher and 85% and 90% in MD and HD Triple (Table 2). This clinical heterogeneity would raise a concern for intransitivity especially for exacerbation outcomes. As the matter of fact, subgroup analyses suggest that MD and HD triples reduce moderate to severe exacerbations only for those with a history of asthma exacerbation in the previous year but not for those without. The results of pairwise analyses are qualitatively similar to those of the network meta-analysis (NMA) and suggest that triple therapy reduces moderate to severe (steroid-requiring) exacerbations compared to dual therapy for those with a history of exacerbation but not for those without (risk ratio (RR) 0.84 [95% CI 0.77 to 0.92] and 0.96 [0.72 to 1.20], respectively Analysis 7.7).

Agreements and disagreements with other studies or reviews

The results in this study differ in several aspects from other studies. One study included children but did not include Gessner 2020 (Kim 2021) and another study included only five studies (Rogliani 2021) while this study included 17 studies excluding children. We did not include children because the response to different ICS strengths may differ in children and indirectness could cause a significant bias if adults and children are combined and analysed together in a meta-analysis.

This study included both pairwise and network meta-analyses to assure the robustness whereas the others conducted either a pairwise meta-analysis (Kim 2021) or an NMA only (Rogliani 2021). We analysed the impact of medium versus a high dose of ICS in combination therapies because of a concern for increased side effects with higher dose ICS, whereas one of the previous studies did not consider the impact of different ICS strengths in combination therapies (Kim 2021).

The definitions of asthma exacerbation varied from study to study. We classified asthma exacerbations requiring systemic corticosteroids as moderate and requiring a hospitalisation as severe.

The results on steroid-requiring (moderate exacerbations in this study, which was defined as severe exacerbation in the others, are qualitatively similar to those in the others (Kim 2021; Rogliani 2021) except for MD triple versus. MD-ICS/LABA. This study suggested that both MD and HD triple were likely superior to MD-ICS/LABA in reducing steroid-requiring asthma exacerbations, both in the pairwise meta-analysis and NMA (moderate certainty), whereas the superiority of MD triple over MD-ICS/LABA was not confirmed in another study (Rogliani 2021). The difference could be due to data sources. We obtained the data through Clinical Study Report reported by the manufacturer forLee 2020 and personal communications with the manufacturer for Virchow 2019a.

A moderate exacerbation was generally defined in each trial as a progressive increase in one or more asthma symptoms or a decline in lung function for two or more consecutive days that did not meet the definition of severe asthma exacerbation and one study reported a reduced risk of moderate to severe exacerbations (RR 0.79 [95% CrI 0.65 to 0.94]) comparing HD-ICS/LABA to MD-ICS/LABA using the above definition (Rogliani 2021) while this study did not include such outcome because it was felt that other types of exacerbation were clinically more relevant. This study suggests HD-ICS/LABA is unlikely to provide any additional benefit compared to MD-ICS/LABA otherwise.

None of the previous studies reported asthma-related hospitalisations, while this study did include them to better inform various stakeholders and found triple therapy was unlikely to reduce them compared to dual therapy.

We took MCIDs into consideration for the interpretations of continuous outcomes and found no clinically important difference between triple and dual therapies while others concluded that triple therapy was "effective in uncontrolled asthma" and "associated with modest improvement in asthma control" compared with dual therapy based on statistical differences (Kim 2021; Rogliani 2021), which may not be of clinical importance.
In this study, HD triple results in a reduction in all-cause AEs and likely reduces dropouts due to AEs compared to MD-ICS/LABA, whereas the previous study reported "triple therapy was significantly associated with increased dry mouth and dysphonia compared to dual therapy" (Kim 2021). The results on SAEs were qualitatively similar between ours and the others' concluding that triple therapy resulted in little to no difference compared to dual therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Medium-dose (MD) and high-dose (HD)triple therapies reduce steroid-requiring (moderate to severe) asthma exacerbations, but not asthma-related hospitalisations, compared to medium-dose inhaled corticosteroids long-acting beta2-agonist (MD-ICS/LABA)MD-ICS/LABA) especially in those with a history of asthma exacerbations. High-dose triple therapy is likely superior to MD triple therapy in reducing steroid-requiring asthma exacerbations.

Triple therapy is unlikely to result in clinically meaningful improvement in symptoms or quality of life compared to dual therapy considering the minimal clinically important differences (MCIDs).

HD triple therapy, but not MD triple, results in a reduction in all-cause adverse events (AEs) and likely reduces dropouts due to AEs compared to MD-ICS/LABA. Triple therapy results in little to no difference in all-cause or asthma-related SAEs compared to dual therapy.

HD-ICS/LABA is unlikely to result in any significant benefit or harm compared to MD-ICS/LABA.

Above findings would help to guide the choice of treatment when asthma is not controlled with MD-ICS/LABA.

Implications for research

Long-term side effects of high-dose dual and triple combination therapies need to be addressed in phase 4 or observational studies as the maximum duration of included studies was 12 months. Studies including active smokers are also needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bernstein 2011

Study characteristics	
Methods	**DESIGN:** randomised controlled trial

Bernstein 2011 *(Continued)*

	GROUP: parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Merck Sharp & Dohme **COUNTRY**: Canada, Colombia, Costa Rica, Czech Republic, Ecuador, Estonia, Finland, Former Serbia and Montenegro, Germany, Latvia, Lithuania, the Netherlands, Puerto Rico, Romania, Russian Federation, Serbia, Slovenia, Ukraine, United
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 722 **Mean age:** 44.9 **Male %**: 86 **White %:** 86 **Current and Ex smoker excluded: y**es. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.33 **Baseline FEV1 % predicted**: 74.1 **Hx of asthma exacerbation**: not required **INCLUSION CRITERIA**: participants must have a diagnosis of asthma for at least 12 months' duration. A participant must have been using a medium daily dose of inhaled glucocorticosteroids (alone or in combination with LABA) for at least 12 weeks and must have been on a stable regimen for at least 2 weeks prior to Screening. If there is no inherent harm in changing the participant's current asthma therapy, the participant must be willing to discontinue his/her prescribed ICS or ICS/LABA prior to initiating MF MDI run-in medication. The diagnosis of asthma must be documented by either demonstrating an increase in absolute fFEV1 of at least 12% and a volume increase of at least 200 mL within approximately 15 to 20 minutes after administration of 4 inhalations of albuterol/salbutamol or of nebulised SABA or PEF variability of more than 20% or a diurnal variation PEF of more than 20% based on the difference between pre-bronchodilator (before taking albuterol/salbutamol) morning value and the post-bronchodilator value (after taking albuterol/salbutamol) from the evening before, expressed as a percentage of the mean daily PEF value on any day during the open-label Run-in Period. A participant must have a history of >: 2 asthma-related unscheduled visits to a physician or to an emergency room within the past year AND >: 3 asthma-related unscheduled visits within the past 2 years. Prior to randomisation participants must have used a total of 12 or more inhalations of SABA rescue medication during the last 10 days of run-in. Clinical laboratory tests (complete blood counts (CBC), blood chemistries, including serum pregnancy for females of child-bearing potential, and urinalysis) conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator/sponsor before the participant is instructed to start using open-label MF MDI run-in medication. An ECG performed at the Screening Visit, using a centralised trans-telephonic technology, must be clinically acceptable to the investigator. A chest x-ray performed at the Screening Visit, or within 12 months prior to the Screening Visit, must be clinically acceptable to the investigator. A non-pregnant female participant of childbearing potential must be using a medically acceptable, adequate form of birth control. A female participant of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for enrolment. **EXCLUSION CRITERIA**: a participant who demonstrates a change in absolute FEV1 of > 20% at any time between the Screening and Baseline Visits on any 2 consecutive days between the Screening and Baseline visits. A participant who requires the use of greater than 8 inhalations per day of SABA MDI or 2 or more nebulised treatments per day of 2.5 mg SABA on any 2 consecutive days between the Screening and Baseline Visits. A participant who experiences a decrease in AM or PM PEF below the Run-in Period stability limit on any 2 consecutive days prior to randomisation. The average AM and average PM PEF respective values from the preceding 7 days are added, divided by the number of non-missing values, and multiplied by 0.70 to determine the stability limit. A participant who experiences a clinical asthma exacerbation: defined as a clinical deterioration of asthma as judged by the clinical investigator between the Screening and Baseline Visits, that results in emergency treatment, hospitalisation due to

Bernstein 2011 *(Continued)*

	asthma, or treatment with additional, excluded asthma medication (including oral or other systemic corticosteroids, but allowing SABA).
Interventions	FP/SAL 250/50 µg twice daily MF/FM 200/10 µg twice daily
Outcomes	Moderate to severe exacerbations All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT00424008

Bernstein 2015

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Chile, Germany, Mexico, Netherlands, Poland, Romania, Russian Federation, Sweden, Ukraine, USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 692 **Mean age:** 45.3 **Male %**: 38 **White %:** 88 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 1.97 **Baseline FEV1 % predicted**: 62.4 **Hx of asthma exacerbation**: Not required (71% did not have a hx of exacerbations) **INCLUSION CRITERIA**: participants must give their signed and dated (written) informed consent to participate. Written informed consent must be obtained if a participant's current medication is changed as a result of study participation Outpatient >12 years of age at Visit 1 who have had a diagnosis of asthma, as defined by the National Institutes of Health. Countries with local restrictions prohibiting enrolment of adolescents will only enrol subjects >18 years of age Male or an eligible female. Eligible female is defined as having non-childbearing potential or having childbearing potential and using an acceptable method of birth control consistently and correctly. Best pre-bronchodilator FEV1 of 40% to 80% of their predicted normal value. Demonstrate ≥ 12% and ≥ 200 mL reversibility of FEV1 within 10 to 40 minutes following 4 inhalations of albuterol/salbutamol inhalation aerosol (or an equivalent nebulised treatment with albuterol/salbutamol solution) or have documented reversibility testing within the 6 months prior to Visit 1 meeting this measure of reversibility. A spacer device may be used for testing, if required. If participants have received ICS for at least 12 weeks prior to Visit 1 and their treatment during the 4 weeks immediately prior to Visit 1 consisted of either of the two regimens (a or b).a.) A stable

Bernstein 2015 *(Continued)*

	mid-dose or high-dose of ICS alone (e.g., ≥ FP 250 µg twice daily) or b.) A stable dose of a mid-dose ICS/LABA combination (e.g., FP/Salm 250/50 µg twice daily) or an equivalent combination via separate inhalers. Use of ICS/LABA are not permitted with LABA on the day of Visit 1. Must be able to replace current SABA treatment with albuterol/salbutamol aerosol inhaler at Visit 1 for use as needed, during the study. Participants must be able to withhold albuterol/salbutamol for at least 6 hours prior to study visits. **EXCLUSION CRITERIA**: history of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 5 years. Upper or lower respiratory tract, sinus, or middle ear that is: not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the investigator, expected to affect the participant's asthma status or the participant's ability to participate in the study. Any asthma exacerbation that required oral corticosteroids within the 12 weeks prior to Visit 1 or, resulted in an overnight hospitalisation requiring additional treatment for asthma within 6 months prior to Visit 1. A subject must not have current evidence of atelectasis (segmental or larger), bronchopulmonary dysplasia, COPD, or any evidence of concurrent respiratory disease other than asthma A subject must not have any clinically significant, uncontrolled condition or disease state that, in the opinion of the investigator, would put the safety of the subject at risk through study participation or would confound the interpretation of the efficacy results if the condition/disease exacerbated during the study Chronic stable hepatitis B or C are acceptable provided their screening ALT is < 2x uULN and the y otherwise meet the entry criteria. Chronic co-infection with both hepatitis B and hepatitis C are not eligible Clinical visual evidence of candidiasis at Visit 1 Use of any investigational drug within 30 days prior to Visit 1 or within five half-lives (t½), whichever is longer of the two. Allergies to drug or milk protein: any adverse reaction, to any beta2-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy or known or suspected sensitivity to the constituents of the NDPI, or history of severe milk protein allergy Administration of medication that would significantly affect the course of asthma, or interact with study drug Use of immunosuppressive medications during the study. Use of potent CYP3A4 inhibitor within 4 weeks of Visit 1. A subject or his/her parent or legal guardian has any infirmity, disability, disease, or resides in a geographical location which seems likely, in the opinion of the Investigator, to impair compliance with any aspect of this study protocol, including visit schedule, and completion of the daily diaries. Current smoker or has a smoking history of 10 pack-years (20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 3 months (i.e., cigarettes, cigars, or pipe tobacco). If participant is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator. Participant previously randomised to treatment with FF/VI or FF in another Phase III study. Participants working on night shift a week prior to Visit 1 or during the study period. Adolescents who are wards of the state or government **SYMPTOM CRITERIA**: asthma symptoms (a score of 3 on the combined day- and nighttime asthma symptom scale) and/or daily salbutamol use on 4 of the last 7 days of the run-in period.
Interventions	MD-ICS/LABA HD-ICS/LABA
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events All-cause adverse events Dropouts due to adverse event
Notes	NCT01686633 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=116863

Bodzenta-Lukaszyk 2012

Study characteristics

Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Mundipharma Research Ltd **COUNTRY**: Bulgaria, Hungary, India, Poland, Romania
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 279 **Mean age:** 49 **Male %**: 32 **White %:** 96 **Current and Ex smoker excluded: y**es. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator: n**ot reported **Baseline FEV1 % predicted**: 64.4 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria:** 1. Male or female participants at least 12 years old 2. Female participants less than 1 year post-menopausal must have a negative urine pregnancy test recorded at the screening visit prior to the first dose of study medication, be non-lactating, & willing to use adequate & highly effective methods of contraception throughout the study. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently & correctly such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (Intrauterine Device, hormonal), sexual abstinence or vasectomised partner. 3. Known history of moderate to severe persistent, reversible asthma for ≥ 6 months prior to the Screening Visit characterised by: Treatment with an ICS at a dose of 250 µ to 1000 µg fluticasone or equivalent OR Treatment with ICS at a dose of 200 µ to500 µg fluticasone or equivalent in combination with a LABA. 4. Demonstrated a FEV1 of ≥ 50% to ≤ 80% for predicted normal values (Quanjer et al., 1993 (adults), & 1995 (adolescents)) during the Screening Period (Visit 1 or Visit 2) following appropriate withholding of asthma medications (if applicable).No β2-agonist use on day of testingNo use of inhaled combination asthma therapy on day of testing.Inhaled corticosteroids are allowed on day of testing. 5. Documented reversibility of ≥ 15% in FEV1 at visit 1 or visit 2. 6. Demonstrated satisfactory technique in the use of the study medications i.e. pMDI and DPI devices. 7. Willing & able to enter information in the electronic diary & attend all study visits. 8. Willing & able to substitute study medication for their pre study prescribed asthma medication for the duration of the study. 9. Written informed consent obtained. Inclusion criteria required following run-in: Participant has used rescue medication for at least 3 days & had at least 1 night with sleep disturbance (i.e. sleep disturbance score of ≥ 1) during the last 7 days of the run in period,OR participant has used rescue medication for at least 3 days & had at least 3 days with asthma symptoms (i.e., a symptom score of ≥ 1) during the last 7 days of the run-in period. **Exclusion criteria:** 1. Near fatal or life-threatening (including intubation) asthma within the past year. 2. Hospitalisation or an emergency visit for asthma within the 4 weeks before the Screening Visit. 3. Known history of systemic (injectable or oral) corticosteroid medication use within 1 month of the Screening Visit. 4. Known history of omalizumab use within the past 6 months.

Bodzenta-Lukaszyk 2012 *(Continued)*

5. Current evidence or known history of any clinically significant disease or abnormality including uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia. 'Clinically significant' is defined as any disease that, in the opinion of the Investigator, would put the subject at risk through study participation, or which would affect the outcome of the study.
6. In the investigator's opinion a clinically significant upper or lower respiratory infection within 4 weeks prior to the Screening Visit.
7. Significant, non-reversible, active pulmonary disease (e.g., cCOPD, cystic fibrosis, bronchiectasis, tuberculosis).
8. Known HIV-positive status.
9. Participant has a smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes/day for 10 years or 10 packs/day for 1 year, etc.).
10. Current smoking history within 12 months prior to the Screening Visit.
11. Current evidence or known history of alcohol and/or substance abuse within 12 months prior to the Screening Visit.
12. Participant has taken B-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine type antiarrhythmics, or potent CYP 3A4 inhibitors such as ketoconazole within the past week.
13. Current use of medications other than those allowed in the protocol that will have an effect on bronchospasm &/or pulmonary function.
14. Current evidence or known history of hypersensitivity or idiosyncratic reaction to test medications or components.
15. Participant has received an investigational drug within 30 days of the Screening Visit (12 weeks if an oral or injectable steroid).
16. Participant is currently participating in a clinical study.

Interventions	FP/FM 250/10 µg twice daily BUD/FM 400/12 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT01099722

Busse 2008

Study characteristics

Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 833 **Mean age:** 39.1 **Male %**: 38 **White %:** 83

Busse 2008 *(Continued)*

	Current and Ex smoker excluded: Yes. > 20 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.55 **Baseline FEV1 % predicted**: 78.6 **Hx of asthma exacerbation**: Not required. **Inclusion Criteria:** • Diagnosis of asthma • Baseline lung function tests as determined by protocol • Required and received treatment with ICS within timeframe and doses specified in protocol **Exclusion Criteria:** • Has required treatment with any non-inhaled corticosteroid within previous 30 days, sensitivity to drugs specified in the protocol, or requires treatment with a beta-blockers • Had cancer within previous 5 years or currently has any other significant disease or disorder as judged by the investigator
Interventions	FP/SAL 250/50 µg twice daily BUD/FM 320/9 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations Dropouts due to adverse event
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT00646594 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=106839

Cukier 2013

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Libbs Pharmaceutical Ltd **COUNTRY**: 11 research centres in Brazil
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 196 **Mean age:** 35.1 **Male %**:26 **White %:** 69 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.5 **Baseline FEV1 % predicted**: 85.3 **Hx of asthma exacerbation**: Not required. **Inclusion criteria**

Cukier 2013 *(Continued)*

	1. Male or female from 18 to 65 years old with known history of asthma according toGINA update 2008 criteria for at least three months. 2. Patients with partially controlled or non-controlled asthma using therapeutic doses of ICS combined with LABA (daily doses equal or more than 400 mcg of budesonide or similar drugs) for at least four weeks 3. FEV1 > 60 % of predicted normal value 4. Willing and able to keep diary and attend all visits 5. Written informed consent obtained **Exclusion criteria** 1. Pregnant or nursing women 2. Females of childbearing potential without an effective method of birth control 3. Use of systemic corticosteroid within 30 days before randomisation 4. Three or more treatments with oral corticosteroid or history of asthma hospitalisation in the previous six months 5. Use of the following drugs within two weeks before randomisation: 5.1. meltixantines 5.2. monoaminurias 5.3. beta-blockers 5.4. acetylcysteine 5.5. carbocisteine 5.6. tricyclic antidepressive 5.7. sodium channel blockers 5.8. leukotriene 5.9. anticholinergic 5.10. phenothiazines 5.11. immunotherapy 5.12. levodopa 5.13. ritonavir 5.14. oral ketoconazole 6. Current evidence of history of hypersensitivity to the study drug 7. Evidence of non-adhesion to the treatment during run-in phase 8. A smoking history equivalent to "10 pack years" (i.e., at least 1 pack of 20 cigarettes/day for 10 years or 10 packs/day for 1 year, etc) 9. Clinically significant laboratory test results during the screening phase 10. Morning serum level of cortisol < 5 mcg/dL 11. Inability to perform the lung function test 12. Current evidence of other pulmonary disease 13. Patients with asthma exacerbation during the run-in period 14. Evidence of clinically significant oral candidiasis
Interventions	FP/FM 250/12 µg twice daily BUD/FM 400/12 µg twice daily
Outcomes	Moderate to severe exacerbations All-cause serious adverse events All-cause adverse events Dropouts due to adverse event
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. ISRCTN60408425

Gessner 2020

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group

Gessner 2020 *(Continued)*

	DURATION OF THE STUDY: 24 weeks **SPONSORSHIP SOURCE**: Novartis **COUNTRY**: Argentina, Chile, Colombia, Czechia, Germany, Greece, Hungary, India, Israel, Mexico, Peru, Poland, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Turkey, Vietnam
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 1426 **Mean age:** 52.6 **Male %**: 37 **White %:** 83 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** not reported. **Baseline FEV1 % predicted**: 63 **Hx of asthma exacerbation**: required a history of at least one asthma exacerbation that required medical care from a physician, emergency room visit or hospitalisation and systemic corticosteroid in the previous year. **Inclusion Criteria:** • Patients with a diagnosis of asthma for a period of at least 6 months prior to Visit 1 with current asthma severity ≥ step 4 (GINA 2017). • Patients who had used ICS/LABA combinations for asthma for at least 3 months and at stable medium or high dose of ICS/LABA for at least 1 month prior to Visit 1. • Patients were required to be symptomatic at screening despite treatment with medium or high stable doses of ICS/LABA as defined by ACQ-7 score ≥ 1.5 at visits 101 and 201 (randomisation visit). • Patients with history of at least one severe asthma exacerbation which required medical care from a physician, emergency room visit (or local equivalent structure) or hospitalisation in the 12 months prior to Visit 1 and required systemic corticosteroid treatment for at least 3 days including physician guided self-management treatment with oral corticosteroids as part of written asthma action plan. • Pre-bronchodilator FEV1 of < 85 % of the predicted normal value for the patient after withholding bronchodilators prior to spirometry at both Visit 101 and Visit 201. • Patients who demonstrated an increase in FEV1 of ≥ 12% and 200 mL. **Exclusion Criteria:** • Patients who had a smoking history > 20 pack years. • Patients diagnosed with COPD. • Patients who had an asthma attack/exacerbation requiring systemic steroids or hospitalisation or emergency room visit within 6 weeks of Visit 1 (Screening). • Patients treated with a LAMA for asthma within 3 months prior to Visit 1. • Patients who had a respiratory tract infection or clinical significant asthma worsening as defined by Investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 201.
Interventions	LD TRIPLE: MF/GLY/IND µg 80/50/150 daily MD TRIPLE: MF/GLY/IND µg 160/50/150 daily HD TRIPLE: FP/SAL 500/50 µg twice daily + Tio 5 µg daily
Outcomes	Moderate to severe exacerbations All-cause serious adverse events All-cause adverse events

Gessner 2020 *(Continued)*

	Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 3 months CFB in ACQ at 6 months CFB in AQLQ at 3 months CFB in AQLQ at 6 months
Notes	NCT03158311

Kerstjens 2012

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 48 weeks **SPONSORSHIP SOURCE**: Boehringer Ingelheim **COUNTRY**: Australia, Canada, Denmark, Germany, Italy, Japan, the,Russian Federation, Serbia, South Africa, Turkey, Ukraine,the UK, the USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 3092 **Mean age:** 52.2 **Male %**: 38 **White %:** 74 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 1.6 **Baseline FEV1 % predicted**: 54.8 **Hx of asthma exacerbation**: Required at least one asthma exacerbation that required medical care from a physician, emergency room visit, hospitalisation, and systemic corticosteroid treatment in the previus year. **Inclusion criteria:** 1. All patients must sign and date an Informed Consent Form consistent with ICH-GCP guidelines and local legislation prior to participation in the trial (i.e. prior to any trial procedures, including any pre-trial washout of medications and medication restrictions for pulmonary function test at Visit 1). 2. Male or female patients aged at least 18 years but not more than 75 years. 3. All patients must have at least a 5-year history of asthma at the time of enrolment into the trial and the diagnosis of asthma must have been made before the patient's age of 40. 4. All patients must have a diagnosis of severe persistent asthma and must be symptomatic despite treatment with high, stable doses of ICS and a LABA 5. All patients must have a history of one or more asthma exacerbation in the past year. 6. Patients must have evidence of treated, severe, persistent asthma in post bronchodilator pulmonary function tests. 7. Patients should be never-smokers or ex-smokers who stopped smoking at least one year prior to enrolment and who have a smoking history of less than 10 pack years

Kerstjens 2012 *(Continued)*

8. Patients must be able to use the Respimat® inhaler correctly
9. Patients must be able to perform all trial related procedures including technically acceptable pulmonary function tests and use of the electronic diary/peak flow meter.

Exclusion criteria:

1. Patients with a significant disease other than asthma. A significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.
2. Patients with clinically relevant abnormal screening haematology or blood chemistry.
3. Patients with a recent history (i.e. six months or less) of myocardial infarction, hospitalisation for cardiac failure during the past year, any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy within the past year, known active tuberculosis, malignancy for which the patient has undergone resection, radiation therapy or chemotherapy within the last five years (treated basal cell carcinoma allowed), lung diseases other than asthma (e.g. COPD), significant alcohol or drug abuse within the past two years, patients who have undergone thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per exclusion criterion No. 1.
4. Patients who are currently in a pulmonary rehabilitation programme or have completed a pulmonary rehabilitation programme in the 6 weeks prior to the screening visit (Visit 1).
5. Patients using OCS medication at stable doses exceeding 5 mg prednisolone or prednisolone equivalent every day or 10 mg prednisolone or prednisolone equivalent every second day.
6. Patients with known hypersensitivity to anticholinergic drugs, BAC, EDTA or any other components of the tiotropium inhalation solution.
7. Pregnant or nursing women or women of childbearing potential not using a highly effective method of birth control. Female patients will be considered to be of childbearing potential unless surgically sterilised by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.
8. Patients who have taken an investigational drug within four weeks or six half-lives (whichever is greater) prior to Visit 1.
9. Patients who have been treated with the long-acting anticholinergic tiotropium (Spiriva®), beta-blocker medication, oral beta-adrenergics, other non-approved and according to international guidelines not recommended 'experimental' drugs for routine asthma therapy (e.g. TNF-alpha blockers, methotrexate, cyclosporin) within four weeks prior to the Screening Visit (Visit 1) or during the screening period.
10. Patients with any asthma exacerbation or respiratory tract infection in the four weeks prior to the trial.
11. Patients who have previously been randomised in this trial or in the respective twin trial (205.416 versus 205.417) or are currently participating in another trial.
12. Patients with a known narrow-angle glaucoma.

Interventions	HD-ICS/LABA (Not specified) HD TRIPLE (Not specified)
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months CFB in ACQ at 6 months CFB in ACQ at 12 months CFB in AQLQ at 6 months CFB in AQLQ at 12 months

Kerstjens 2012 *(Continued)*

Notes	NCT00772538, NCT00776984

Kerstjens 2012a

Study characteristics	
Methods	See Kerstjens 2012
Participants	
Interventions	
Outcomes	
Notes	NCT00772538

Kerstjens 2012b

Study characteristics	
Methods	See Kerstjens 2012
Participants	
Interventions	
Outcomes	
Notes	NCT00776984

Kerstjens 2020

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Novartis **COUNTRY**: Argentina, Austria, Belgium, Bulgaria, Canada, Chile, China, Colombia, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Jordan, Latvia, Lebanon, Lithuania, Mexico, the Netherlands, Peru, Philippines, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland, Thailand, the UK, Vietnam
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 3092 **Mean age:** 52.2 **Male %**: 38

Kerstjens 2020 *(Continued)*

White %: 74

Current and Ex smoker excluded: Yes. > 10 PYs for ex-smokers
Baseline FEV1 (L) pre-bronchodilator: 1.6
Baseline FEV1 % predicted: 54.8
Hx of asthma exacerbation: required at least one asthma exacerbation that required medical care from a physician, emergency room visit, hospitalisation, and systemic corticosteroid treatment in the previus year.

Inclusion Criteria:

- Patients with a diagnosis of asthma, (GINA 2015) for a period of at least 1 year prior to Visit 1 (Screening).
- Patients who have used medium or high dose of ICS/LABA combinations for asthma for at least 3 months and at stable medium or high doses of ICS/LABA for at least 1 month prior to Visit 1.
- Patients must be symptomatic at screening despite treatment with mid or high stable doses of ICS/LABA. Patients with ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (before randomisation).
- Patients with documented history of at least one asthma exacerbation which required medical care from a physician, ER visit (or local equivalent structure) or hospitalisation in the 12 months prior to Visit 1, and required systemic corticosteroid treatment.
- Pre-bronchodilator FEV1 of < 80 % of the predicted normal value for the patient according to ATS/ERS guidelines after withholding bronchodilators at both visits 101 and 102.
- Withholding period of bronchodilators prior to spirometry: SABA for ≥ 6 hours, Twice daily LABA (or FDC of ICS/LABA) for ≥ 12 hours, Once daily LABA (or FDC of ICS/LABA) for ≥ 24 hours, SAMA for ≥ 8 hours, Short-acting xanthines for 12 hrs, Long-acting xanthines for 24 hours,
- Washout period of each drug should be kept as close as possible as above and should not be longer. If longer washout period is needed due to scheduling issues, please contact Novartis Medical monitor.
- A one-time repeat of percentage predicated FEV1 (Pre-bronchodilator) at Visit 101 and/or Visit 102 is allowed in an ad-hoc visit. Repeat of Visit 101 spirometry should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomisation. Run-in medication should be dispensed once spirometry assessment met inclusion criteria (ATS/ERS quality criteria, FEV1 % predicted normal value, and reversibility) as per equipment
- A one-time rescreen is allowed in case the patient fails to meet the criteria at the repeat, provided the patient returned to the required treatment as per inclusion criteria 4
- Patients who demonstrate an increase in FEV1 of 12% and 200 mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101.All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101 then one of the following criteria need to be met.
- Reversibility should be repeated once.
- Patients may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1.
- Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1. If reversibility is not demonstrated at Visit 101 (or after repeated assessment in an ad-hoc visit) and historical evidence of reversibility/bronchoprovocation is not available (or was not performed according to the ATS/ERS guidelines patients must be screen-failed
- Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing

Exclusion Criteria:

- Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalisation or emergency room visit within 6 weeks of Visit 1 (Screening). If patients experience an asthma attack/exacerbation requiring systemic steroids or hospitalisation or emergency room visit between Visit 1 and Visit 102 they may be re-screened 6 weeks after recovery from the exacerbation.
- Patients who have ever required intubation for a severe asthma attack/exacerbation.

Kerstjens 2020 *(Continued)*

- Patients who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgement at risk participating in the study.
- Patients treated with a LAMA for asthma within 3 months prior Visit 1 (Screening).
- Patients with narrow-angle glaucoma, symptomatic BPH or bladder-neck obstruction or severe renal impairment or urinary retention. BPH patients who are stable on treatment can be considered).
- Patients who have had a respiratory tract infection or asthma worsening as determined by investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
- Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis at Visit 102 or earlier, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.
- Patients with any chronic conditions affecting the upper respiratory tract (e.g. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
- Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
- Patients with Type I diabetes or uncontrolled Type II diabetes.
- Patients who, either in the judgement of the investigator or the responsible Novartis personnel, have a clinically significant condition such as (but not limited to) unstable ischaemic heart disease, NYHA Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
- Patients with paroxysmal (e.g., intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blockers, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at the run-in visit (Visit 101) with a resting ventricular rate < 100/min. At Visit 101 the atrial fibrillation must be confirmed by central reading.
- Patients with a history of myocardial infarction (this should be confirmed clinically by the investigator) within the previous 12 months.
- Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study
- Patients with a history of long QT syndrome or whose QTc measured at Visit 101 (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females) and confirmed by a central assessor (these patients should not be re-screened).
- Patients with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
- Patients who have not achieved an acceptable spirometry result at Visit 101 in accordance with ATS/ERS criteria for acceptability and repeatability. A one-time repeat spirometry is allowed in an ad-hoc visit scheduled as close as possible from the first attempt (but not on the same day) if the spirometry did not qualify due to ATS/ERS criteria at Visit 101 and/or Visit 102. If the patient fails the repeat assessment, the patient may be re-screened once, provided the patient returns to the required treatment as per inclusion criteria 4.
- Patients unable to use the Concept1 dry powder inhaler, Accuhaler or a metered dose inhaler. Spacer devices are not permitted.
- History of alcohol or other substance abuse.
- Patients with a known history of non-compliance to medication or who were unable or unwilling to complete a patient diary or who are unable or unwilling to use Electronic Peak Flow with e-diary device.
- Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).

Interventions	MD-ICS/LABA: MF/IND 160/150 µg daily

Kerstjens 2020 *(Continued)*

	HD-ICS/LABA: MF/IND 320/150 µg daily, FP/SAL 500/50 µg twice daily LD TRIPLE: MF/GLY/IND 80/50/150 µg daily MD TRIPLE: MF/GLY/IND 160/50/150 µg daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months CFB in ACQ at 6 months CFB in ACQ at 12 months CFB in AQLQ at 12 months
Notes	NCT02571777

Lee 2020

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 24-52 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Australia, Canada, Germany, Italy, Japan, Korea, Republic of,the Netherlands, Poland, Romania, Russian Federation, South Africa, Spain, UK, USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 1627 **Mean age:** 53.5 **Male %**: 38 **White %:** 80 **Current and Ex smoker excluded:** Yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 1.73 **Baseline FEV1 % predicted**:58.7 **Hx of asthma exacerbation**: Not required (37% did not have a hx of exacerbation) **Inclusion Criteria** • Inadequately controlled asthma: participants with inadequately controlled asthma (ACQ-6 score >:1.5) at Visit 2.

Lee 2020 *(Continued)*

- Percent-predicted FEV1: a best pre-bronchodilator morning (AM) FEV1 > 30% and < 90% of the predicted normal value at Visit 2. Predicted values will be based upon the ERS Global Lung Function Initiative
- Liver function tests at Visit 1: ALT < 2 x ULN; alkaline phosphatase < 1.5xULN; bilirubin <:1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
- Compliance with completion of the Daily eDiary reporting defined as completion of all questions/assessments on >:4 of the last 7 days during the run-in period.

Exclusion Criteria

- Respiratory Infection: occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the participant's ability to participate in the study.
- Severe asthma exacerbation: evidence of a severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids.
- Asthma medication: changes in asthma medication (excluding run-in medication and albuterol/salbutamol inhalation aerosol provided at Visit 1).
- Laboratory test abnormalities: evidence of clinically significant abnormal laboratory tests during screening or run-in which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality

Interventions	MD-ICS/LABA: FF/VI 100/25 µg daily HD-ICS/LABA: FF/VI 200/25 µg daily MD TRIPLE: FF/UMEC/VI 100/62.5/25 µg daily HD TRIPLE: FF/UMEC/VI 200/62.5/25 µg daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months CFB in ACQ at 3 months CFB in ACQ at 6 months CFB in ACQ at 12 months
Notes	NCT02924688 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=205715

Mansfield 2017

Study characteristics

Mansfield 2017 *(Continued)*

Methods	**DESIGN**: multicentre randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: Teva Branded Pharmaceutical **COUNTRY**:USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 218 **Mean age:** 46.0 **Male %**: 47 **White %:** 72 **Current and Ex smoker excluded: y**es. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.37 **Baseline FEV1 % predicted**: not reported. **Hx of asthma exacerbation**: not required. **Inclusion Criteria**: 1. Best pre-bronchodilator FEV1 of greater than 40% of their predicted normal value. 2. Patients must have a treatment regimen that includes a SABA (albuterol) for use as needed and either an ICS) or an ICS/LABA as a preventative treatment for a minimum of 8 weeks before the SV. Patients currently taking low-dose ICS without LABA are not eligible for this study. Patients currently taking low-dose ICS/LABA may only be entered into the mid ICS strength. All patients must have been maintained on a stable dose of ICS or ICS/LABA for 4 weeks prior to the SV (or pre-SV if necessary) at 1 qualifying doses 3. To meet reversibility of disease criteria, the patient must demonstrate a ≥12% reversibility of FEV1 (and 200 mL for patients aged 18 years and older) within 30 minutes following 4 inhalations of albuterol at the SV. Historic reversibility within the past 12 months of the SV may be used to meet this criterion. 4. Written informed consent/assent is obtained. For adult patients (aged 18 years and older, or as applicable per local regulations), the written informed consent form must be signed and dated by the patient before conducting any study-related procedure. For minor patients (aged 12 to 17 years, or as applicable per local regulations), the written ICF must be signed and dated by the parent/legal guardian and the written assent form must be signed and dated by the patient (if applicable) before conducting any study-related procedure. Note: age requirements are as specified by local regulations. 5. Outpatient ≥ 12 years of age on the date of consent/assent. 6. Asthma diagnosis: The patient has a diagnosis of asthma as defined by the NIH. The asthma diagnosis has been present for a minimum of 3 months and has been stable (defined as no exacerbations and no changes in medication) for at least 30 days before providing informed consent. 7. The patient is able to perform acceptable and repeatable spirometry. 8. The patient is able to perform PEF with a handheld peak flow meter. 9. The patient is able to use a MDI device without a spacer device and a MDPI device. 10. The patient is able to withhold (as judged by the investigator) his or her regimen of ICS or study drug, and rescue medication for at least 6 hours before the SV and before all treatment visits where spirometry is performed. 11. The patient/parent/legal guardian/caregiver is capable of understanding the requirements, risks, and benefits of study participation, and, as judged by the investigator, capable of giving informed consent/assent and being compliant with all study requirements. 12. SABAs: All patients must be able to replace their current SABA with albuterol/salbutamol HFA inhalation aerosol at the SV for use as needed for the duration of the study. 13. Female patients may not be pregnant, breastfeeding, or attempting to become pregnant.-Other criteria may apply, please contact the investigator for more information

Mansfield 2017 *(Continued)*

Exclusion Criteria:

1. The patient has a history of a life-threatening asthma exacerbation that is defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest, or hypoxic seizures.
2. The patient is pregnant or lactating, or plans to become pregnant during the study period or for 30 days after the study.
3. The patient has participated as a randomised patient in any investigational drug study within the 30 days preceding the SV (or prescreening visit, as applicable) or plans to participate in another investigational drug study at any time during this study.
4. The patient has previously participated in an Fp MDPI or FS MDPI study.
5. The patient has a known hypersensitivity to any corticosteroid, salmeterol, or any of the excipients in the study drug or rescue medication formulation (i.e., lactose).
6. The patient has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, azole antifungals, ritonavir, or clarithromycin) within 30 days before the SV or plans to be treated with any strong CYP3A4 inhibitor during the study.
7. The patient has been treated with any of the prohibited medications during the prescribed (per protocol) washout periods before the SV.
8. The patient currently smokes or has a smoking history of 10 pack-years or more (a pack-year is defined as smoking 1 pack of cigarettes/day for 1 year). The patient may not have used tobacco products within the past year (eg, cigarettes, cigars, chewing tobacco, or pipe tobacco).
9. The patient has a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that has not resolved at least 2 weeks before the SV.
10. The patient has a history of alcohol or drug abuse within 2 years preceding the SV.
11. The patient has had an asthma exacerbation requiring systemic corticosteroids within 30 days before the SV, or has had any hospitalisation for asthma within 2 months before the SV.
12. Initiation or dose escalation of immunotherapy (administered by any route) is planned during the study period. However, patients who initiated immunotherapy 90 days or more before the SV and have been on a stable (maintenance) dose for 30 days or more before the SV may be considered for inclusion.
13. The patient has used immunosuppressive medications within 4 weeks before the SV.
14. The patient is unable to tolerate or unwilling to comply with the appropriate washout periods and withholding of all applicable medications. (Patients that require continuous treatment with β-blockers, monoamine oxidase inhibitors, tricyclic antidepressants, anticholinergics, and/or systemic corticosteroids are excluded).
15. The patient has untreated oral candidiasis at the SV. Patients with clinical visual evidence of oral candidiasis who agree to receive treatment and comply with appropriate medical monitoring may enter the study.
16. The patient has a history of a positive test for human immunodeficiency virus, active hepatitis B virus, or hepatitis C infection.
17. The patient is either an employee or an immediate relative of an employee of the clinical investigational centre.
18. A member of the patient's household is participating in the study at the same time. However, after the enroled patient completes or discontinues participation in the study, another patient from the same household may be screened.
19. The patient has a disease/condition that in the medical judgement of the investigator would put the safety of the patient at risk through participation or that could affect the efficacy or safety analysis if the disease/condition worsened during the study.Other criteria may apply, please contact the investigator for more information

Interventions	MD-ICS/LABA: FP/SAL 250/50 µg twice daily, FP/SAL 200/12.5 µg twice daily HD-ICS/LABA: FP/SAL 500/50 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations

Mansfield 2017 *(Continued)*

	All-cause serious adverse events
	All-cause adverse events
	Asthma-related serious adverse events
	Dropouts due to adverse event
Notes	NCT02175771

Papi 2007

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: Parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Chiesi Farmaceutici **COUNTRY**: Poland, Ukraine
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 228 **Mean age:** 48.5 **Male %**: 44 **White %:** not reported **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.03 **Baseline FEV1 % predicted**: 67.3 **Hx of asthma exacerbation**: not required. **Inclusion Criteria:** • Clinical diagnosis of moderate to severe persistent asthma for at least 6 months, according to GINA revised version 2002 guidelines (11):FEV1 or PEFR ^{3} 50% and £ 80% of the predicted normal; Asthma not adequately controlled with the current therapies, defined as presence of daily asthma symptoms > once a week and night-time asthma symptoms > twice a month, and daily use of SABA. These findings are to be based on recent medical history and are to be confirmed in the 2-week run-in period. • Treatment with inhaled corticosteroids at a daily dose ≤ 1000 µg of BDP or equivalent. The daily dose of inhaled corticosteroids taken at visit 1 will be assessed taking into account the following ratios between the doses of the different steroids: fluticasone propionate : BDP CFC : 1 : 2; budesonide : BDP CFC : 4 : 5; flunisolide : BDP CFC : 1 : 1. The ratios between inhaled steroids are irrespective of the formulations (i.e. spray aerosol or powder) used. When BDP is given in the new extra-fine HFA-134a formulation (as QVAR®, 3M Healthcare), the ratio with BDP CFC is set as 2: 5. Therefore, the maximum allowed daily dose of inhaled corticosteroids at study entry will be: budesonide 800 µg, fluticasone propionate 500 µg, flunisolide 1000 µg, BDP 1000 mg, BDP HFA extra-fine 400 µg. • Positive response to the reversibility test in the screening visit, defined as an increase of at least 12% (or, alternatively, of 200mL) from baseline value in the measurement of FEV1 30 minutes following 2 puffs (2 ´ 100 µg) of inhaled salbutamol administered via pMDI. The reversibility test can be avoided in patients having a documented positive response in the previous 6 months. • A co-operative attitude and ability to be trained to correctly use the metered dose inhalers and to complete the diary cards. • Written informed consent obtained.

Papi 2007 *(Continued)*

- At the end of the 2-week run-in period, the presence of daily asthma symptoms (of at least mild intensity) and nighttime asthma symptom (of at least mild intensity) > once a week, as well as of daily use of relief salbutamol is to be confirmed by reviewing the diary cards for run-in.

Exclusion Criteria:

- Inability to carry out pulmonary function testing;
- Diagnosis of COPD as defined by the NHLBI/WHO GOLD guidelines (30);
- History of near fatal asthma;
- Evidence of severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks;
- Three or more courses of oral corticosteroids or hospitalisation due to asthma during the previous 6 months;
- Patients treated with long-acting β2-agonists, anticholinergics and antihistamines during the previous 2 weeks, with topical or intranasal corticosteroids and leukotriene antagonists during the previous 4 weeks;
- Patients who have changed their dose of inhaled corticosteroids during the previous 4 weeks, or treatment with inhaled corticosteroids at a daily dose > 1000 µg of BDP or equivalent (except for extra-fine formulations, see inclusion criteria);
- Current smokers or recent (less than one year) ex-smokers, defined as smoking at least 10 cigarettes/day;
- History or current evidence of heart failure, coronary artery disease, myocardial infarction, severe hypertension, cardiac arrhythmias;
- Diabetes mellitus;
- PTCA or CABG during the previous six months;
- Patients with an abnormal QTc interval value in the ECG test, defined as > 450 msec in males or > 470 msec in females;
- Other haemodynamic relevant rhythm disturbances (including atrial flutter or atrial fibrillation with ventricular response, bradycardia (≤ 55 bpm), evidence of atrial-ventricular (AV) block on ECG of more than 1st degree;
- Clinically significant or unstable concurrent diseases: uncontrolled hyperthyroidism, significant hepatic impairment, poorly controlled pulmonary (tuberculosis, active mycotic infection of the lung), gastrointestinal (e.g. active peptic ulcer), neurological or haematological autoimmune diseases;
- Cancer or any chronic diseases with prognosis < 2 years;
- Pregnant or lactating females or females at risk of pregnancy, i.e. those not demonstrating adequate contraception (i.e. barrier methods, intrauterine devices, hormonal treatment or sterilization). A pregnancy test is to be carried out in women of a fertile age.
- History of alcohol or drug abuse;
- Patients treated with monoamine oxidase inhibitors, tricyclic antidepressants or beta-blockers as regular use;
- Allergy, sensitivity or intolerance to study drugs and/or study drug formulation ingredients;
- Patients unlikely to comply with the protocol or unable to understand the nature, scope and possible consequences of the study;
- Patients who received any investigational new drug within the last 12 weeks;
- Patients who have been previously enroled in this study;
- At the end of the run-in period, patients will not be admitted to the treatment period in the case of an increase of PEFR (L/sec) measured at the clinics at the end of the run-in period ^{3} 15% in respect of values measured at the start of the run-in period;
- Patients with asthma exacerbations during the run-in period will also be excluded from the study.

Interventions	FP/SAL 250/50 µg twice daily BDP/FM 200/12 µg twice daily
Outcomes	Moderate to severe exacerbations

Papi 2007 *(Continued)*

Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT00394368

Peters 2008

Study characteristics	
Methods	**DESIGN**: multicentre randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 52 weeks **SPONSORSHIP SOURCE**: AstraZeneca **COUNTRY**: USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 575 **Mean age:** 40.4 **Male %**: 38 **White %:** 87 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.4 **Baseline FEV1 % predicted**: 74.2 **Hx of asthma exacerbation**: not required **Inclusion Criteria:** • Diagnosis of asthma and baseline lung function tests, symptoms and medication use as determined by the protocol • Required and received treatment with inhaled corticosteroids within the timeframe and doses specified in the protocol **Exclusion Criteria:** • Has required treatment with non-inhaled corticosteroids within previous 30 days, has sensitivity to drugs specified in the protocol or requires treatment with a beta-blocker. • Has had cancer within previous 5 years or has a condition that may put the patient at risk in this study.
Interventions	MD-ICS/LABA: BUD/FM 320/9 µg twice daily HD-ICS/LABA: BUD/FM 640/18 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events Al- cause adverse events Dropouts due to adverse event
Notes	NCT00651768 Clinical Study Report available at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=964

Stempel 2016

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY**: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czechia, Denmark, Germany, Hungary, Indonesia, Italy, Korea, Republic of, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Taiwan, Ukraine, UK, USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 1562 **Mean age:** 43.4 **Male %**: 34 **White %:** 75 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** not reported **Baseline FEV1 % predicted**: not reported (Baseline PEF to be >:50% to be enroled) **Hx of asthma exacerbation**: Required at least one asthma exacerbation that required medical care from a physician, hospitalisation, and systemic corticosteroid treatment in the previous year **Inclusion Criteria:** • Provided consent to participate in the study • Male or female, 12 years of age and older • Clinical diagnosis of asthma for at least 1 year prior to the randomisation • Clinic PEF of greater than or equal to 50% of predicted normal value • Participant must be appropriately using one of the treatments for asthma listed in the protocol • Participant t must be able to complete the asthma control questionnaire, daily questions about asthma, and use a DISKUS inhaler • Participant must have history of at least 1 asthma exacerbation including one of the following in the year prior to randomisation: • requiring treatment with systemic corticosteroids • an asthma-related hospitalisation **Exclusion Criteria:** • History of life-threatening asthma defined for this protocol as asthma episode that required intubation and/or was associated with hypercapnia requiring non-invasive ventilatory support • Concurrent respiratory disease other than asthma • Current evidence of, or ever been told by a physician that they have chronic bronchitis, emphysema, or chronic obstructive pulmonary disease. • Exercise induced asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine • Presence of a bacterial or viral respiratory infection that is not resolved at randomisation • An asthma exacerbation requiring systemic corticosteroids within 4 weeks of randomisation or more than 4 separate exacerbations in the 12 months preceding randomisation • More than 2 hospitalisations for treatment of asthma in the 12 months preceding randomisation • Participant must not meet unstable asthma severity criteria as listed in the protocol

Stempel 2016 *(Continued)*

	• Potent cytochrome P450 3A4 (CYP3A4) inhibitors within the last 4 weeks (e.g., ritonavir, ketoconazole, triaconazole) • Pregnancy, breast-feeding or planned pregnancy during the study • A Child in Care is a child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation.
Interventions	MD-ICS/LABA: FP/SAL 250/50 µg twice daily HD-ICS/LABA: FP/SAL 500/50 µg twice daily
Outcomes	Severe exacerbations All cause serious adverse events Asthma-related serious adverse events
Notes	NCT01475721

van Zyl-Smit 2020

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Novartis **COUNTRY**: Bulgaria, China, Croatia, Czechia, Egypt, Estonia, Germany, Guatemala, Hungary, India, Ireland, Japan, Korea, Republic of, Latvia, Lithuania, Mexico, Poland, Romania, Russian Federation, Serbia, Slovakia, South Africa, UK, USA
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review:** 1330 **Mean age:** 47.8 **Male %**: 42 **White %:** 70 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator:** 2.10 **Baseline FEV1 % predicted**:67.1 **Hx of asthma exacerbation**: not required (69 % of patients had no hx of exacerbations) **Inclusion Criteria:** • Participants with a diagnosis of asthma, for a period of at least 1 year prior to Visit 1 (Screening) • Participants who have used medium or high dose inhaled corticosteroids (ICS) or low dose of long acting beta-2 agonist (LABA)/ICS combinations for asthma for at least 3 months and at stable doses for at least 1 month prior to Visit 1 • Participants must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualify for treatment with medium or high dose LABA/ICS • Pre-bronchodilator ≥ 50% Forced expiratory volume in 1 second (FEV1) of < 85 % of the predicted normal value for the participants after withholding bronchodilators at both Visit 101 and 102, according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria.

van Zyl-Smit 2020 *(Continued)*

- Withholding period of bronchodilators prior to spirometry: short-acting beta-2 agonist (SABA) for ≥ 6 hours and FDC or free combinations of ICS/LABA for ≥ 48 hours, short-acting anticholinergics (SAMA) for ≥ 8 hours, xanthines >:07 days
- A one-time repeat/re-testing of percent predicted FEV1 (pre-bronchodilator FEV1) is allowed at Visit 101 and at Visit 102.

Spacer devices are permitted for reversibility testing only.

-Participants who demonstrate an increase in FEV1 of 12% and 200 mL within 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101 All participants must perform a reversibility test at Visit 101

If reversibility is not demonstrated at Visit 101:

- Reversibility should be repeated once-
- Participants may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1
- Alternatively, participants may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1.

Exclusion Criteria:

- Participants who have smoked or inhaled tobacco products within the six-month period prior to Visit 1, or who have a smoking history of greater than 10 pack years. This includes use of nicotine inhalers such as e-cigarettes at the time of Visit 1
- Participants who have had an asthma attack/exacerbation requiring systemic steroids or hospitalisation or emergency room visit within 6 weeks of Visit 1 (Screening)
- Participants who have ever required intubation for a severe asthma attack/exacerbation.
- Participants who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgement at risk participating in the study.
- Participants who have had a respiratory tract infection or asthma worsening as determined by the investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Participants may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
- Participants with a history of chronic lung diseases other than asthma, including (but not limited to) Chronic Obstructive Pulmonary Disease (COPD), sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
- Participants with severe narcolepsy and/or insomnia.
- Participants who have a clinically significant electrocardiogram (ECG) abnormality at Visit 101 (Start of Run-In epoch) and at any time between Visit 101 and Visit 102 (including unscheduled ECG). ECG evidence of myocardial infarction at Visit 101 (via central reader) should be clinically assessed by the investigator with supportive documentation
- Participants with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof
- Participants who have not achieved an acceptable spirometry results at Visit 101 in accordance with ATS/ERS criteria for acceptability and repeatability (prescreening allowed only once).

Interventions	MD-ICS/LABA: MF/IND 160/150 µg daily HD-ICS/LABA: MF/IND 320/150 µg qd, FP/SAL 500/50 µg twice daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All cause serious adverse events All cause adverse events Asthma-related serious adverse events

van Zyl-Smit 2020 *(Continued)*

	Dropouts due to adverse event
	ACQ responder at 6 months
	ACQ responder at 12 months
	CFB in ACQ at 3 months
	CFB in ACQ at 6 months
	CFB in ACQ at 12 months
	CFB in AQLQ at 6 months
	CFB in AQLQ at 12 months
Notes	NCT02554786

Virchow 2019

Study characteristics	
Methods	See Virchow 2019a and 2019b
Participants	
Interventions	
Outcomes	
Notes	NCT02676076; NCT02676089

Virchow 2019a

Study characteristics	
Methods	**DESIGN**: multicentre randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Chiesi **COUNTRY:** Germany
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review**: 1150 **Mean age**: 53.2 **Male %**: 39 **White %**: 100 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator**: 1.7 **Baseline FEV1 % predicted**: 55.4 **Hx of asthma exacerbation**: at least 1 documented asthma exacerbation in the previous year.

Virchow 2019a *(Continued)*

	Inclusion Criteria: • History of asthma ≥ 1 year and diagnosed before 40 years old • Uncontrolled asthma with double therapy only on medium doses of ICS in combination with LABA with ACQ-7 ≥1.5 • Pre-bronchodilator FEV1 < 80% of the predicted normal value • Positive reversibility test • At least 1 documented asthma exacerbation in the previous year **Exclusion Criteria:** • Pregnant or lactating women • Diagnosis of COPD • Patients with any asthma exacerbation or respiratory tract infection in the 4 weeks prior screening • Current or ex-smokers (≥ 10 packs year) • Any change in dose, schedule or formulation of ICS + LABA combination in the 4 weeks prior screening
Interventions	MD-ICS/LABA: BDP/FM 200/12 µg twice daily MD TRIPLE: BDP/FM/G 200/12/20 µg twice daily
Outcomes	All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months
Notes	NCT02676076

Virchow 2019b

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 26-52 weeks **SPONSORSHIP SOURCE**: Chiesi **COUNTRY:** Argentina, Belarus, Bulgaria, Czechia, Germany, Hungary, Italy, Lithuania, Poland, Portugal, Romania, Russian Federation, Slovakia, Spain, Turkey, Ukraine, UK
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review**: 1431 **Mean age**: 53.2 **Male %**: 39 **White %**: 100 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers

Virchow 2019b *(Continued)*

	Baseline FEV1 (L) pre-bronchodilator: 1.6 **Baseline FEV1 % predicted**: 51.9 **Hx of asthma exacerbation**: at least 1 documented asthma exacerbation in the previous year. **Inclusion Criteria:** • History of asthma ≥ 1 year and diagnosed before 40 years old • Uncontrolled asthma with double therapy only on high doses of ICS in combination with LABA with ACQ-7 ≥1.5 • Pre-bronchodilator FEV1 < 80% of the predicted normal value • Positive reversibility test • At least 1 documented asthma exacerbation in the previous year **Exclusion Criteria:** • Pregnant or lactating women • Diagnosis of COPD • Patients with any asthma exacerbation or respiratory tract infection in the 4 weeks prior screening • Current smoker or ex-smoker (≥ 10 packs year) • Any change in dose, schedule or formulation of ICS + LABA combination in the 4 weeks prior screening
Interventions	HD-ICS/LABA: BDP/FM 400/12 µg twice daily HD TRIPLE: BDP/FM/GLY 400/12/20 µg twice daily, BDP/FM 400/12 µg twice daily +Tio 5 µg daily
Outcomes	All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event ACQ responder at 6 months ACQ responder at 12 months
Notes	NCT02676089

Weinstein 2010

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 12 weeks **SPONSORSHIP SOURCE**: Merck Sharp & Dohme **COUNTRY:** North America, Latin America, Russia, Ukraine, and Europe
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review**: 488 **Mean age**: 48 **Male %**: 44

Weinstein 2010 *(Continued)*

White %: 89

Current and Ex smoker excluded: yes. > 10 PYs for ex-smokers
Baseline FEV1 (L) pre-bronchodilator: 2.05
Baseline FEV1 % predicted: 66.2
Hx of asthma exacerbation: at least one severe exacerbation requiring a course of oral glucocorticosteroid 2 to 12 months prior to Screening.

Inclusion Criteria:

- A participant must be at least 12 years of age, of either sex, and of any race, with a diagnosis of asthma of at least 12 months duration that is consistent with the following definition:The diagnosis of asthma is based upon clinical history and examination, pulmonary function parameters, and response to beta2-agonists, according to international guidelines.
- A participant must have been using a high dose of ICS either alone or in combination with a LABA for at least 12 weeks prior to Screening, with no use of OCS within 30 days prior to Screening. A participant must have been on a stable asthma regimen (daily dose unchanged) for at least 2 weeks prior to Screening. High daily doses of ICS are defined as follows: > 1000 µg beclomethasone CFC>500 µg beclomethasone HFA > 1000 µg budesonide dry powder inhaler (DPI)>2000 µg flunisolide> 500 µg fluticasone > 400 µg MF >2000 µg triamcinolone acetonide > 320 µg ciclesonide

Note: Dose delivery by method or modality other than those noted above must be equivalent.

- A participant must have experienced at least one severe exacerbation requiring a course of oral glucocorticosteroid 2 to 12 months prior to screening.
- If, based upon the medical judgement of the investigator, there is no inherent harm in changing the participant's current asthma therapy, then the participant (and parent/guardian, if applicable) must be willing to discontinue his/her prescribed ICS or ICS/LABA prior to initiating MF MDI run-in medication.
- To document the diagnosis of asthma and assure the participant's responsiveness to bronchodilators before randomisation, one of the following methods can be used at the Screening Visit, Day-14, or thereafter, but prior to the Baseline Visit:The participant must demonstrate an increase in absolute FEV1 of at least 12% and at least 200 mL within approximately 15 to 20 minutes after administration of four inhalations of albuterol/salbutamol (total dose of 360 to 400 µg). The participant must demonstrate a PEF variability of more than 20% expressed as a percent of the best and lowest morning pre-bronchodilator PEF over at least 1 week. The participant must demonstrate a diurnal variation in PEF of more than 20% based on the difference between the pre-bronchodilator (before taking albuterol/salbutamol) morning value and the post-bronchodilator value (after taking albuterol/salbutamol) from the evening before, expressed as a percentage of the mean daily PEF value. Note: If a participant is to qualify using diurnal variation, the participant should be instructed to perform his/her PEF evaluation after using his/her bronchodilator in the evening.
- At the Screening Visit, the participant's FEV1 must be ≥ 50% predicted when all restricted medications have been withheld for the appropriate intervals.
- At the Baseline Visit, the participant's FEV1 must be ≥ 50% and ≤ 85% predicted when all restricted medications have been withheld for the appropriate intervals.
- The participant (and parent/guardian for a participant under the age of legal consent) must be willing to give written informed consent and be able to adhere to dose and visit schedules.
- A female participant of childbearing potential must be using a medically acceptable, adequate form of birth control. This includes:hormonal contraceptive as prescribed by a physician (oral combined, hormonal vaginal ring, hormonal implant or depot-injectable);medically prescribed IUD; medically prescribed topically-applied transdermal contraceptive patch;condom in combination with a spermicide (double-barrier method);monogamous relationship with a male partner who has had a vasectomy. The participant must have started this birth control method at least 3 months prior to Screening (with the exception of condom in combination with spermicide), and must agree to continue its use for the duration of the study. A female participant of childbearing potential who is not currently sexually active must agree and consent to using a medically acceptable method should she become sexually active during the course of this study. Women who have been surgically sterilised or are at least 1 year postmenopausal are not considered to be of childbearing potential. A female participant of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for the open-label MF MDI Run-in period.

Weinstein 2010 *(Continued)*

Exclusion Criteria:

- A participant who demonstrates a change (increase or decrease) in absolute FEV1 of >20% at any time from the Screening Visit up to and including the Baseline Visit. Pulmonary function tests (PFTs) will be performed in the morning.
- A participant who requires the use of >8 inhalations per day of short-acting beta agonists (SABA) MDI or >:2 nebulised treatments per day of 2.5 mg SABA, on any 2 consecutive days from the Screening Visit up to and including the Baseline Visit.
- A participant who experiences a decrease in AM or PM peak expiratory flow (PEF) below the run-in period stability limit on any 2 consecutive days prior to randomisation.
- A participant who experiences a clinical asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalisation due to asthma, or treatment with additional, excluded asthma medication [including oral or other systemic corticosteroids, but allowing SABAs]), at any time from the Screening Visit up to and including the Baseline Visit.
- A participant who has been treated in the emergency room (for a severe asthma exacerbation), or admitted to the hospital for management of airway obstruction, within the last 3 months.
- A participant who has ever required ventilator support for respiratory failure secondary to asthma.
- A participant who has experienced an upper or lower respiratory tract infection (viral or bacterial) within the previous 2 weeks prior to Screening and Baseline Visits. Visits can be rescheduled 2 weeks after complete resolution of the event to re-assess eligibility.
- A participant who is a smoker or ex-smoker and has smoked within the previous year or has had a cumulative smoking history >10 pack-years.
- A participant with a clinically significant abnormal vital sign.
- A participant with evidence (upon visual inspection, laboratory culture is not required) of clinically significant oropharyngeal candidiasis at Baseline (Visit 3) with or without treatment. If there is evidence of oropharyngeal candidiasis at Screening or Pre-Baseline Visit, the participant may be treated as appropriate and the Baseline Visit can be scheduled upon resolution. If there is evidence of oropharyngeal candidiasis at the Baseline Visit, the participant may be treated as appropriate and the visit can be rescheduled upon resolution.
- A participant with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, haematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder which, in the judgement of the investigator, could interfere with the study, or require treatment that might interfere with the study. Specific examples include (but are not limited to) insulin-dependent diabetes, hypertension being treated with beta blockers, active hepatitis, coronary artery disease, arrhythmia, stroke, severe rheumatoid arthritis, chronic open-angle glaucoma or posterior subcapsular cataracts, AIDS, or conditions that may interfere with respiratory function such as clinically diagnosed COPD, chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, etc. Other conditions that are well-controlled and stable (eg, hypertension not requiring beta blockers) will not prohibit participation if deemed appropriate per the investigator's judgement.
- A participant who is known to be allergic to or intolerant of ICS, beta2 agonists, or any of the excipients present in the medications used in this study.
- A female participant who is breast-feeding, pregnant, or intends to become pregnant while participating in this study.
- A participant is a known illicit drug user.
- A participant who is known to be HIV positive (HIV testing will not be conducted in this study).
- A participant who is unable to correctly use an oral MDI inhaler.
- A participant who has been taking any of the restricted medications prior to Screening without meeting the required washout time frames.
- A participant who cannot adhere to the permitted concomitant medications and prohibited medications.
- A participant participating in this study may not participate in this same study at another investigational site. In addition, a participant cannot participate in a different investigational study at any site, during the same timeframe of this study.
- A participant must not be randomised into this study more than once.
- No person directly associated with the administration of the study may participate as a study participant. No family member of the investigational study staff may participate in this study.
- A participant who previously participated in a trial with MF/F.

Weinstein 2010 *(Continued)*

	• Participants with a history of significant QTC prolongation (i.e., QTc > 500 msec) are excluded from participation in the study.
Interventions	MD-ICS/LABA: MF/FM 200/10 µg twice daily HD-ICS/LABA: MF/FM 400/10 µg twice daily
Outcomes	All-cause serious adverse events A-l cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in ACQ at 3 months
Notes	NCT00381485

Woodcock 2013

Study characteristics	
Methods	**DESIGN**: randomised controlled trial **GROUP**: parallel group **DURATION OF THE STUDY**: 24 weeks **SPONSORSHIP SOURCE**: GlaxoSmithKline **COUNTRY:** Argentina, Chile, Korea, Republic of, Netherlands, Philippines, USA.
Participants	**BASELINE CHARACTERISTICS:** **No. of patients included in this review**: 806 **Mean age**: 42.9 **Male %**: 39 **White %**: 59 **Current and Ex smoker excluded:** yes. > 10 PYs for ex-smokers **Baseline FEV1 (L) pre-bronchodilator**: 2.0 **Baseline FEV1 % predicted**: 68.4 **Hx of asthma exacerbation**: not required **Inclusion Criteria:** • Clinical diagnosis of asthma • Reversibility of at least 12% and at least 200 mL within 10-40 minutes following 2-4 inhalations of albuterol • FEV1 of 40%-85% predicted normal • Currently using inhaled corticosteroid therapy **Exclusion Criteria**: • History of life-threatening asthma within previous 5 years (requiring intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures) • Respiratory infection or oral candidiasis • Asthma exacerbation requiring oral corticosteroids or that resulted in overnight hospitalisation requiring additional asthma treatment • Uncontrolled disease or clinical abnormality • Allergies

Woodcock 2013 *(Continued)*	• Taking another investigational medication or prohibited medication • Night shift workers • Current smokers or subjects with smoking history of at least 10 pack years
Interventions	FP/SAL 250/50 µg twice daily FF/VI 100/25 µg daily
Outcomes	Moderate to severe exacerbations Severe exacerbations All-cause serious adverse events All-cause adverse events Asthma-related serious adverse events Dropouts due to adverse event CFB in ACQ at 6 months CFB in AQLQ at 6 months
Notes	Intragroup comparison of MD-ICS/LABAs. NMA only. NCT01147848 Clinical Study Report available at https://www.gsk-studyregister.com/en/trial-details/?id=113091

ACQ: asthma control questionnaire; **AIDS:** acquired immune deficiency syndrome; **ALT:** alanine transaminase; **ATS**: American Thoracic Society; **BDP: :** beclomethasone dipropionate ;**CFC:** budesonide propionate - chlorofluorocarbon;**BPH**: benign prostatic hyperplasia; **BUD:** budesonide; **CABG:** coronary artery by-pass graft;**CBC: CFB: ; CFC:** chlorofluorocarbon; **COPD:** chronic obstructive pulmonary disease; **CYP:** Cytochromes;**DPI:** dry powder inhaler; **ECG:** electrocardiogram;**EDTA:** ethylenediamine tetra-acetic acid; **ERS:** European Respiratory Society; **FEV1;** forced expiratory volume in one second;**FF:** fluticasone furoate;**FM:** ; **FP:** fluticasone propionate;**GINA:** Global Initiative for Asthma; **HD:** high dose;**HFA**: hydrofluoroalkane; **HIV:** Human Immunodeficiency Virus; I**CF: i**nformed consent form**; ICH-GCP:** ;International Conference for Harmonisation Clinical Practice guidelines; **ICS**: inhaled corticosteroid; **IUD:** intra-uterine device; **LABA: l**ong-acting beat2-agonist; **LAMA:** long-acting muscarinic antagonist; **LD:** low dose; **MD:** medium dose; **MDF: ; MF: ;NIH:** National Institute of Health; **NHLBI:** National Heart Lung and Blood Institute; **NMA:** network meta-analysis; NYHA: New York Heart Association;S: **OCS:** oral corticosteroid**; PEF:** peak expiratory flow; **PEFR:** peak expiratory flow rate; **pMDI:** pressurised metered dose inhaler; **PTCA:** Percutaneous transluminal coronary angioplasty;**PY:** Pack year;**QT:** s a measurement made on an electrocardiogram;**SABA:** short-acting beta2-agonist;**SALM:** salmeterol; **Tio:** tiotropium; **TNF:** Tumour necrosis factor; **ULN:** upper limit of normal; **UMEC:** umeclidinium; VI: vilanterol; **WHO:** World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akpinarli 1999	Six-week paediatric trial
Allbers 2010	Not pre-registered.
Antilla 2014	Clinically stable for at least 1 month with ACQ-7 score ≤ 3
Aubier 1999	Not pre-registered.
Bailey 2008	No qualifying comparisons
Balki 2018	No qualifying comparisons

Study	Reason for exclusion
Barnes 2013	Stable asymptomatic patients
Bateman 2011	No breakdown on ICS dose. B16-Arg/Arg patients
Bateman 2014	No qualifying comparisons
Beasley 2015	No qualifying comparisons
Bernstein 2018	Patients had to be symptom free
Blais 2016	168 hour trial
Blais 2017	Cross-over design
Bleecker 2012	No qualifying comparisons
Bodzenta-Lukaszyk 2011	No qualifying comparisons
Boyd 1995	No qualifying comparisons
Buhl 2003	No qualifying comparisons
Busse 2013	Safety trial. Not clear if patients were symptomatic before study entry. Seventy per cent of patients did not have a history of exacerbation within 12 months prior to study entry.
Dahl 2006	Not pre-registered.
Devillier 2018	No qualifying treatment comparisons.
D'Urzo 2001	No qualifying treatment comparisons.
EUCTR2008-004833-70	BUDESONIDE-SALMETEROL DPI is not approved nor commercially available
Fitzgerald 1999	Inclusion criteria for age was not described
Gardiner 1994	Eight-week trial
Godard 2008	No qualifying treatment comparisons.
Green 2006	Six-week trial
Hamelmann 2016	No qualifying treatment comparisons.
Hamelmann 2017	Significant proportion of patients received low-dose ICS
Hoshino 2016	Not pre-registered.
Houghton 2007	Four-week trial
Hultquist 2000	Four-week trial
Ind 2003	Not pre-registered.
Ishiura 2018	No qualifying comparisons. eight-week trial

Study	Reason for exclusion
Katial 2011	No qualifying comparisons
Kerstjens 2015	ICS/LAMA study. No qualifying treatment comparisons.
Kerwin 2009	No qualifying comparisons
Kerwin 2011	No qualifying comparisons
Kerwin 2021	ICS dose was not described. Glycopyrronium has not been approved or commercially available.
Koenig 2008	Low dose ICS included and no breakdown.
Kuna 2007	Not pre-registered.
Kupczyk 2021	Not clear if the new formulation HFA qualifies as medium- or high-dose ICS/LABA.
Langton Hewer 1995	Eight-week trial
Lee 2015	Fourteen-day trial
Lenney 2013	Low-dose ICS
Li 2010	Paediatric trial
Lin 2015	No qualifying treatment comparisons.
Lotvall 2014	No qualifying treatment comparisons.
Malone 2005	Paediatric trial
Maspero 2010	Wrong study design. Baseline characteristics were different between MD and HD-ICS combos.
Maspero 2014	Wrong patient population
Meijer 1995	Paediatric trial
Morice 2008	Paediatric trial
Muraki 2013	Not randomised
NCT00118690	Four-week trial
NCT00118716	Four-week trial
NCT01192178	Paediatric trial
NCT01570478	ACT 20-25. Not symptomatic at entry
NCT02127697	Withdrawn
NCT02296411	Cross-over design
NCT02433834	Cross-over design
NCT02892344	No qualifying treatment comparisons. LD-ICS vs LD-ICS/LABA

Study	Reason for exclusion
NCT03063086	Three-week trial
NCT03184987	Non-randomised controlled study
NCT03376932	Trial withdrawn
Norhaya 1999	Four-week trial
O'Byrne 2014	No qualifying treatment comparisons.
O'Byrne 2016	Non-randomised controlled study
Ohta 2015	Only 54% to 61% of patients received LABA. No breakdown on with and without LABA.
Paggiaro 2016	ICS/LAMA study. No qualifying treatment comparisons.
Peters 2010	No qualifying treatment comparisons.
Peters 2016	No qualifying treatment comparisons
Ploszczuk 2018	Paediatric trial
Pohunek 2006	Paediatric trial
Price 2002	Cost-effectiveness analysis
Rajanandh 2014	No qualifying data
Raphael 2017	No qualifying treatment comparisons. Low dose-ICS/LABA vs medium dose-ICS/LABA
Reddel 2007	Eight-week trial
Renzi 2010	No qualifying treatment comparisons. Low dose-ICS/LABA vs medium dose-ICS/LABA. Not pre-registered.
Russell 1995	Paediatric trial
Sher 2017	No qualifying comparisons
Simons 1997	Four-week trial
Stelmach 2008	Eight-week trial
Stempel 2016x	Paediatric trial
Svedsater 2018	No qualifying comparisons
Tal 2002	Paediatric trial
Teper 2005	Paediatric trial
Verberne 1998	Paediatric trial
Watz 2019	Three-week study

Study	Reason for exclusion
Wechsler 2016	No qualifying treatment comparisons. Eighty-seven per cent of the population received low-dose ICS.
Weiler 2005	Four-week trial
Weinstein 2019	Patients had to be stable enough to be able to stepdown to mometasone monotherapy.
Yang 2015	Fourteen-day trial
Zhang 2018	Not pre-registered. Eight-week study
Zimmerman 2004	Paediatric trial

ACT 20-25; HD: **ICS:** inhaled corticostroids; **LABA:** ; : long-acting bronchodilator inhaler; **LAMA:** long-acting muscarinic antagonists; LD: ; MD;

Characteristics of ongoing studies *[ordered by study ID]*

NCT03387241

Study name	Efficacy of FLUTIFORM ® vs Seretide® in moderate to severe persistent asthma in subjects aged ≥12 years
Methods	A double-blind, double-dummy, randomised, multicentre, two-arm parallel group study to assess the efficacy and safety of FLUTIFORM® pMDI (2 puffs twice daily) vs Seretide® pMDI (2 puffs twice daily)
Participants	in participants aged ≥12 years with moderate to severe persistent, reversible asthma
Interventions	FLUTIFORM® pMDI (Fluticasone/ Formoterol Low dose: 50/5 µg Mid dose: 125/5 µg High dose 250/10 µg 2 puffs twice daily) vs Seretide® pMDI (fluticasone/ salmeterol Low dose: 50/25 µg Mid dose: 125/25 µg High dose 250/25 µg 2 puffstwice aily)
Outcomes	Change from the pre-doseFEV1 at baseline to 2 hours post-dose FEV1 at Week 12
Starting date	June 2, 2017
Contact information	Ling Li 8610 65636891 ling.li@mundipharma.com.cn
Notes	Mundipharma (China) Pharmaceutical Co. Ltd

NCT04191434

Study name	Efficacy andsSafety of flamboyant 125/12 association in the treatment of adults with moderate asthma
Methods	Multicentre, randomized, double-blind, double-dummy, National, Phase III Clinical Trial
Participants	Adults with masthma
Interventions	Flamboyant 125/12 2 puffs twice dailyvs Budesonide/formoterol 200/6 2 puffs twice daily

NCT04191434 *(Continued)*

Outcomes	Change from baseline in Forced expiratory volume in 1 second (FEV1), obtained through espirometry. [Time Frame: 12 weeks] Incidence and severity of adverse events recorded during the study. [Time Frame: 14 weeks]
Starting date	September 2021
Contact information	Monalisa FB Oliveira, MD +551938879851 pesquisa.clinica@ncfarma.com.br
Notes	EMS

NCT04191447

Study name	Efficacy and safety of Flamboyant 200/12 association in the treatment of adults With severe asthma
Methods	Multicente, randomised, double-blind, double-dummy, National, Phase III Clinical Trial
Participants	Adults with severe asthma
Interventions	Flamboyant 200/12 2 puffs twice daily vs Budesonide / Formoterol 400/12 2 puffs twice daily
Outcomes	Change from baseline in Forced expiratory volume in 1 second (FEV1), obtained through espirometry. [Time Frame: 12 weeks] Incidence and severity of adverse events recorded during the study. [Time Frame: 14 weeks]
Starting date	September 2021
Contact information	Monalisa FB Oliveira, MD +551938879851 pesquisa.clinica@ncfarma.com.br
Notes	EMS

NCT04609878

Study name	Study to Assess PT010 in adult and adolescent participants with inadequately controlled asthma (KALOS) (KALOS)
Methods	A Randomised, double-blind, double dummy, parallel group, multicenrer variable length study
Participants	Adult and adolescent participants With inadequately controlled asthma
Interventions	Budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (BGF MDI) 320/28.8/9.6 µg; BGF MDI 320/14.4/9.6 µg; Budesonide and formoterol fumarate metered dose inhaler (BFF MDI) 320/9.6 µg; BFF pMDI 320/9 µg
Outcomes	Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) at Week 24 [Time Frame: 24 Weeks] Primary end point(s) of Pooled Studies D5982C00007 and D5982C00008: Rate of severe asthma exacerbations
Starting date	December 15, 2020
Contact information	AstraZeneca Clinical Study Information Center 1-877-240-9479 information.center@astrazeneca.com

NCT04609878 *(Continued)*

Notes	Estimated Study Completion Date:July 25, 2023

NCT04609904

Study name	Study to assess PT010 in adult and adolescent participants with inadequately controlled asthma (LOGOS) (LOGOS)
Methods	A randomised, double-blind, double dummy, parallel group, multicenter 24 to 52 week variable length study to assess the efficacy and safety of budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (MDI) relative to budesonide and formoterol fumarate MDI and Symbicort® pressurised MDI
Participants	Adult and adolescent participants with inadequately controlled asthma. Approximately 2800 participants will be randomised globally.
Interventions	Budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (BGF MDI) 320/28.8/9.6 µg; BGF MDI 320/14.4/9.6 µg; Budesonide and formoterol fumarate metered dose inhaler (BFF MDI) 320/9.6 µg; BFF pMDI 320/9 µg
Outcomes	Change from baseline in forced expiratory volume in 1 second (FEV1) area under the curve 0 to 3 hours (AUC0-3) at Week 24; Rate of severe asthma exacerbations.
Starting date	March 1, 2021
Contact information	AstraZeneca Clinical Study Information Center 1-877-240-9479 information.center@astrazeneca.com
Notes	Estimated Study Completion Date: September 22, 2023

NCT04937387

Study name	Efficacy and safety of Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) in Chinese participants with inadequately controlled asthma
Methods	A Phase III, 12-week, randomised, double-blind, 4-arm parallel Ggroup bridgins Study
Participants	Chinese participants with inadequately controlled asthma
Interventions	FF/UMEC/VI vs. FF/VI
Outcomes	FEV1, Change from baseline in Asthma Control Questionnaire (7 items) (ACQ-7)
Starting date	June 24, 2021
Contact information	US GSK Clinical Trials Call Center 877-379-3718GSKClinicalSupportHD@gsk.com
Notes	Last Update Posted: November 16, 2021

NCT05018598	
Study name	Step-up to medium strength triple therapy vs High strength ICS/LABA in adult asthmatics uncontrolled on medium strength ICS/LABA (MiSTIC)
Methods	A 26-week, randomised, double-blind, multinational, multicentre, active controlled, 2-arm parallel group trial
Participants	Participants with asthma uncontrolled on medium doses of Inhaled Corticosteroids in combination with long-Acting β2-Agonists
Interventions	CHF 5993 100/6/12.5 µg pMDI (Fixed Combination of Extrafine Formulation of Beclometasone Dipropionate Plus Formoterol Fumarate Plus Glycopyrronium Bromide) to CHF 1535 22/6 µg pMDI (Fixed Combination of Extrafine Formulation of Beclometasone Dipropionate Plus Formoterol Fumarate)
Outcomes	Proportion of participants exhibiting no Airflow Obstruction on average over 26 weeks of treatment in the study sub-population with Airflow Obstruction status at screening Change from baseline in pre-dose FEV1 at Week 26
Starting date	August 24, 2021
Contact information	Chiesi Farmaceutici S.p.A. Chiesi Clinical Trial Info +39 0521 2791 clinicaltrials_info@chiesi.com
Notes	Last Update Posted: August 24, 2021

FEV1:
pMID:

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 7.1 HD-ICS/LABA vs MD-ICS/LABA

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 7.1.1 High Risk						
Kerstjens 2020	✓	✓	✓	✓	✓	✓
Subgroup 7.1.2 Low Risk						
Bernstein 2015	✓	✓	✓	✓	✓	✓
Lee 2020	✓	✓	✓	✓	✓	✓
Mansfield 2017	✓	~	✓	✓	✓	~

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Peters 2008	✓	✓	✓	✓	✓	✓
van Zyl-Smit 2020	✓	✓	✓	✓	✓	✓

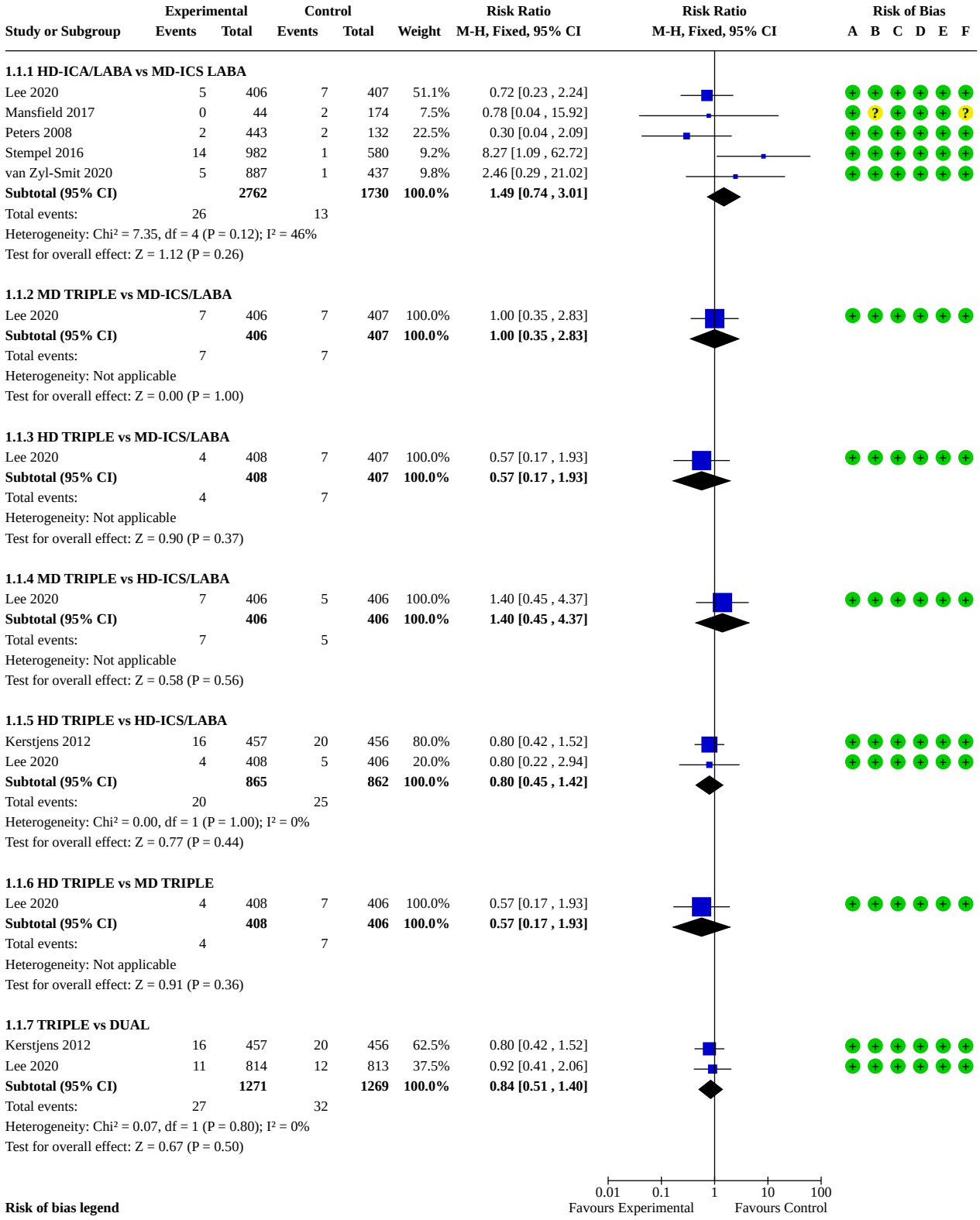
DATA AND ANALYSES

Comparison 1. Asthma exacerbations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Severe exacerbations	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 HD-ICA/LABA vs MD-ICS LABA	5	4492	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.74, 3.01]
1.1.2 MD TRIPLE vs MD-ICS/LA-BA	1	813	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.83]
1.1.3 HD TRIPLE vs MD-ICS/LA-BA	1	815	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.17, 1.93]
1.1.4 MD TRIPLE vs HD-ICS/LA-BA	1	812	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.45, 4.37]
1.1.5 HD TRIPLE vs HD-ICS/LA-BA	2	1727	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.42]
1.1.6 HD TRIPLE vs MD TRIPLE	1	814	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.17, 1.93]
1.1.7 TRIPLE vs DUAL	2	2540	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.40]
1.2 Moderate to severe exacerbations	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 HD-ICS/LABA vs MD-ICS/LABA	6	5452	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.05]
1.2.2 MD TRIPLE vs MD-ICS/LA-BA	3	3184	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 0.99]
1.2.3 HD TRIPLE vs MD-ICS/LA-BA	2	2037	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.66, 0.92]
1.2.4 MD TRIPLE vs HD-ICS/LA-BA	2	2651	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.5 HD TRIPLE vs HD-ICS/LA-BA	4	4989	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.75, 0.92]
1.2.6 HD TRIPLE vs MD TRIPLE	3	3470	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
1.2.7 TRIPLE vs DUAL	5	8173	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.78, 0.92]

Analysis 1.1. Comparison 1: Asthma exacerbations, Outcome 1: Severe exacerbations

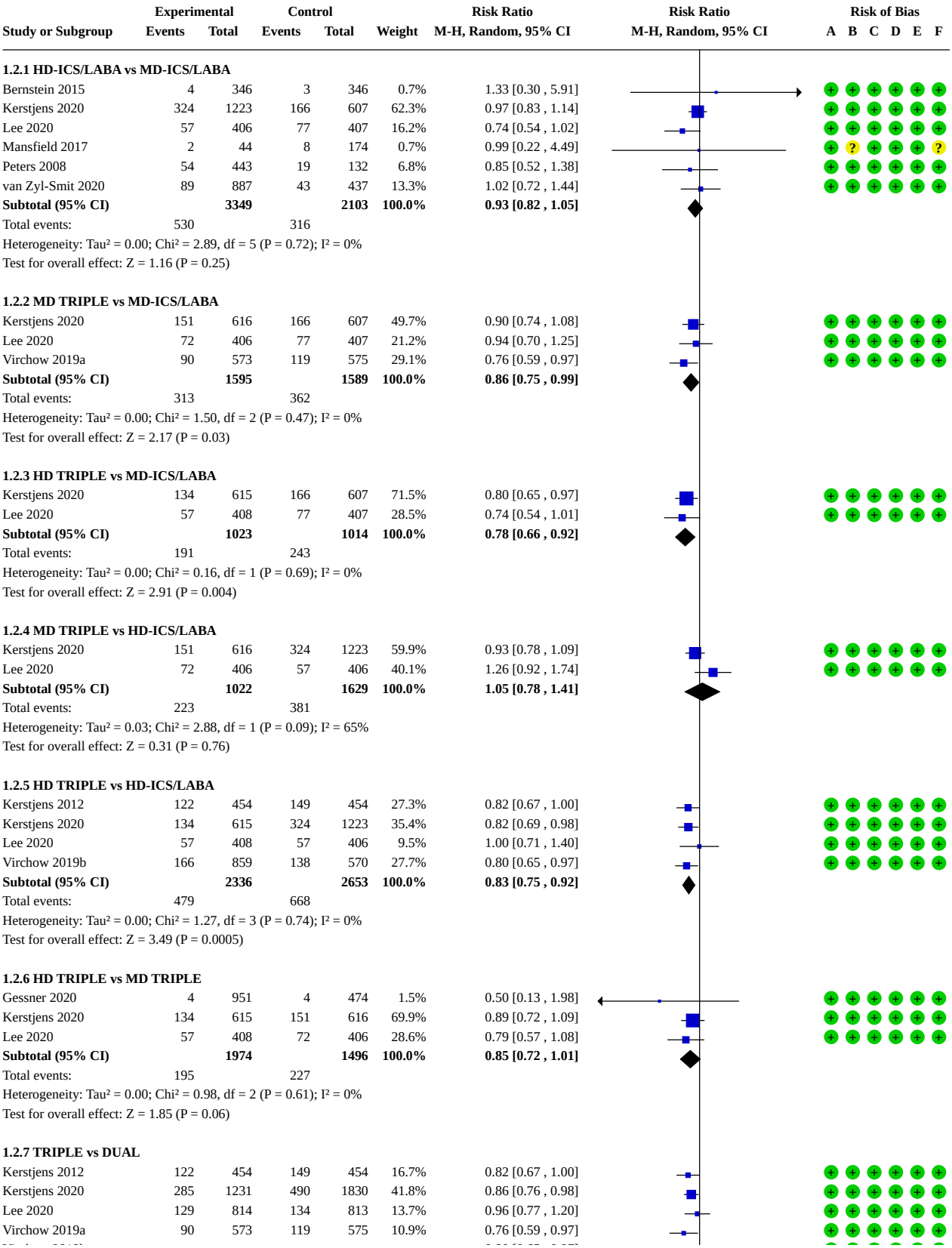


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data

Analysis 1.1. (Continued)

(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Asthma exacerbations, Outcome 2: Moderate to severe exacerbations

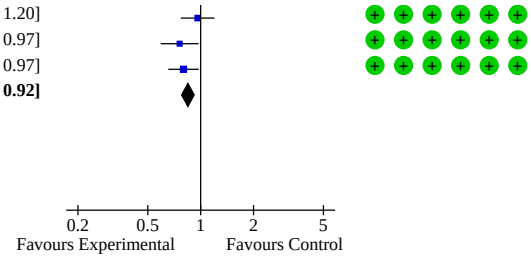


Analysis 1.2. (Continued)

Lee 2020	129	814	134	813	13.7%	0.96 [0.77 , 1.20]
Virchow 2019a	90	573	119	575	10.9%	0.76 [0.59 , 0.97]
Virchow 2019b	166	859	138	570	16.9%	0.80 [0.65 , 0.97]
Subtotal (95% CI)		**3931**		**4242**	**100.0%**	**0.85 [0.78 , 0.92]**
Total events:	792		1030			

Heterogeneity: Tau² = 0.00; Chi² = 2.56, df = 4 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)

Test for subgroup differences: Chi² = 4.97, df = 6 (P = 0.55), I² = 0%



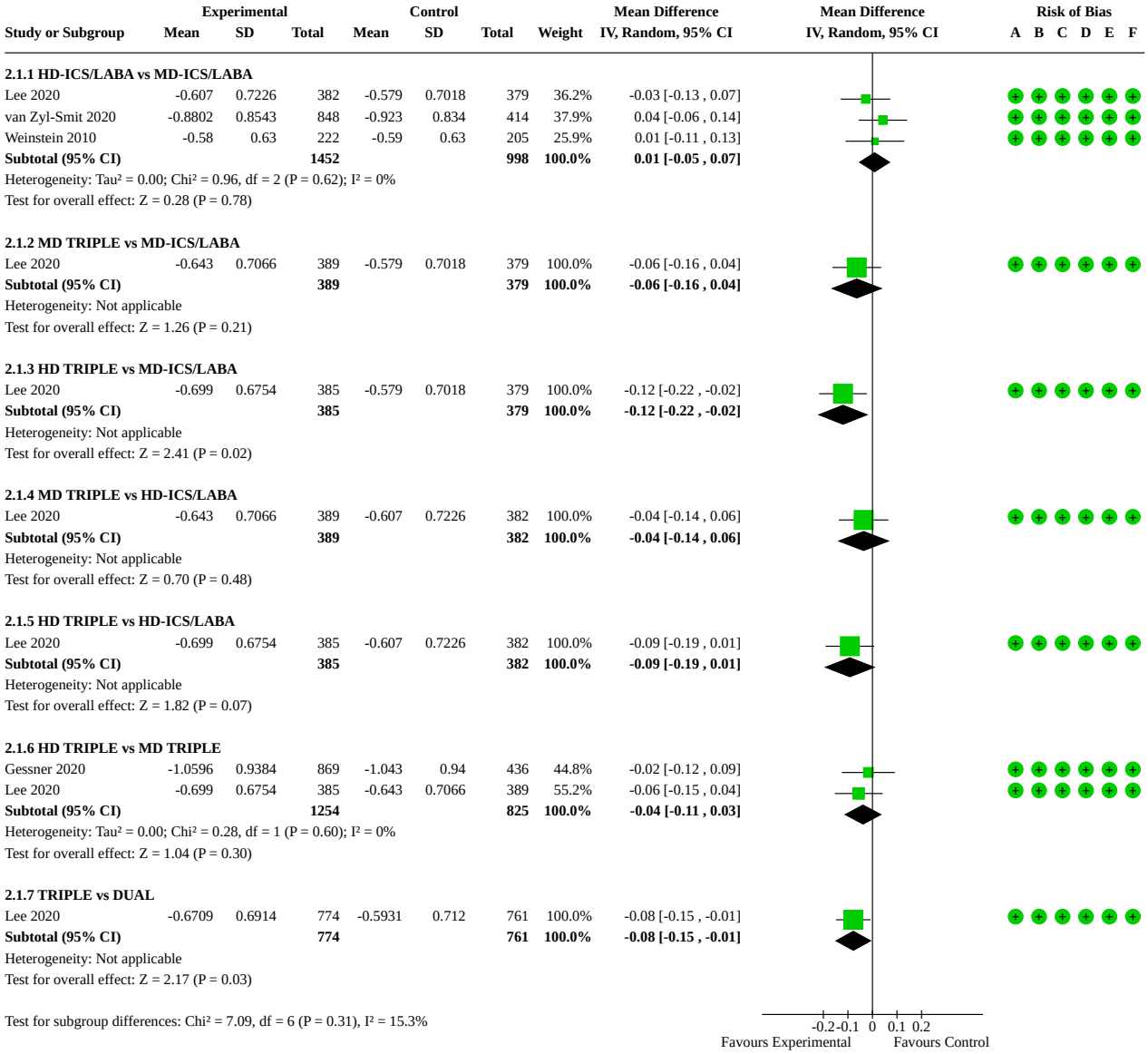
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Asthma Control Questionnaire: change from baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 CFB in ACQ at 3 months	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1.1 HD-ICS/LABA vs MD-ICS/LABA	3	2450	Mean Difference (IV, Random, 95% CI)	0.01 [-0.05, 0.07]
2.1.2 MD TRIPLE vs MD-ICS/LABA	1	768	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.16, 0.04]
2.1.3 HD TRIPLE vs MD-ICS/LABA	1	764	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.22, -0.02]
2.1.4 MD TRIPLE vs HD-ICS/LABA	1	771	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.14, 0.06]
2.1.5 HD TRIPLE vs HD-ICS/LABA	1	767	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.19, 0.01]
2.1.6 HD TRIPLE vs MD TRIPLE	2	2079	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.11, 0.03]
2.1.7 TRIPLE vs DUAL	1	1535	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.15, -0.01]
2.2 CFB in ACQ at 6 months	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 HD-ICS/LABA vs MD-ICS/LABA	3	3762	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.12, 0.04]
2.2.2 MD TRIPLE vs MD-ICS/LABA	2	1961	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.17, -0.02]
2.2.3 HD TRIPLE vs MD-ICS/LABA	2	1952	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.18, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.4 MD TRIPLE vs HD-ICS/LABA	2	2561	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.08, 0.06]
2.2.5 HD TRIPLE vs HD-ICS/LABA	3	3459	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.15, 0.03]
2.2.6 MD TRIPLE vs LD TRIPLE	2	2091	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.13, 0.05]
2.2.7 HD TRIPLE vs LD TRIPLE	1	873	Mean Difference (IV, Random, 95% CI)	0.03 [-0.10, 0.16]
2.2.8 HD TRIPLE vs MD TRIPLE	3	3288	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.08, 0.04]
2.2.9 TRIPLE vs DUAL	4	5408	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.14, -0.01]
2.3 CFB in ACQ at 12 months	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 HD-ICS/LABA vs MD-ICS/LABA	3	3152	Mean Difference (IV, Random, 95% CI)	0.00 [-0.12, 0.12]
2.3.2 MD TRIPLE vs MD-ICS/LABA	2	1366	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.11, 0.08]
2.3.3 HD TRIPLE vs MD-ICS/LABA	2	1379	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.23, 0.06]
2.3.4 MD TRIPLE vs HD-ICS/LABA	2	1967	Mean Difference (IV, Random, 95% CI)	0.01 [-0.20, 0.21]
2.3.5 HD TRIPLE vs HD-ICS/LABA	3	2887	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.15, 0.00]
2.3.6 HD TRIPLE vs MD TRIPLE	2	1381	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.23, 0.09]
2.3.7 DUAL vs TRIPLE	4	4253	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.10, 0.02]

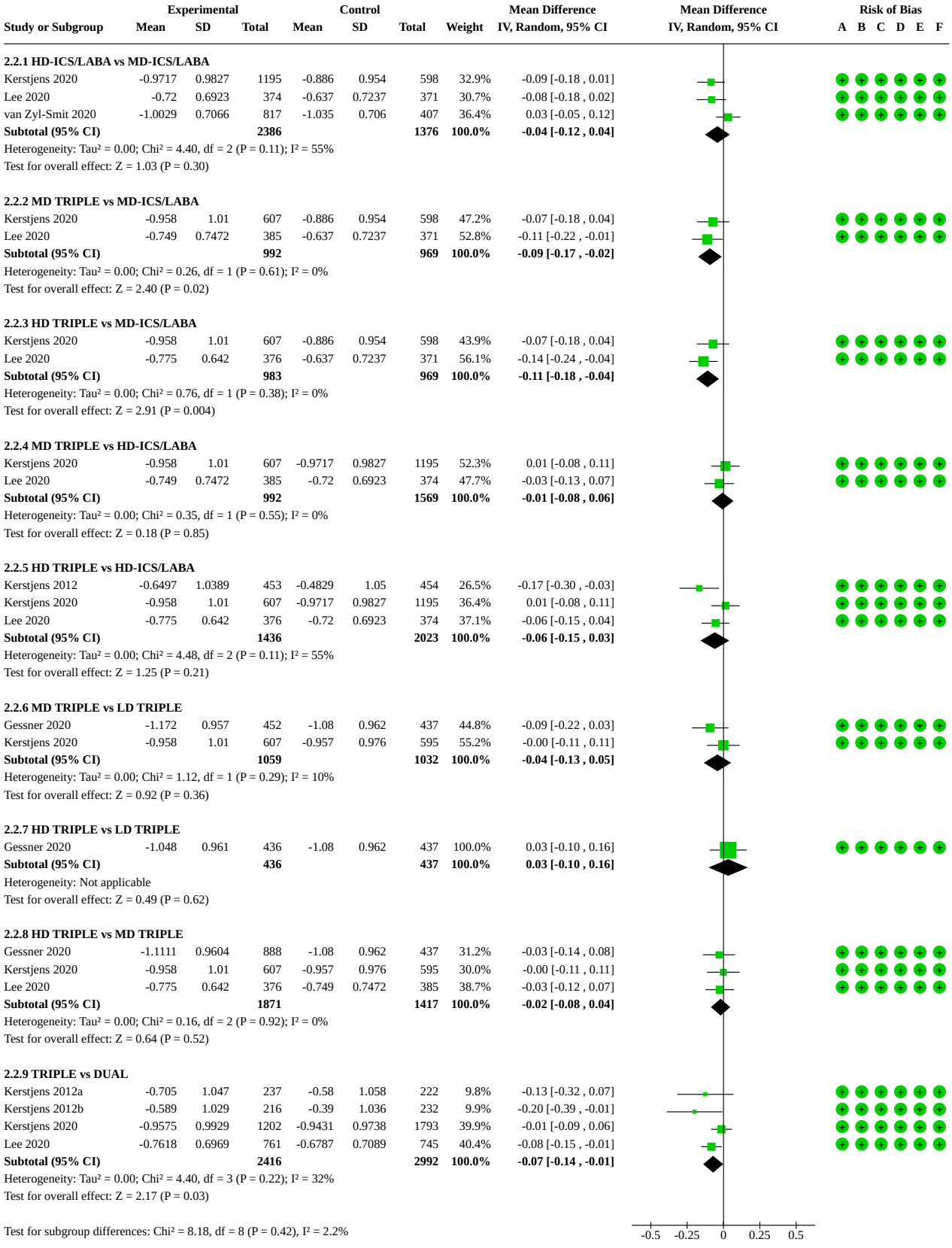
Analysis 2.1. Comparison 2: Asthma Control Questionnaire: change from baseline, Outcome 1: CFB in ACQ at 3 months



Risk of bias legend

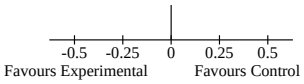
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Asthma Control Questionnaire: change from baseline, Outcome 2: CFB in ACQ at 6 months



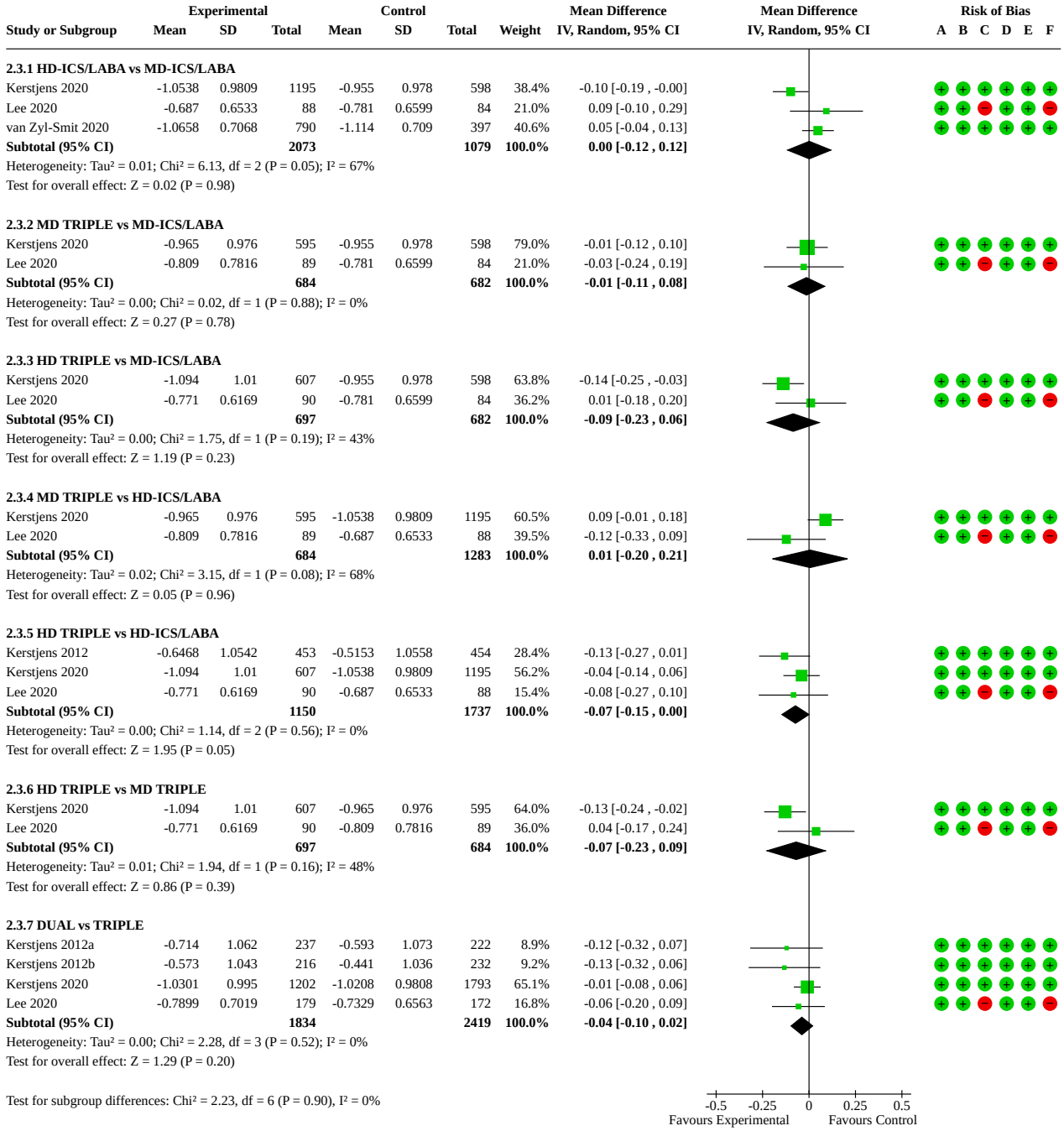
Analysis 2.2. (Continued)

Test for subgroup differences: Chi² = 8.18, df = 8 (P = 0.42), I² = 2.2%



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Asthma Control Questionnaire: change from baseline, Outcome 3: CFB in ACQ at 12 months



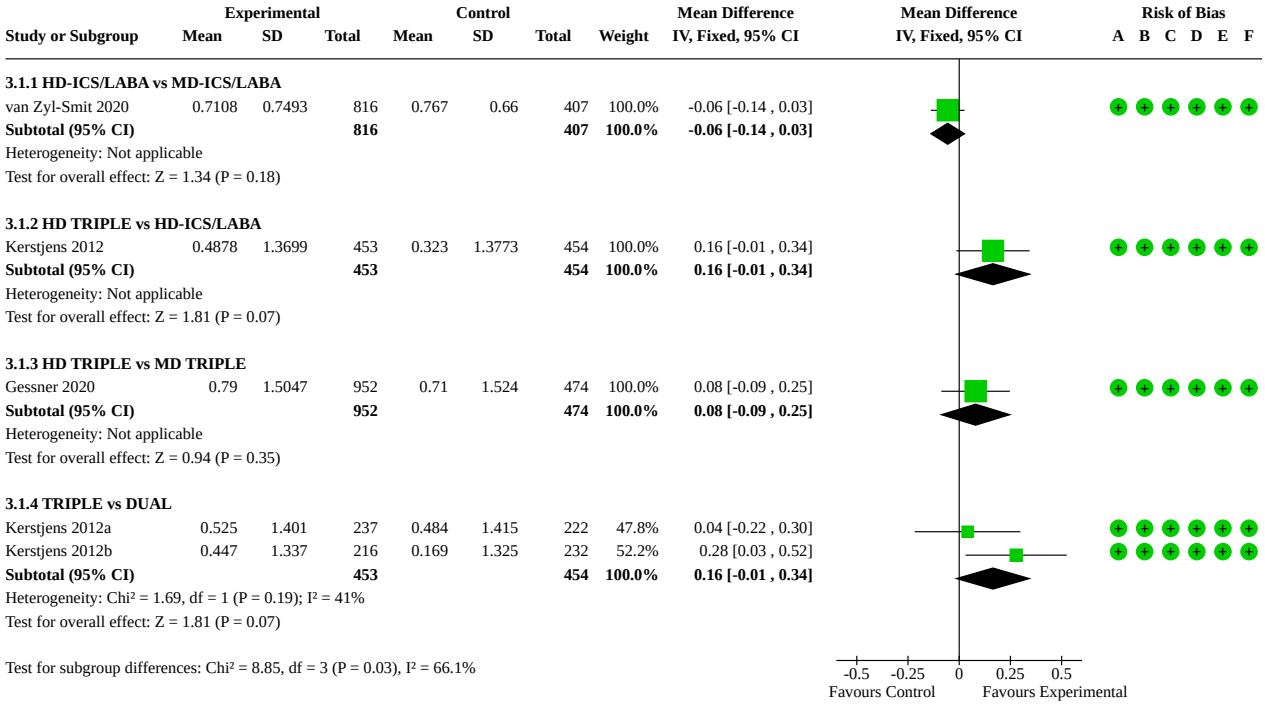
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Asthma Quality of Life Questionnaire: change from baseline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 CFB in AQLQ at 6 months	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1.1 HD-ICS/LABA vs MD-ICS/LABA	1	1223	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.14, 0.03]
3.1.2 HD TRIPLE vs HD-ICS/LABA	1	907	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.01, 0.34]
3.1.3 HD TRIPLE vs MD TRIPLE	1	1426	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.09, 0.25]
3.1.4 TRIPLE vs DUAL	2	907	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.01, 0.34]
3.2 CFB in AQLQ at 12 months	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2.1 HD-ICS/LABA vs MD-ICS/LABA	2	2815	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.04]
3.2.2 MD TRIPLE vs MD-ICS/LABA	1	1071	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.15, 0.05]
3.2.3 HD TRIPLE vs MD-ICS/LABA	1	1058	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.04, 0.16]
3.2.4 MD TRIPLE vs HD-ICS/LABA	1	1628	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.16, 0.02]
3.2.5 HD TRIPLE vs HD-ICS/LABA	3	2552	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.02, 0.14]
3.2.6 TRIPLE vs DUAL	3	3623	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.07]

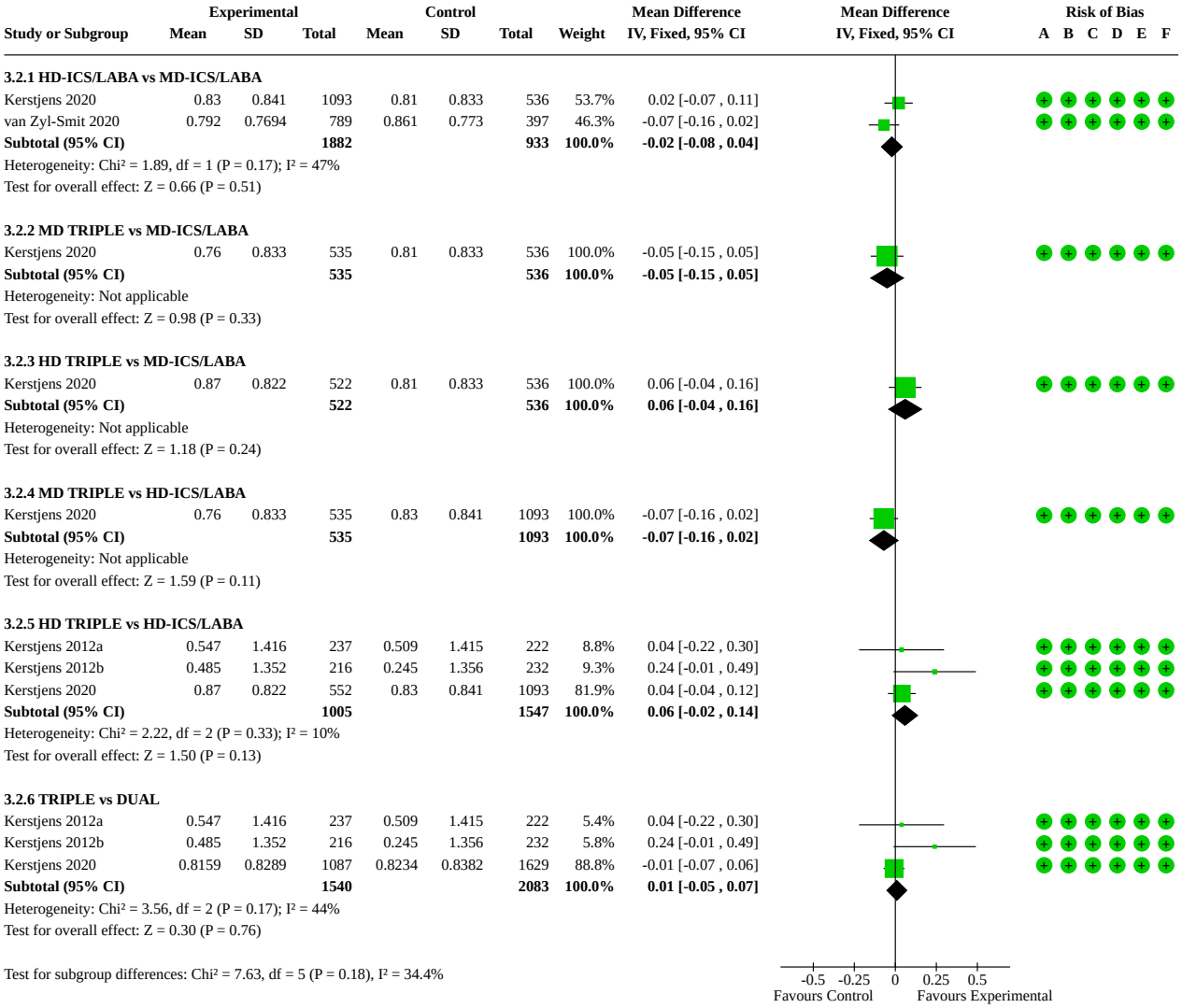
Analysis 3.1. Comparison 3: Asthma Quality of Life Questionnaire: change from baseline, Outcome 1: CFB in AQLQ at 6 months



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Asthma Quality of Life Questionnaire: change from baseline, Outcome 2: CFB in AQLQ at 12 months



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 4. Asthma Control Questionnaire responders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 ACQ responders at 6 months	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 HD-ICS/LABA vs MD-ICS/LABA	3	3700	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 MD TRIPLE vs MD-ICS/LABA	3	3063	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.99, 1.19]
4.1.3 HD TRIPLE vs MD-ICS/LABA	2	1916	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.91, 1.35]
4.1.4 MD TRIPLE vs HD-ICS/LABA	2	2487	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.96, 1.08]
4.1.5 HD TRIPLE vs HD-ICS/LABA	4	4818	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.01, 1.14]
4.1.6 HD TRIPLE vs MD TRIPLE	3	2821	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.03]
4.1.7 TRIPLE vs DUAL	5	7881	Risk Ratio (M-H, Random, 95% CI)	1.09 [1.02, 1.15]
4.2 ACQ responders at 12 months	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 HD-ICS/LABA vs MD-ICS/LABA	2	2817	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.07]
4.2.2 MD TRIPLE vs MD-ICS/LABA	2	2222	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.95, 1.07]
4.2.3 MD TRIPLE vs HD-ICS/LABA	1	1088	Risk Ratio (M-H, Random, 95% CI)	1.08 [1.01, 1.15]
4.2.4 MD TRIPLE vs HD-ICS/LABA	1	1631	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.03]
4.2.5 HD TRIPLE vs HD-ICS/LABA	3	3982	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.99, 1.23]
4.2.6 HD TRIPLE vs MD TRIPLE	1	1089	Risk Ratio (M-H, Random, 95% CI)	1.08 [1.01, 1.16]
4.2.7 TRIPLE vs DUAL	4	6204	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.99, 1.17]

Analysis 4.1. Comparison 4: Asthma Control Questionnaire responders, Outcome 1: ACQ responders at 6 months

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
4.1.1 HD-ICS/LABA vs MD-ICS/LABA							
Kerstjens 2020	796	1124	395	559	42.3%	1.00 [0.94 , 1.07]	+ + + + + +
Lee 2020	231	397	205	396	16.3%	1.12 [0.99 , 1.28]	+ + + + + +
van Zyl-Smit 2020	622	817	310	407	41.4%	1.00 [0.94 , 1.07]	+ + − + + −
Subtotal (95% CI)		**2338**		**1362**	**100.0%**	**1.02 [0.96 , 1.08]**	
Total events:	1649		910				
Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 2 (P = 0.23); I² = 33%							
Test for overall effect: Z = 0.70 (P = 0.49)							
4.1.2 MD TRIPLE vs MD-ICS/LABA							
Kerstjens 2020	401	559	395	559	40.5%	1.02 [0.94 , 1.09]	+ + + + + +
Lee 2020	247	400	205	396	28.2%	1.19 [1.06 , 1.35]	+ + + + + +
Virchow 2019a	317	575	291	574	31.3%	1.09 [0.97 , 1.21]	+ + + + + +
Subtotal (95% CI)		**1534**		**1529**	**100.0%**	**1.09 [0.99 , 1.19]**	
Total events:	965		891				
Heterogeneity: Tau² = 0.00; Chi² = 5.19, df = 2 (P = 0.07); I² = 61%							
Test for overall effect: Z = 1.72 (P = 0.09)							
4.1.3 HD TRIPLE vs MD-ICS/LABA							
Kerstjens 2020	403	566	395	559	52.9%	1.01 [0.93 , 1.09]	+ + + + + +
Lee 2020	251	395	205	396	47.1%	1.23 [1.09 , 1.39]	+ + + + + +
Subtotal (95% CI)		**961**		**955**	**100.0%**	**1.11 [0.91 , 1.35]**	
Total events:	654		600				
Heterogeneity: Tau² = 0.02; Chi² = 7.67, df = 1 (P = 0.006); I² = 87%							
Test for overall effect: Z = 1.00 (P = 0.32)							
4.1.4 MD TRIPLE vs HD-ICS/LABA							
Kerstjens 2020	403	566	796	1124	75.6%	1.01 [0.94 , 1.07]	+ + + + + +
Lee 2020	247	400	231	397	24.4%	1.06 [0.95 , 1.19]	+ + + + + +
Subtotal (95% CI)		**966**		**1521**	**100.0%**	**1.02 [0.96 , 1.08]**	
Total events:	650		1027				
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 1 (P = 0.41); I² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
4.1.5 HD TRIPLE vs HD-ICS/LABA							
Kerstjens 2012	244	453	213	454	16.9%	1.15 [1.01 , 1.31]	+ + + + + +
Kerstjens 2020	403	566	796	1124	36.0%	1.01 [0.94 , 1.07]	+ + + + + +
Lee 2020	251	395	231	397	20.6%	1.09 [0.98 , 1.22]	+ + + + + +
Virchow 2019b	530	858	319	571	26.6%	1.11 [1.01 , 1.21]	+ + + + + +
Subtotal (95% CI)		**2272**		**2546**	**100.0%**	**1.07 [1.01 , 1.14]**	
Total events:	1428		1559				
Heterogeneity: Tau² = 0.00; Chi² = 5.38, df = 3 (P = 0.15); I² = 44%							
Test for overall effect: Z = 2.16 (P = 0.03)							
4.1.6 HD TRIPLE vs MD TRIPLE							
Gessner 2020	375	447	387	454	54.3%	0.98 [0.93 , 1.04]	+ + + + + +
Kerstjens 2020	403	566	401	559	31.0%	0.99 [0.92 , 1.07]	+ + + + + +
Lee 2020	251	395	247	400	14.7%	1.03 [0.92 , 1.15]	+ + + + + +
Subtotal (95% CI)		**1408**		**1413**	**100.0%**	**0.99 [0.95 , 1.03]**	
Total events:	1029		1035				
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.32 (P = 0.75)							
4.1.7 TRIPLE vs DUAL							
Kerstjens 2012	244	453	213	454	13.4%	1.15 [1.01 , 1.31]	+ + + + + +
Kerstjens 2020	804	1125	1191	1683	29.1%	1.01 [0.96 , 1.06]	+ + + + + +
Lee 2020	498	795	436	793	21.3%	1.14 [1.05 , 1.24]	+ + + + + +
Virchow 2019a	317	575	291	574	16.4%	1.09 [0.97 , 1.21]	+ + + + + +
Virchow 2019b	530	858	319	571	19.8%	1.11 [1.01 , 1.21]	+ + + + + +
Subtotal (95% CI)		**3806**		**4075**	**100.0%**	**1.09 [1.02 , 1.15]**	
Total events:	2393		2450				

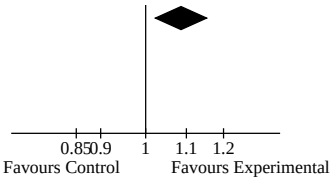
Analysis 4.1. (Continued)

Subtotal (95% CI)	**3806**	**4075**	**100.0%**	**1.09 [1.02 , 1.15]**	
Total events:	2393	2450			

Heterogeneity: Tau² = 0.00; Chi² = 9.71, df = 4 (P = 0.05); I² = 59%

Test for overall effect: Z = 2.71 (P = 0.007)

Test for subgroup differences: Chi² = 9.52, df = 6 (P = 0.15), I² = 37.0%



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

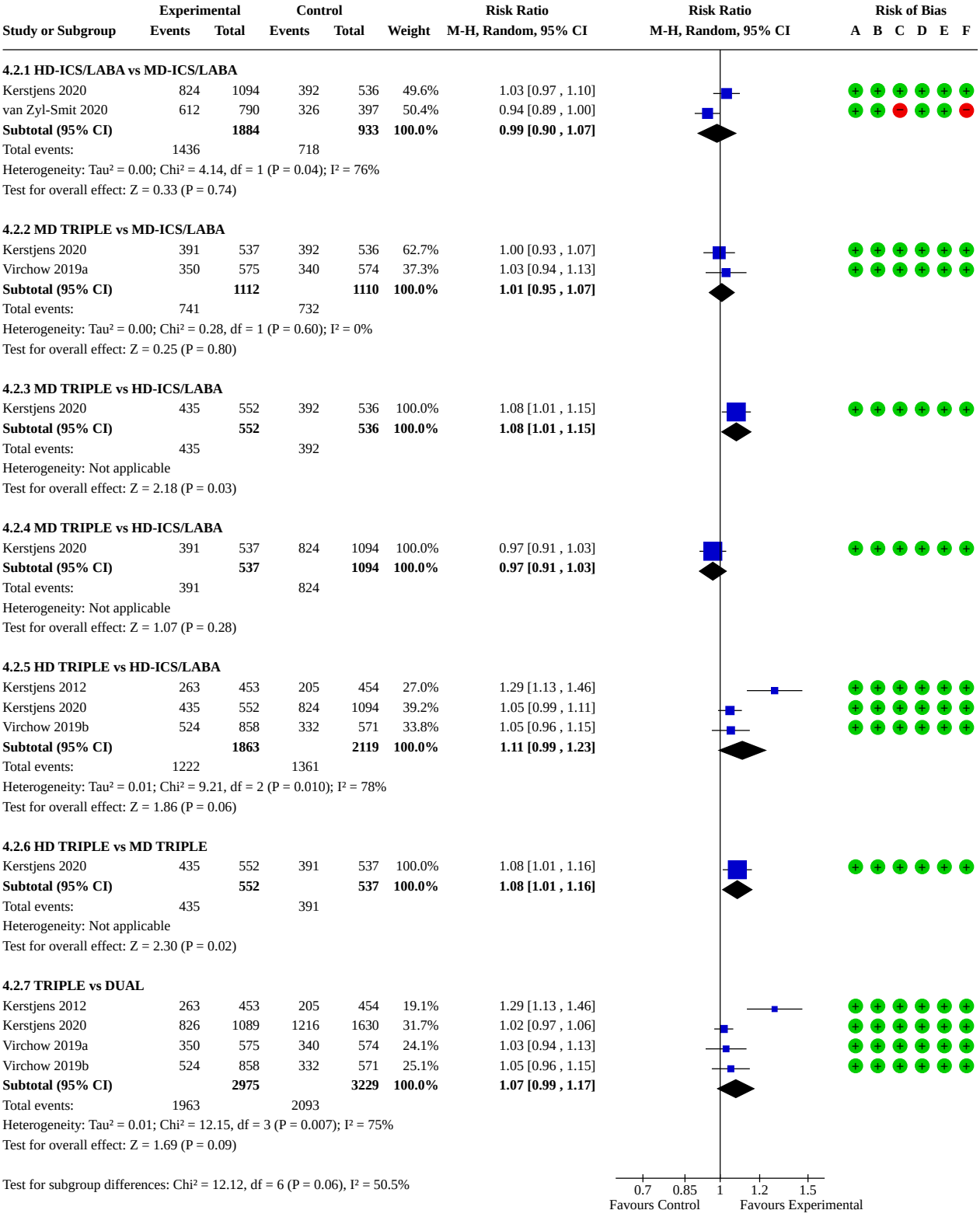
(C) Bias due to missing outcome data

(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 4.2. Comparison 4: Asthma Control Questionnaire responders, Outcome 2: ACQ responders at 12 months



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

Analysis 4.2. (Continued)

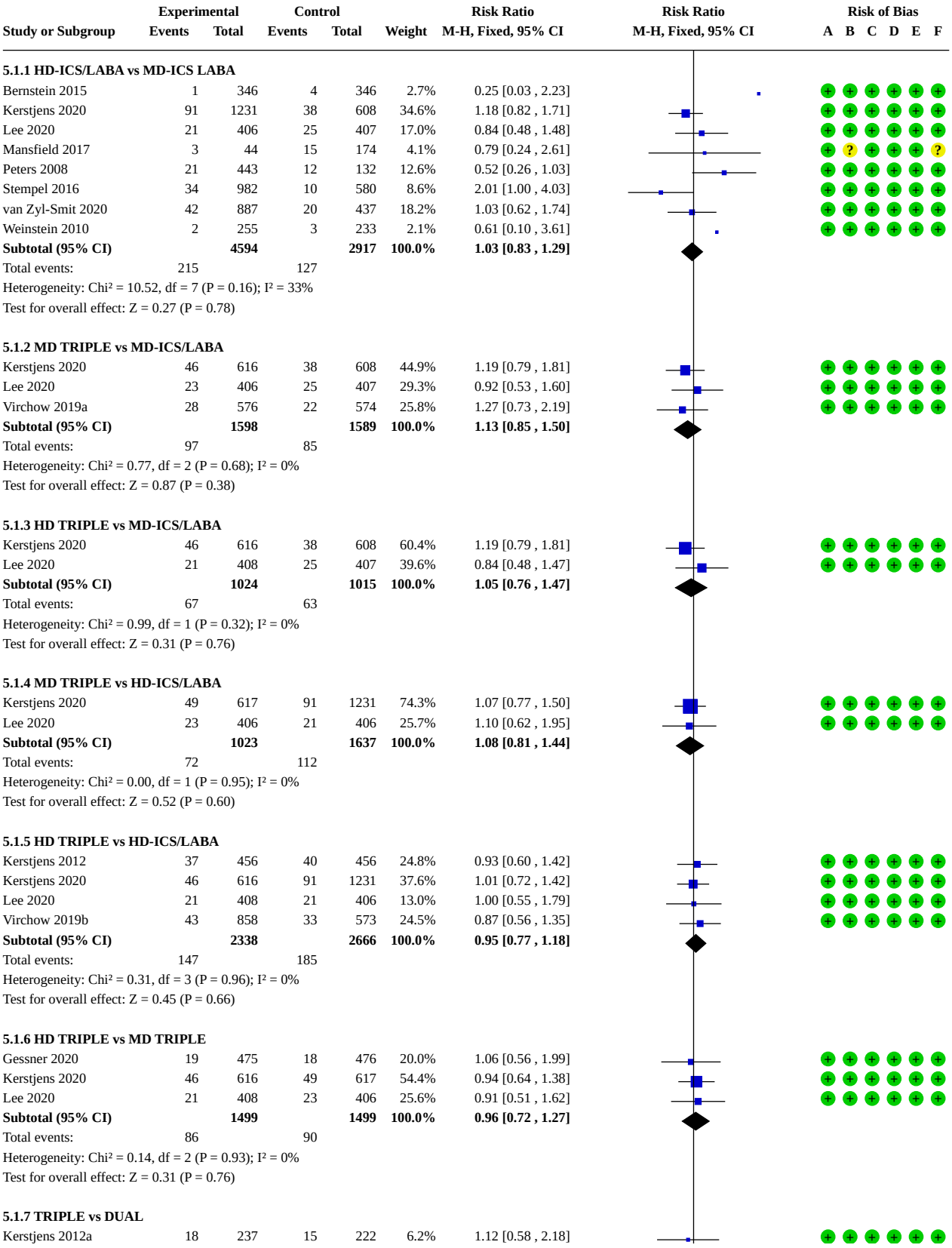
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 5. Serious adverse events, adverse events, and dropouts due to adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All cause SAEs	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 HD-ICS/LABA vs MD-ICS LABA	8	7511	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.83, 1.29]
5.1.2 MD TRIPLE vs MD-ICS/LABA	3	3187	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.85, 1.50]
5.1.3 HD TRIPLE vs MD-ICS/LABA	2	2039	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.76, 1.47]
5.1.4 MD TRIPLE vs HD-ICS/LABA	2	2660	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.81, 1.44]
5.1.5 HD TRIPLE vs HD-ICS/LABA	4	5004	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.18]
5.1.6 HD TRIPLE vs MD TRIPLE	3	2998	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.27]
5.1.7 TRIPLE vs DUAL	6	8192	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
5.2 Asthma-related SAEs	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 HD-ICS/LABA vs MD-ICS LABA	6	6244	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.80, 2.21]
5.2.2 MD TRIPLE vs MD-ICS/LABA	3	3188	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.85, 2.69]
5.2.3 HD TRIPLE vs MD-ICS/LABA	2	2039	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.41, 1.80]
5.2.4 MD TRIPLE vs HD-ICS/LABA	2	2660	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.77, 2.36]
5.2.5 HD TRIPLE vs HD-ICS/LABA	4	5004	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.27]
5.2.6 HD TRIPLE vs MD TRIPLE	3	3472	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.31, 1.05]
5.2.7 TRIPLE vs DUAL	6	8192	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.76, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 All cause AEs	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.3.1 HD-ICS/LABA vs MD-ICS LABA	7	5949	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.97, 1.06]
5.3.2 MD TRIPLE vs MD-ICS/LABA	3	3188	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.91, 1.00]
5.3.3 HD TRIPLE vs MD-ICS/LABA	2	2039	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 1.00]
5.3.4 MD TRIPLE vs HD-ICS/LABA	2	2659	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.18]
5.3.5 HD TRIPLE vs HD-ICS/LABA	4	5004	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.87, 0.96]
5.3.6 HD TRIPLE vs MD TRIPLE	3	2998	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.89, 1.02]
5.3.7 TRIPLE vs DUAL	6	8192	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.90, 0.96]
5.4 Dropouts due to adverse event	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.4.1 HD-ICS/LABA vs MD-ICS LABA	7	5969	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.68, 1.48]
5.4.2 MD TRIPLE vs MD-ICS/LABA	3	3205	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.08, 2.14]
5.4.3 HD TRIPLE vs MD-ICS/LABA	2	2670	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.19, 1.18]
5.4.4 MD TRIPLE vs HD-ICS/LABA	2	2668	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.76, 2.02]
5.4.5 HD TRIPLE vs HD-ICS/LABA	4	5018	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.38, 0.95]
5.4.6 HD TRIPLE vs MD TRIPLE	2	1765	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.29, 3.44]
5.4.7 TRIPLE vs DUAL	5	8223	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.03]

Analysis 5.1. Comparison 5: Serious adverse events, adverse events, and dropouts due to adverse event, Outcome 1: All cause SAEs

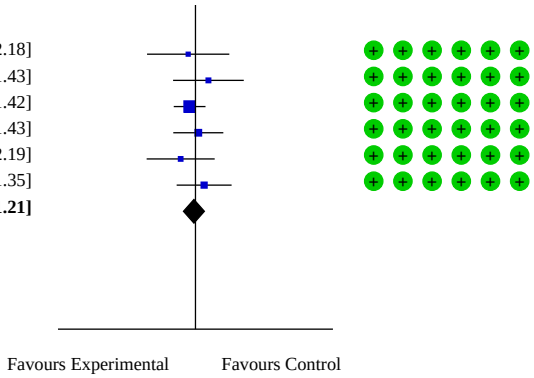


Analysis 5.1. (Continued)

5.1.7 TRIPLE vs DUAL						
Kerstjens 2012a	18	237	15	222	6.2%	1.12 [0.58 , 2.18]
Kerstjens 2012b	19	219	25	234	9.6%	0.81 [0.46 , 1.43]
Kerstjens 2020	95	1233	129	1839	41.3%	1.10 [0.85 , 1.42]
Lee 2020	44	814	46	813	18.3%	0.96 [0.64 , 1.43]
Virchow 2019a	28	576	22	574	8.8%	1.27 [0.73 , 2.19]
Virchow 2019b	43	858	33	573	15.8%	0.87 [0.56 , 1.35]
Subtotal (95% CI)		**3937**		**4255**	**100.0%**	**1.03 [0.87 , 1.21]**
Total events:	247		270			

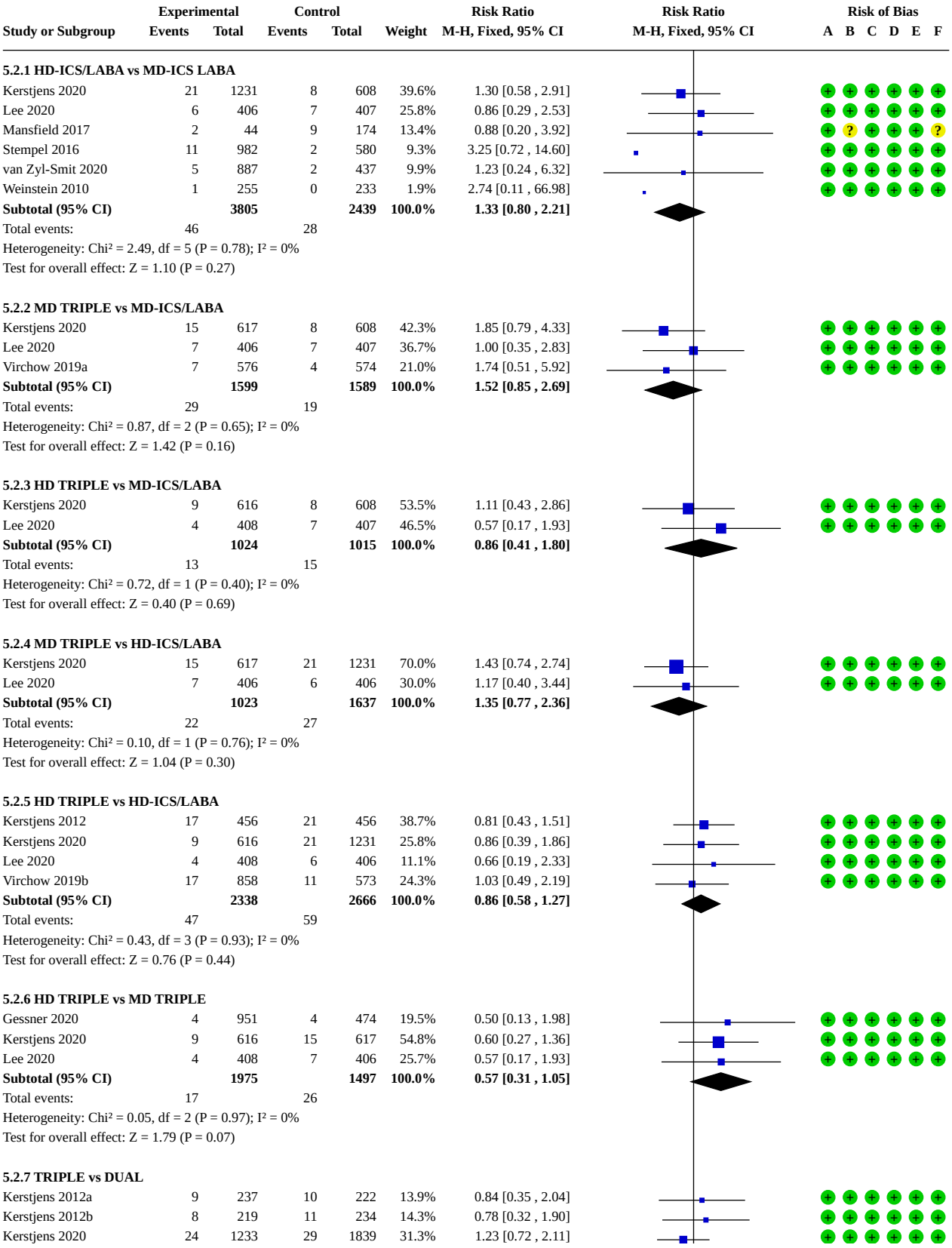
Heterogeneity: Chi² = 2.24, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Chi² = 1.33, df = 6 (P = 0.97), I² = 0%



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: Serious adverse events, adverse events, and dropouts due to adverse event, Outcome 2: Asthma-related SAEs

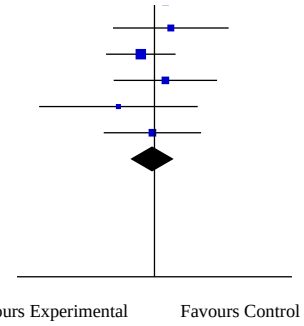


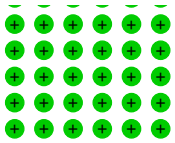
Analysis 5.2. (Continued)

Kerstjens 2012b	8	219	11	234	14.3%	0.78 [0.32 , 1.90]
Kerstjens 2020	24	1233	29	1839	31.3%	1.23 [0.72 , 2.11]
Lee 2020	11	814	13	813	17.5%	0.85 [0.38 , 1.88]
Virchow 2019a	7	576	4	574	5.4%	1.74 [0.51 , 5.92]
Virchow 2019b	17	858	11	573	17.7%	1.03 [0.49 , 2.19]
Subtotal (95% CI)		**3937**		**4255**	**100.0%**	**1.04 [0.76 , 1.42]**
Total events:	76		78			

Heterogeneity: Chi² = 1.97, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Chi² = 8.23, df = 6 (P = 0.22), I² = 27.1%

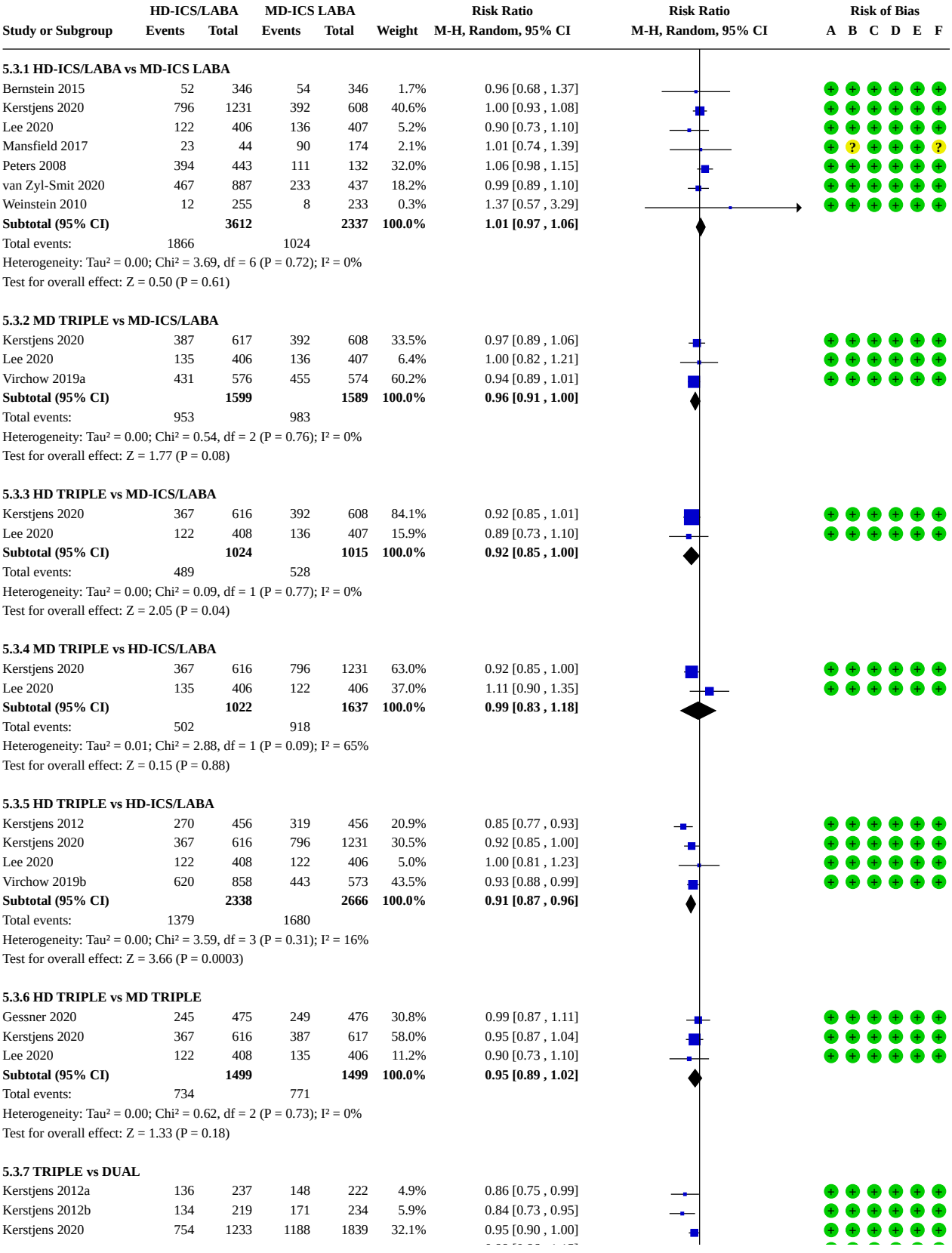




Favours Experimental Favours Control

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.3. Comparison 5: Serious adverse events, adverse events, and dropouts due to adverse event, Outcome 3: All cause AEs



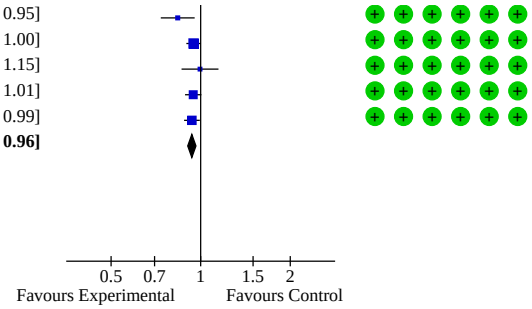
Analysis 5.3. (Continued)

Kerstjens 2012b	134	219	171	234	5.9%	0.84 [0.73 , 0.95]
Kerstjens 2020	754	1233	1188	1839	32.1%	0.95 [0.90 , 1.00]
Lee 2020	257	814	258	813	4.9%	0.99 [0.86 , 1.15]
Virchow 2019a	431	576	455	574	25.1%	0.94 [0.89 , 1.01]
Virchow 2019b	620	858	443	573	27.2%	0.93 [0.88 , 0.99]
Subtotal (95% CI)		**3937**		**4255**	**100.0%**	**0.93 [0.90 , 0.96]**
Total events:	2332		2663			

Heterogeneity: Tau² = 0.00; Chi² = 5.01, df = 5 (P = 0.41); I² = 0%

Test for overall effect: Z = 4.22 (P < 0.0001)

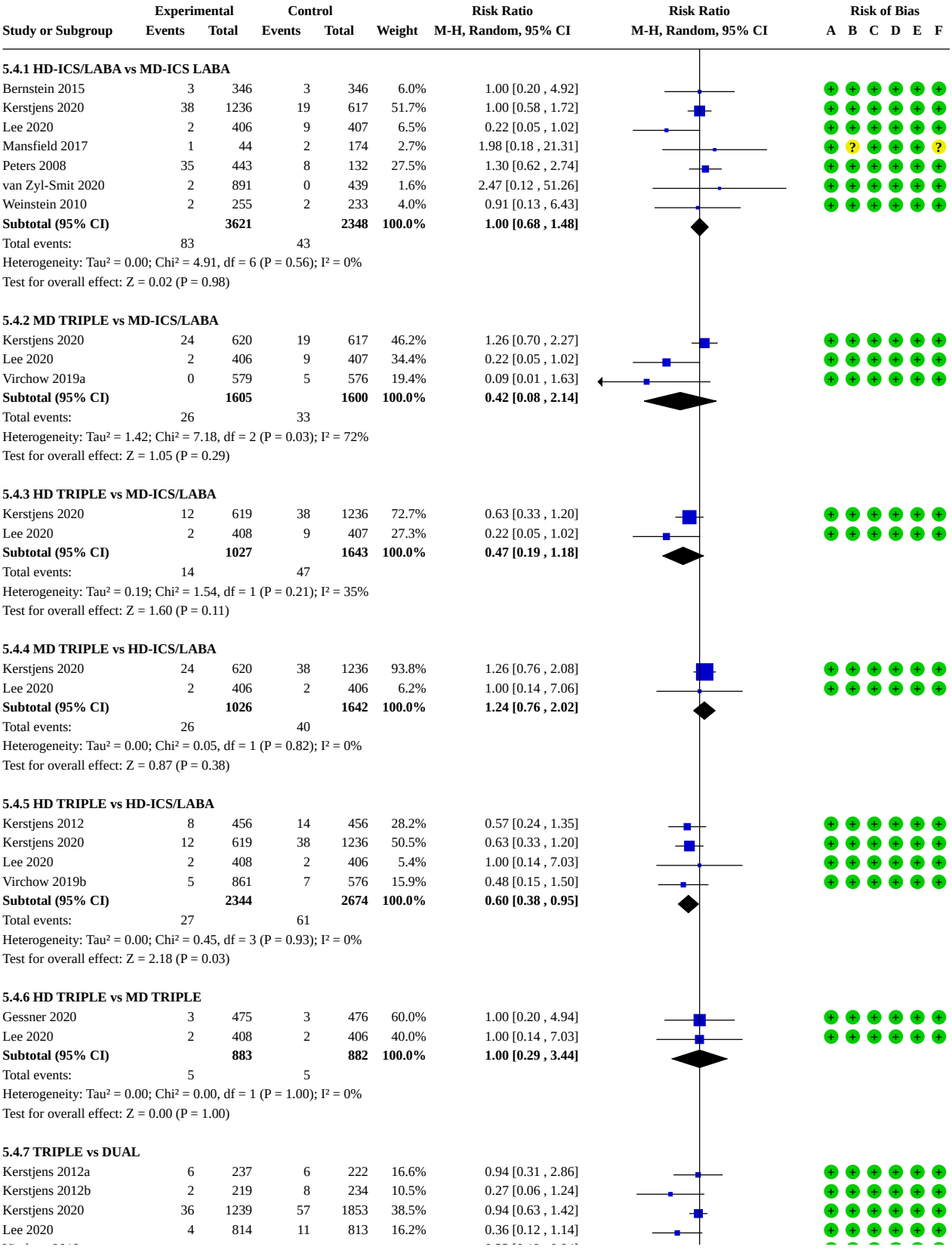
Test for subgroup differences: Chi² = 11.70, df = 6 (P = 0.07), I² = 48.7%



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.4. Comparison 5: Serious adverse events, adverse events, and dropouts due to adverse event, Outcome 4: Dropouts due to adverse event



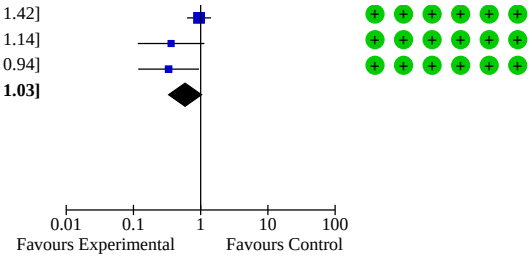
Analysis 5.4. (Continued)

Kerstjens 2020	36	1239	57	1853	38.5%	0.94 [0.63 , 1.42]
Lee 2020	4	814	11	813	16.2%	0.36 [0.12 , 1.14]
Virchow 2019	5	1440	12	1152	18.2%	0.33 [0.12 , 0.94]
Subtotal (95% CI)		**3949**		**4274**	**100.0%**	**0.59 [0.33 , 1.03]**
Total events:	53		94			

Heterogeneity: Tau² = 0.17; Chi² = 7.00, df = 4 (P = 0.14); I² = 43%

Test for overall effect: Z = 1.87 (P = 0.06)

Test for subgroup differences: Chi² = 9.10, df = 6 (P = 0.17), I² = 34.1%



Risk of bias legend

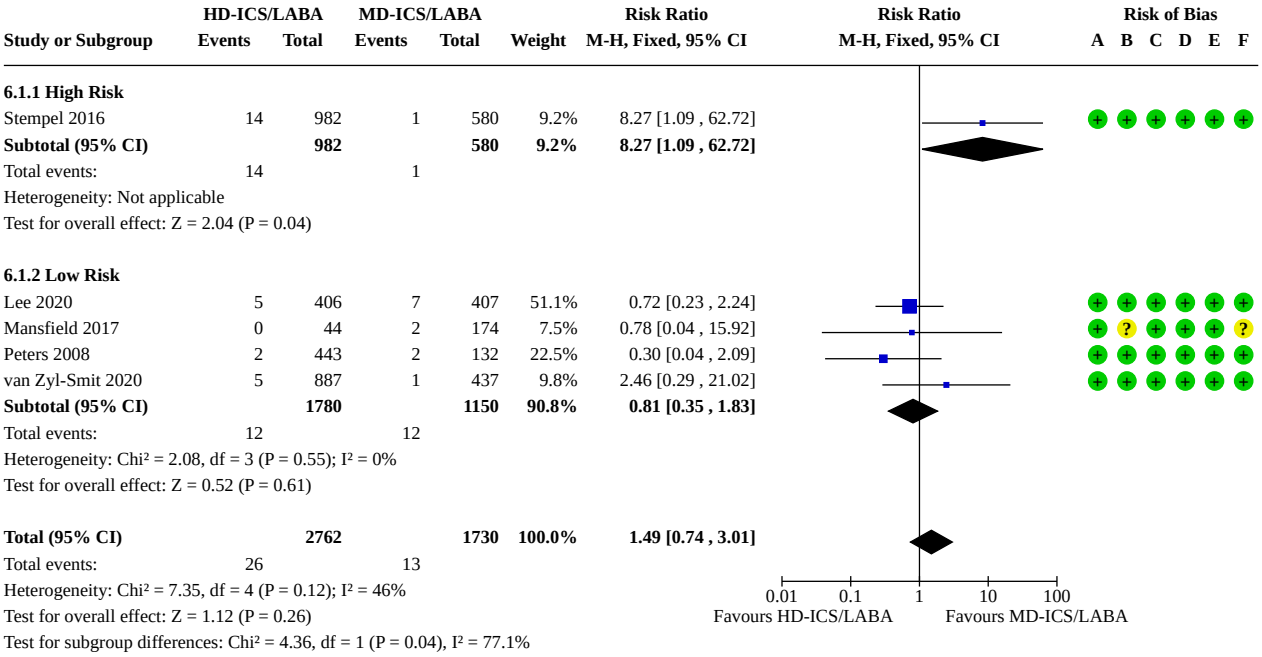
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. Severe exacerbations (high and low risk subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 HD-ICS/LABA vs MD-ICS/LABA	5	4492	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.74, 3.01]
6.1.1 High Risk	1	1562	Risk Ratio (M-H, Fixed, 95% CI)	8.27 [1.09, 62.72]
6.1.2 Low Risk	4	2930	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.35, 1.83]
6.2 MD TRIPLE vs MD-ICS/LABA	1	813	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.88]
6.2.1 Low Risk	1	813	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.35, 2.88]
6.3 HD TRIPLE vs MD-ICS/LABA	1	815	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.16, 1.95]
6.3.1 Low Risk	1	815	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.16, 1.95]
6.4 MD TRIPLE vs HD-ICS/LABA	1	812	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.44, 4.47]
6.4.1 Low Risk	1	812	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.44, 4.47]
6.5 HD TRIPLE vs HD-ICS/LABA	2	1727	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.44, 1.44]
6.5.1 High Risk	1	913	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.55]
6.5.2 Low Risk	1	814	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.21, 2.98]
6.6 HD TRIPLE vs MD TRIPLE	1	814	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.16, 1.94]
6.6.1 Low Risk	1	814	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.16, 1.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7 TRIPLE vs DUAL	2	2540	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.50, 1.41]
6.7.1 High Risk	1	913	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.55]
6.7.2 Low Risk	1	1627	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.40, 2.08]

Analysis 6.1. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 1: HD-ICS/LABA vs MD-ICS/LABA

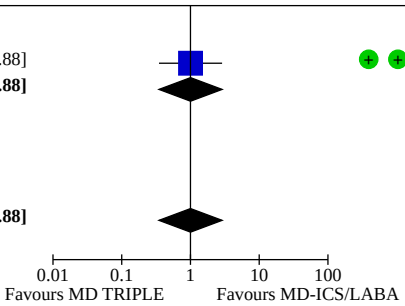


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 2: MD TRIPLE vs MD-ICS/LABA

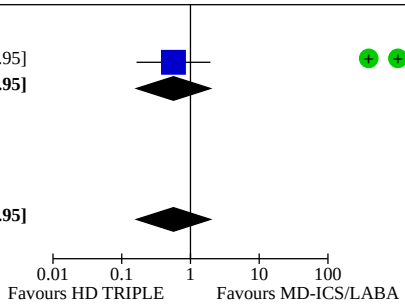
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
6.2.1 Low Risk							
Lee 2020	7	406	7	407	100.0%	1.00 [0.35 , 2.88]	+ + + + + +
Subtotal (95% CI)		**406**		**407**	**100.0%**	**1.00 [0.35 , 2.88]**	
Total events:	7		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Total (95% CI)		**406**		**407**	**100.0%**	**1.00 [0.35 , 2.88]**	
Total events:	7		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 3: HD TRIPLE vs MD-ICS/LABA

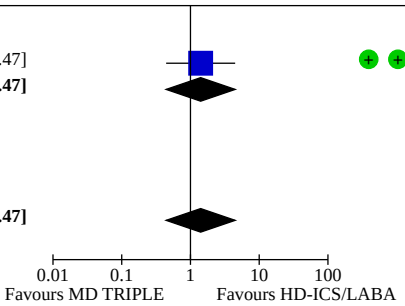
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
6.3.1 Low Risk							
Lee 2020	4	408	7	407	100.0%	0.57 [0.16 , 1.95]	+ + + + + +
Subtotal (95% CI)		**408**		**407**	**100.0%**	**0.57 [0.16 , 1.95]**	
Total events:	4		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
Total (95% CI)		**408**		**407**	**100.0%**	**0.57 [0.16 , 1.95]**	
Total events:	4		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 4: MD TRIPLE vs HD-ICS/LABA

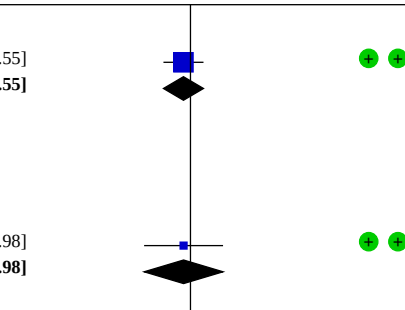
Study or Subgroup	MD-TRIPLE Events	MD-TRIPLE Total	HD-ICS/LABA Events	HD-ICS/LABA Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
6.4.1 Low Risk							
Lee 2020	7	406	5	406	100.0%	1.41 [0.44 , 4.47]	+ + + + + +
Subtotal (95% CI)		**406**		**406**	**100.0%**	**1.41 [0.44 , 4.47]**	
Total events:	7		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
Total (95% CI)		**406**		**406**	**100.0%**	**1.41 [0.44 , 4.47]**	
Total events:	7		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

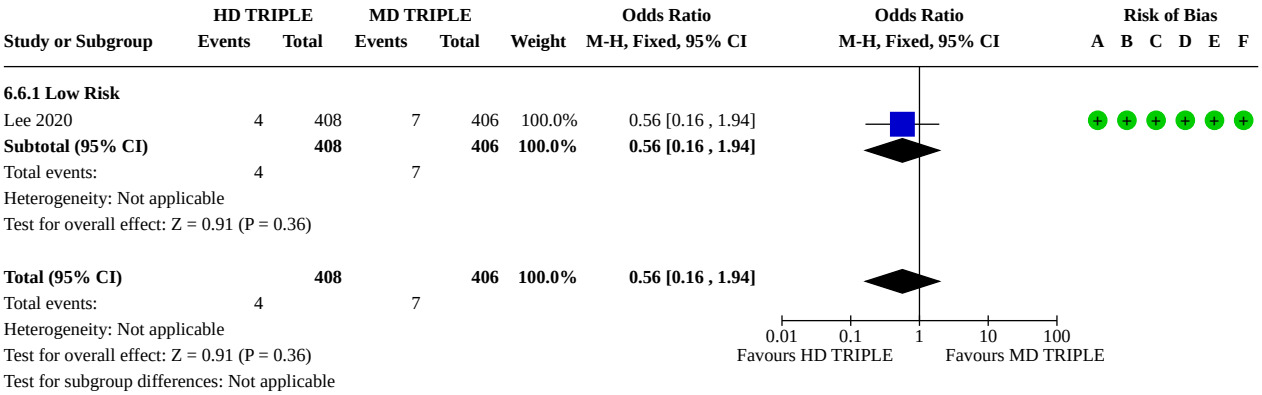
Analysis 6.5. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 5: HD TRIPLE vs HD-ICS/LABA

Study or Subgroup	HD TRIPLE Events	HD TRIPLE Total	HD-ICS/LABA Events	HD-ICS/LABA Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
6.5.1 High Risk							
Kerstjens 2012	16	457	20	456	79.6%	0.79 [0.40 , 1.55]	+ + + + + +
Subtotal (95% CI)		**457**		**456**	**79.6%**	**0.79 [0.40 , 1.55]**	
Total events:	16		20				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.69 (P = 0.49)							
6.5.2 Low Risk							
Lee 2020	4	408	5	406	20.4%	0.79 [0.21 , 2.98]	+ + + + + +
Subtotal (95% CI)		**408**		**406**	**20.4%**	**0.79 [0.21 , 2.98]**	
Total events:	4		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
Total (95% CI)		**865**		**862**	**100.0%**	**0.79 [0.44 , 1.44]**	
Total events:	20		25				
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%							



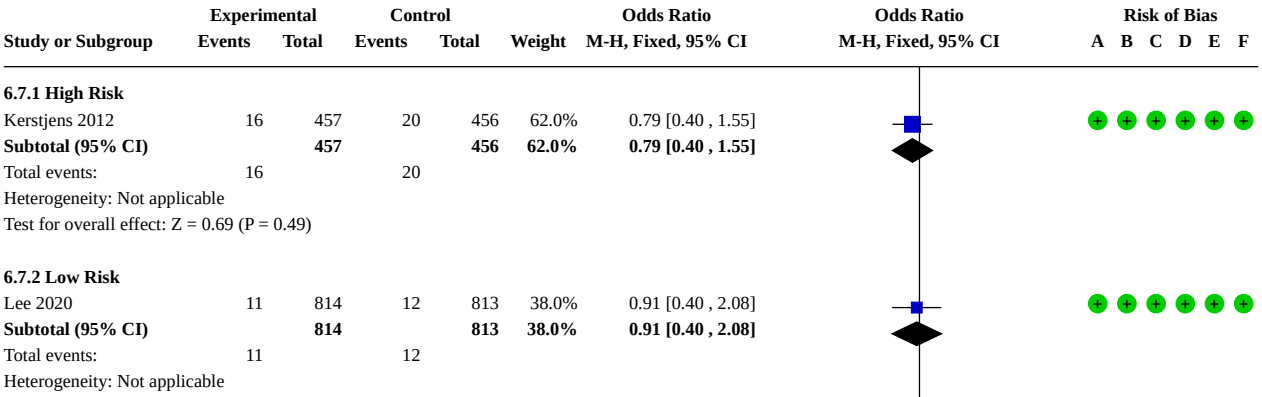
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.6. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 6: HD TRIPLE vs MD TRIPLE



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.7. Comparison 6: Severe exacerbations (high and low risk subgroups), Outcome 7: TRIPLE vs DUAL



Risk of bias legend
(A) Bias arising from the randomization process
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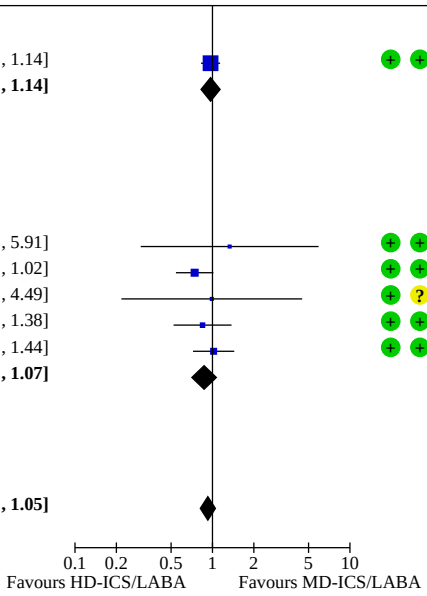
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

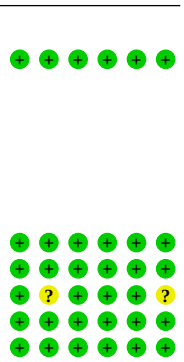
Comparison 7. Moderate to severe exacerbations (high and low risk subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 HD-ICS/LABA vs MD-ICS/LABA	6	5452	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.82, 1.05]
7.1.1 High Risk	1	1830	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.14]
7.1.2 Low Risk	5	3622	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.07]
7.2 MD TRIPLE vs MD-ICS/LABA	3	3184	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.75, 0.98]
7.2.1 High Risk	2	2371	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
7.2.2 Low Risk	1	813	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.70, 1.25]
7.3 HD TRIPLE vs MD-ICS/LABA	1	815	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.01]
7.3.1 Low Risk	1	815	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.01]
7.4 MD TRIPLE vs HD-ICS/LABA	2	2651	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
7.4.1 High Risk	1	1839	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.09]
7.4.2 Low Risk	1	812	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.92, 1.74]
7.5 HD TRIPLE vs HD-ICS/LABA	4	4989	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.92]
7.5.1 High Risk	3	4175	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.73, 0.91]
7.5.2 Low Risk	1	814	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.40]
7.6 HD TRIPLE vs MD TRIPLE	3	2996	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.72, 1.02]
7.6.1 High Risk	2	2182	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.73, 1.09]
7.6.2 Low Risk	1	814	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.08]
7.7 TRIPLE vs DUAL	4	7887	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.79, 0.93]
7.7.1 High Risk	3	6260	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.77, 0.92]
7.7.2 Low Risk	1	1627	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.20]

Analysis 7.1. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 1: HD-ICS/LABA vs MD-ICS/LABA

Study or Subgroup	HD-ICS/LABA Events	HD-ICS/LABA Total	MD-ICS/LABA Events	MD-ICS/LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 High Risk						
Kerstjens 2020	324	1223	166	607	56.6%	0.97 [0.83 , 1.14]
Subtotal (95% CI)		**1223**		**607**	**56.6%**	**0.97 [0.83 , 1.14]**
Total events:	324		166			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.70)						
7.1.2 Low Risk						
Bernstein 2015	4	346	3	346	0.8%	1.33 [0.30 , 5.91]
Lee 2020	57	406	77	407	19.6%	0.74 [0.54 , 1.02]
Mansfield 2017	2	44	8	174	0.8%	0.99 [0.22 , 4.49]
Peters 2008	54	443	19	132	7.5%	0.85 [0.52 , 1.38]
van Zyl-Smit 2020	89	887	43	437	14.7%	1.02 [0.72 , 1.44]
Subtotal (95% CI)		**2126**		**1496**	**43.4%**	**0.87 [0.71 , 1.07]**
Total events:	206		150			
Heterogeneity: Chi² = 2.15, df = 4 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		**3349**		**2103**	**100.0%**	**0.93 [0.82 , 1.05]**
Total events:	530		316			
Heterogeneity: Chi² = 2.89, df = 5 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² = 0%						



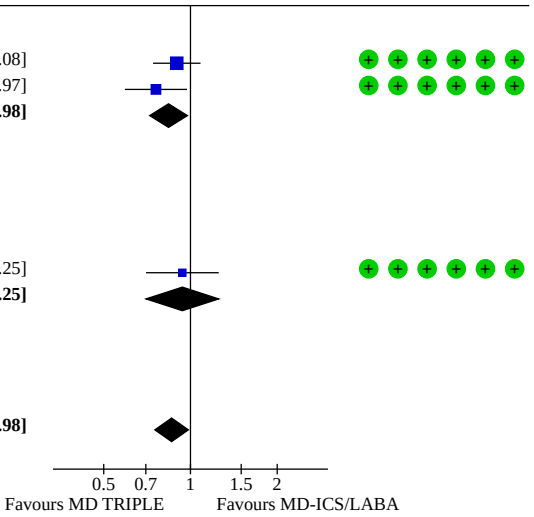


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 2: MD TRIPLE vs MD-ICS/LABA

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 High Risk						
Kerstjens 2020	151	616	166	607	46.1%	0.90 [0.74 , 1.08]
Virchow 2019a	90	573	119	575	32.7%	0.76 [0.59 , 0.97]
Subtotal (95% CI)		**1189**		**1182**	**78.8%**	**0.84 [0.72 , 0.98]**
Total events:	241		285			
Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 9%						
Test for overall effect: Z = 2.28 (P = 0.02)						
7.2.2 Low Risk						
Lee 2020	72	406	77	407	21.2%	0.94 [0.70 , 1.25]
Subtotal (95% CI)		**406**		**407**	**21.2%**	**0.94 [0.70 , 1.25]**
Total events:	72		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**1595**		**1589**	**100.0%**	**0.86 [0.75 , 0.98]**
Total events:	313		362			
Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%						



Risk of bias legend
(A) Bias arising from the randomization process
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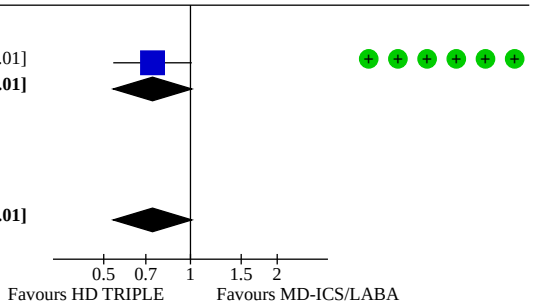
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.3. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 3: HD TRIPLE vs MD-ICS/LABA

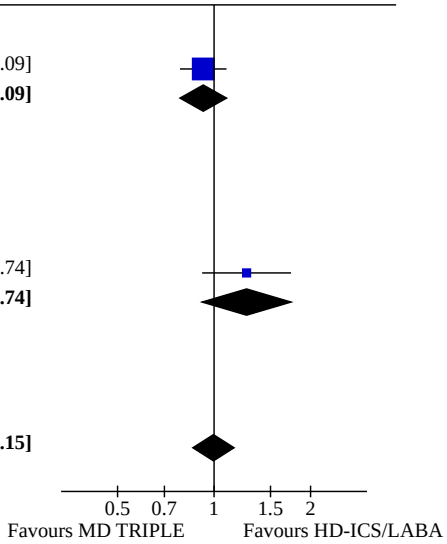
Study or Subgroup	HD TRIPLE Events	HD TRIPLE Total	MD-ICS/LABA Events	MD-ICS/LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 Low Risk						
Lee 2020	57	408	77	407	100.0%	0.74 [0.54 , 1.01]
Subtotal (95% CI)		**408**		**407**	**100.0%**	**0.74 [0.54 , 1.01]**
Total events:	57		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
Total (95% CI)		**408**		**407**	**100.0%**	**0.74 [0.54 , 1.01]**
Total events:	57		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

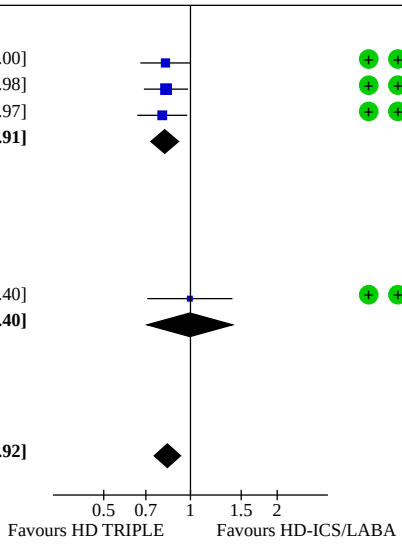
Analysis 7.4. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 4: MD TRIPLE vs HD-ICS/LABA

Study or Subgroup	MD TRIPLE Events	MD TRIPLE Total	HD-ICS/LABA Events	HD-ICS/LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 High Risk						
Kerstjens 2020	151	616	324	1223	79.2%	0.93 [0.78 , 1.09]
Subtotal (95% CI)		**616**		**1223**	**79.2%**	**0.93 [0.78 , 1.09]**
Total events:	151		324			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
7.4.2 Low Risk						
Lee 2020	72	406	57	406	20.8%	1.26 [0.92 , 1.74]
Subtotal (95% CI)		**406**		**406**	**20.8%**	**1.26 [0.92 , 1.74]**
Total events:	72		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**1022**		**1629**	**100.0%**	**1.00 [0.86 , 1.15]**
Total events:	223		381			
Heterogeneity: Chi² = 2.88, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Test for subgroup differences: Chi² = 2.87, df = 1 (P = 0.09), I² = 65.1%						



Analysis 7.5. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 5: HD TRIPLE vs HD-ICS/LABA

Study or Subgroup	HD TRIPLE Events	HD TRIPLE Total	HD-ICS/LABA Events	HD-ICS/LABA Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
7.5.1 High Risk							
Kerstjens 2012	122	454	149	454	25.3%	0.82 [0.67 , 1.00]	+ + + + + +
Kerstjens 2020	134	615	324	1223	36.8%	0.82 [0.69 , 0.98]	+ + + + + +
Virchow 2019b	166	859	138	570	28.2%	0.80 [0.65 , 0.97]	+ + + + + +
Subtotal (95% CI)		**1928**		**2247**	**90.3%**	**0.81 [0.73 , 0.91]**	
Total events:	422		611				
Heterogeneity: Chi² = 0.05, df = 2 (P = 0.97); I² = 0%							
Test for overall effect: Z = 3.65 (P = 0.0003)							
7.5.2 Low Risk							
Lee 2020	57	408	57	406	9.7%	1.00 [0.71 , 1.40]	+ + + + + +
Subtotal (95% CI)		**408**		**406**	**9.7%**	**1.00 [0.71 , 1.40]**	
Total events:	57		57				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.03 (P = 0.98)							
Total (95% CI)		**2336**		**2653**	**100.0%**	**0.83 [0.75 , 0.92]**	
Total events:	479		668				
Heterogeneity: Chi² = 1.27, df = 3 (P = 0.74); I² = 0%							
Test for overall effect: Z = 3.44 (P = 0.0006)							
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.5%							

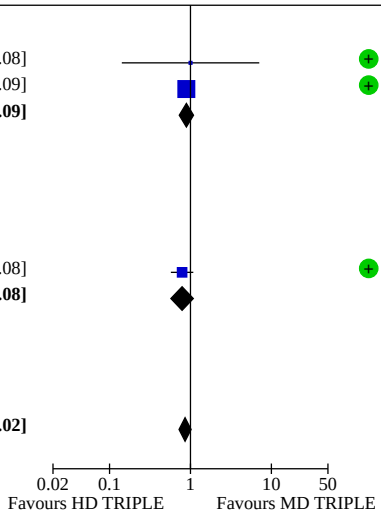


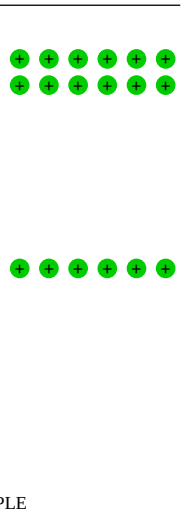
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.6. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 6: HD TRIPLE vs MD TRIPLE

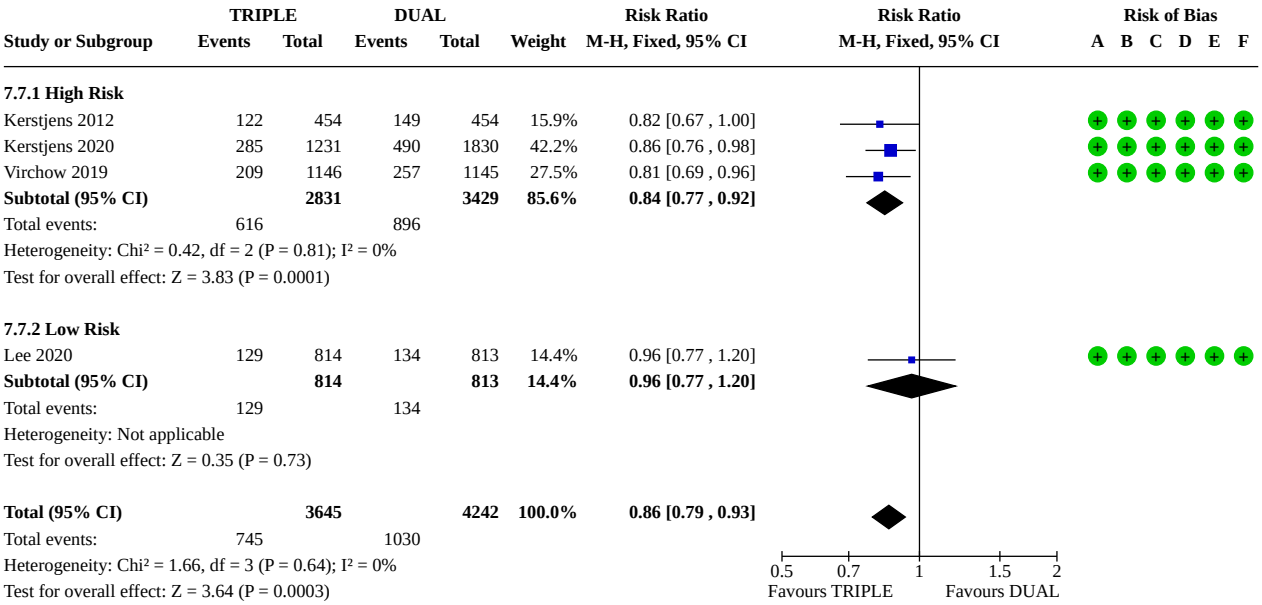
Study or Subgroup	HD TRIPLE Events	HD TRIPLE Total	MD TRIPLE Events	MD TRIPLE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.6.1 High Risk						
Gessner 2020	2	475	2	476	0.9%	1.00 [0.14 , 7.08]
Kerstjens 2020	134	615	151	616	67.0%	0.89 [0.72 , 1.09]
Subtotal (95% CI)		**1090**		**1092**	**67.9%**	**0.89 [0.73 , 1.09]**
Total events:	136		153			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
7.6.2 Low Risk						
Lee 2020	57	408	72	406	32.1%	0.79 [0.57 , 1.08]
Subtotal (95% CI)		**408**		**406**	**32.1%**	**0.79 [0.57 , 1.08]**
Total events:	57		72			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
Total (95% CI)		**1498**		**1498**	**100.0%**	**0.86 [0.72 , 1.02]**
Total events:	193		225			
Heterogeneity: Chi² = 0.41, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%						





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.7. Comparison 7: Moderate to severe exacerbations (high and low risk subgroups), Outcome 7: TRIPLE vs DUAL



Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Study characteristics of included trials

Study, year	Arms included Dose in micrograms	Duration (weeks)	No. of participants included	Mean age	Male (%)	White (%)	Current smoker excluded/ maximum PYs allowed for ex-smokers	Baseline FEV1 (L) prebronchodilator (% predicted)	History of at least one asthma exacerbation
Bernstein 2011	MF/FM 200/10 bid	12	371	44.8	87	87	Y/10	2.3 (74)	Not required
	FP/SAL 250/50 bid		351	45.1	86	86		2.4 (74)	
Bernstein 2015	FF/VI 100/25 qd	12	346	44.7	41	89	Y/10	2.0 (63)	Not required
	FF/VI 200/25 qd		346	45.9	35	87		2.0 (62)	
Bodzenta-Lukaszyk 2012	FP/FM 250/10 bid	12	140	49.8	37	96	Y/10	NR (65)	Not required
	BUD/FM 400/12 bid		139	48.1	27	96		NR (64)	
Busse 2008	BUD/FM 320/9 bid	24	427	39.4	34	82	N/20	2.5 (79)	Not required
	FP/SAL 250/50 bid		406	38.8	43	84		2.6 (78)	
Cukier 2013	FP/FM 250/12 bid	12	97	34.5	24	67	Y/10	2.5 (86)	Not required
	BUD/FM 400/12 bid		99	35.6	27	72		2.5 (85)	
Gessner 2020	MF/GLY/IND 80/50/150 qd	24	474	51.9	35	85	N/20	NR (63)	Required
	MF/GLY/IND 160/50/150 qd		476	52.7	39	82		NR (62)	
	FP/SAL 500/50 bid + Tio 5 qd		476	53.1	36	82		NR(63)	
Kerstjens 2012a	HD-ICS/LABA	48	237	52.9	38	84	Y/10	1.6 (55)	Required
	HD-ICS/LABA+Tio 5 qd		222	53.9	36	84		1.6 (55)	
Kerstjens 2012b	HD-ICS/LABA	48	219	51.4	42	80	Y/10	1.7 (55)	Required

Table 1. Study characteristics of included trials *(Continued)*

	HD-ICS/LABA+Tio 5 qd		234	53.6	42	84		1.6 (55)	
Kerstjens 2020	MF/GLY/IND 80/50/150 qd	52	620	52.4	42	74	Y/10	1.6 (54)	Required
	MF/GLY/IND 160/50/150 qd		619	52.1	38	74		1.6 (55)	
	MF/IND 160/150 qd		617	51.8	39	73		1.6 (55)	
	MF/IND 320/150 qd		618	52.0	39	73		1.6 (54)	
	FP/SAL 500/50 bid		618	52.9	33	76		1.6 (55)	
Lee 2020	FF/VI 100/25 qd	24-52	407	53.3	38	80	Y/10	1.7 (58)	Not required
	FF/UMEC/VI 100/62.5/25 qd		406	52.9	39	83		1.8 (59)	
	FF/VI 200/25 qd		406	53.9	38	78		1.7 (59)	
	FF/UMEC/VI 200/62.5/25 qd		408	53.7	37	80		1.7 (59)	
Mansfield 2017	FP/SAL 250/50 bid	26	41	45.9	51	78	Y/10	2.4 (NR)	Not required
	FP/SAL 200/12.5 bid		133	46.1	46	71		2.3 (NR)	
	FP/SAL 500/50 bid		44	45.6	48	70		2.5 (NR)	
Papi 2007	BDP/FM 200/12 bid	12	115	47.3	45	NR	Y/10	2.1 (68)	Not required
	FP/SAL 250/50 bid		113	49.7	43			2.0 (67)	
Peters 2008	BUD/FM 640/18 bid	52	443	41.0	37	87	Y/20	2.4 (75)	Not required
	BUD/FM 320/9 bid		132	38.6	41	89		2.4 (72)	
Stempel 2016	FP/SAL 250/50 bid	26	580	43.4	34	75	Y/10	NR (PEF>=50%)	Required
	FP/SAL 500/50 bid		982	43.4	34	75			
van Zyl-Smit 2020	MF/IND 320/150 qd	26-52	445	47.1	41	70	Y/10	2.1 (67)	Not required
	MF/IND 160/150 qd		439	47.4	42	71		2.1 (67)	

Table 1. Study characteristics of included trials *(Continued)*

	FP/SAL 500/50 bid		446	48.9	43	68		2.1 (67)	
Virchow 2019a	BDP/FM/G 200/12/20 bid	26-52	576	52.6	38	100	Y/10	1.7 (55)	Required
	BDP/FM 200/12 bid		574	52.5	39	100		1.7 (56)	
Virchow 2019b	BDP/FM/GLY 400/12/20 bid	26-52	571	53.1	37	100	Y/10	1.6 (52)	Required
	BDP/FM 400/12 bid		573	54.0	43	100		1.6 (52)	
	BDP/FM 400/12 bid +Tio 5 qd		287	51.6	36	100		1.6 (52)	
Weinstein 2010	MF/FM 200/10 bid	12	233	48.4	42	90	Y/10	2.1 (67)	Not required
	MF/FM 400/10 bid		255	47.7	46	89		2.0 (66)	
Woodcock 2013	FF/VI 100/25 qd	24	403	43.8	39	60	Y/10	2.0 (68)	Not required
	FP/SAL 250/50 bid		403	41.9	39	58		2.0 (69)	

Abbreviations: bid= twice daily; BDP= beclomethasone dipropionate; BUD=budesonide; FEV1= forced expiratory volume in 1 second; FF=fluticasone furoate; FM=formoterol; FP=fluticasone propionate; GLY= glycopyrronium; IND=indacaterol; MF=mometasone furoate; NR= not reported; PEF=peak flow; PY= pack-year; qd=once daily; SAL=salmeterol; Tio=tiotropium; UMEC= umeclidinium; VI=vilanterol.

Table 2. Study characteristics of participants across the treatment groups for clinical heterogeneity assessment

Treatment arm	No. of participants included	Mean age	Male %	White %	Maximum pack years allowed for smokers	Baseline FEV1 % predicted	History asthma exacerbation (%)
MD-ICS/LABA	3502	48.4	39	82	10	60.3	33
HD-ICS/LABA	5377	51.2	40	83	10	63.8	60
MD TRIPLE	2652	52.5	39	88	10-20	57.0	85
HD TRIPLE	4151	52.8	37	88	10-20	55.9	90

FEV1: forced expiratory volume in 1 second; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta2 agonist; MD: medium dose.

Table 3. Node-splitting results for severe exacerbations

Model	*p*	Mean LHR (95% CrI)
MD Triple vs. HD-ICS/LABA		
Direct	0.717	0.091 (-0.928, 0.995)
Indirect		0.328 (-0.785, 1.422)
Network		0.184 (-0.586, 0.930)
HD Triple vs. MD-ICS/LABA		
Direct	0.492	-0.189 (-1.519, 0.912)
Indirect		0.250 (-0.606, 1.124)
Network		0.131 (-0.621, 0.880)
HD Triple vs. MD Triple		
Direct	0.506	-0.700 (-2.004, 0.392)
Indirect		-0.261 (-1.234, 0.694)
Network		-0.416 (-1.235, 0.414)

Negative valued LHR favours the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LHR: log hazard ratio; MD: medium dose.

Table 4. Hazard ratio for severe exacerbations (fixed-effect model).

	Median HR (95% CrI)		
Comparison	**Overall**	**High Risk**	**Low Risk**
HD-ICS/LABA vs MD-ICS/LABA	1.43 (0.76, 2.77)	13.41 (2.04, 191.20)*	0.76 (0.33, 1.80)

Table 4. Hazard ratio for severe exacerbations (fixed-effect model). *(Continued)*

MD Triple vs. MD-ICS/LABA	1.73 (0.90, 3.32)	1.89 (0.80, 4.47)	1.03 (0.36, 2.78)
HD Triple vs MD-ICS/LABA	1.14 (0.54, 2.41)	11.77 (1.61, 169.90)*	0.56 (0.14, 1.79)
MD Triple vs. HD-ICS/LABA	1.20 (0.56, 2.53)	0.14 (0.01, 1.14)	1.34 (0.45, 3.87)
HD Triple vs HD-ICS/LABA	0.79 (0.48, 1.29)	0.85 (0.49, 1.48)	0.73 (0.18, 2.45)
HD Triple vs MD Triple	0.66 (0.29, 1.51)	6.23 (0.70, 104.30)*	0.55 (0.14, 1.85)

The second named treatment is the baseline intervention. Hazard ratio less than one favours the first named treatment. *HRs are extremely uncertain due to network sparsity and should be treated with caution. CrI: credible interval; HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 5. Mean and median ranking for severe exacerbations sorted by mean rank (fixed-effect model).

	Overall			High Risk Subgroup			Low Risk Subgroup		
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**	**Mean Rank**	**Median Rank**	**95% CrI**	**Mean Rank**	**Median Rank**	**95% CrI**
MD-ICS/LABA	1.55	1.0	(1.0, 3.0)	1.077	1.0	(1.0, 2.0)	3.05	3.0	(1.0, 4.0)
HD Triple	1.97	2.0	(1.0, 4.0)	3.223	3.0	(2.0, 4.0)	1.64	1.0	(1.0, 4.0)
HD-ICS/LABA	3.01	3.0	(1.0, 4.0)	3.679	4.0	(3.0, 4.0)	2.25	2.0	(1.0, 4.0)
MD Triple	3.47	4.0	(1.0, 4.0)	2.021	2.0	(1.0, 4.0)	3.06	3.0	(1.0, 4.0)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 6. Thresholds for severe exacerbations

	Lower Threshold		Upper Threshold	
Comparison	**New Optimal Treatment**	**Change in lnHR**	**New Optimal Treatment**	**Change in lnHR**
HD-ICS/LABA vs. MD-ICS/LABA	HD Triple	-0.220	N/A	Inf
MD Triple vs. MD-ICS/LABA	HD Triple	-0.481	N/A	Inf
HD Triple vs. MD-ICS/LABA	HD Triple	-0.958	N/A	Inf
MD Triple vs. HD-ICS/LABA	MD Triple	-3.574	HD Triple	1.190
HD Triple vs. HD-ICS/LABA	HD Triple	-0.186	HD-ICS/LABA	2.013
HD Triple vs. MD Triple	HD Triple	-0.807	MD Triple	4.990

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; Inf= Infinity; lnHR=log hazard ratio; LABA: long-acting beta-2 agonist; MD: medium dose; N/A= Not Applicable.

Table 7. Hazard ratio for severe exacerbations for individual treatments (fixed-effect model)

Comparison	Median HR (95% CrI)
BUD/FM 320 vs. FP/SAL 250	0.40 (0.01, 5.33)
FF/VI 100 vs. FP/SAL 250	0.38 (0.01, 4.50)
MF/IND 160 vs. FP/SAL 250	3.00 (0.06, 78.87)*
FP/FM 250 vs. FP/SAL 250	0.07 (0.0001, 5.64)
FP/SAL 200 vs. FP/SAL 250	9.34 (0.59, 464.10)*
FP/SAL 500 vs. FP/SAL 250	6.92 (1.61, 80.79)*
BUD/FM 640 vs. FP/SAL 250	0.11 (0.002, 3.51)
FF/VI 200 vs. FP/SAL 250	0.26 (0.01, 4.13)
MF/IND 320 vs. FP/SAL 250	11.70 (1.00, 237.80)*
MF/GLY/IND 80 vs. FP/SAL 250	5.77 (0.10, 170.20)*
FF/UMEC/VI 100 vs. FP/SAL 250	0.37 (0.010, 5.52)
MF/GLY/IND 160 vs. FP/SAL 250	7.10 (1.17, 93.56)*
FF/UMEC/VI 200 vs. FP/SAL 250	0.20 (0.005, 3.24)
FF/VI 100 vs. BUD/FM 320	0.94 (0.012, 62.44)*
MF/IND 160 vs. BUD/FM 320	7.87 (0.06, 812.80)*

Table 7. Hazard ratio for severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

FP/FM 250 vs. BUD/FM 320	0.20 (0.0004, 5.64)
FP/SAL 200 vs. BUD/FM 320	26.98 (0.53, 3628)*
FP/SAL 500 vs. BUD/FM 320	19.87 (0.88, 1034)*
BUD/FM 640 vs. BUD/FM 320	0.29 (0.03, 2.82)
FF/VI 200 vs. BUD/FM 320	0.64 (0.007, 50.68)*
MF/IND 320 vs. BUD/FM 320	32.17 (0.84, 2463)*
MF/GLY/IND 80 vs. BUD/FM 320	14.87 (0.11, 1687)*
FF/UMEC/VI 100 vs. BUD/FM 320	0.92 (0.01, 70.48)*
MF/GLY/IND 160 vs. BUD/FM 320	19.92 (0.74, 1124)*
FF/UMEC/VI 200 vs. BUD/FM 320	0.49 (0.006, 38.79)
MF/IND 160 vs. FF/VI 100	8.54 (0.08, 785.50)*
FP/FM 250 vs. FF/VI 100	0.18 (0.0002, 46.45)
FP/SAL 200 vs. FF/VI 100	28.91 (0.60, 3650)*
FP/SAL 500 vs. FF/VI 100	21.04 (0.93, 1036)*
BUD/FM 640 vs. FF/VI 100	0.32 (0.003, 39.12)
FF/VI 200 vs. FF/VI 100	0.69 (0.20, 2.21)
MF/IND 320 vs. FF/VI 100	34.58 (0.84, 2500)*
MF/GLY/IND 80 vs. FF/VI 100	16.25 (0.13, 1628)*
FF/UMEC/VI 100 vs. FF/VI 100	0.99 (0.34, 2.93)
MF/GLY/IND 160 vs. FF/VI 100	21.23 (0.79, 1173)*
FF/UMEC/VI 200 vs. FF/VI 100	0.54 (0.14,1.84)
FP/FM 250 vs. MF/IND 160	0.02 (0.00001, 8.51)
FP/SAL 200 vs. MF/IND 160	3.35 (0.09, 372.80)*
FP/SAL 500 vs. MF/IND 160	2.41 (0.20, 100.10)*
BUD/FM 640 vs. MF/IND 160	0.04 (0.0002, 8.01)
FF/VI 200 vs. MF/IND 160	0.08 (0.0007, 10.23)
MF/IND 320 vs. MF/IND 160	3.79 (0.41, 147.00)*
MF/GLY/IND 80 vs. MF/IND 160	1.89 (0.80, 4.47)

Table 7. Hazard ratio for severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

FF/UMEC/VI 100 vs. MF/IND 160	0.12 (0.001, 14.12)
MF/GLY/IND 160 vs. MF/IND 160	2.45 (0.17, 109.20)*
FF/UMEC/VI 200 vs. MF/IND 160	0.06 (0.0006, 8.22)
FP/SAL 200 vs. FP/FM 250	170.90 (0.74, 284800)*
FP/SAL 500 vs. FP/FM 250	121.20 (0.98, 127600)*
BUD/FM 640 vs. FP/FM 250	1.61 (0.03, 949.80)*
FF/VI 200 vs. FP/FM 250	3.81 (0.01, 5159)*
MF/IND 320 vs. FP/FM 250	200.60 (1.10, 272600)*
MF/GLY/IND 80 vs. FP/FM 250	91.20 (0.21, 145100)*
FF/UMEC/VI 100 vs. FP/FM 250	5.51 (0.02, 7370)*
MF/GLY/IND 160 vs. FP/FM 250	122.10 (0.86, 136600)*
FF/UMEC/VI 200 vs. FP/FM 250	2.96 (0.01, 4057)*
FP/SAL 500 vs. FP/SAL 200	**0.82 (0.03, 8.69)**
BUD/FM 640 vs. FP/SAL 200	0.01 (0.0001, 1.03)
FF/VI 200 vs. FP/SAL 200	0.02 (0.0002, 1.38)
MF/IND 320 vs. FP/SAL 200	1.25 (0.03, 30.15)
MF/GLY/IND 80 vs. FP/SAL 200	0.56 (0.005, 23.05)
FF/UMEC/VI 100 vs. FP/SAL 200	0.03 (0.0002, 1.91)
MF/GLY/IND 160 vs. FP/SAL 200	0.81 (0.03, 10.71)
FF/UMEC/VI 200 vs. FP/SAL 200	0.02 (0.0001, 1.13)
BUD/FM 640 vs. FP/SAL 500	**0.01 (0.0002, 0.71)**
FF/VI 200 vs. FP/SAL 500	**0.03 (0.001, 0.93)**
MF/IND 320 vs. FP/SAL 500	1.57 (0.24, 12.53)
MF/GLY/IND 80 vs. FP/SAL 500	0.77 (0.02, 10.92)
FF/UMEC/VI 100 vs. FP/SAL 500	0.05 (0.001, 1.26)
MF/GLY/IND 160 vs. FP/SAL 500	1.00 (0.37, 2.68)
FF/UMEC/VI 200 vs. FP/SAL 500	**0.02 (0.0004, 0.73)**
FF/VI 200 vs. BUD/FM 640	2.15 (0.01, 299.50)*

Table 7. Hazard ratio for severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

MF/IND 320 vs. BUD/FM 640	112.30 (1.463, 15230)*
MF/GLY/IND 80 vs. BUD/FM 640	51.28 (0.23, 9561)*
FF/UMEC/VI 100 vs. BUD/FM 640	3.09 (0.02, 410.20)*
MF/GLY/IND 160 vs. BUD/FM 640	69.57 (1.25, 6911)*
FF/UMEC/VI 200 vs. BUD/FM 640	1.66 (0.01, 228.10)*
MF/IND 320 vs. FF/VI 200	51.33 (1.03, 4278)*
MF/GLY/IND 80 vs. FF/VI 200	23.70 (0.17, 2801)*
FF/UMEC/VI 100 vs. FF/VI 200	1.43 (0.44,4.97)
MF/GLY/IND 160 vs. FF/VI 200	31.90 (0.94, 2048)*
FF/UMEC/VI 200 vs. FF/VI 200	0.78 (0.18, 3.10)
MF/GLY/IND 80 vs. MF/IND 320	0.49 (0.01, 5.52)
FF/UMEC/VI 100 vs. MF/IND 320	0.03 (0.0003, 1.39)
MF/GLY/IND 160 vs. MF/IND 320	0.64 (0.06, 5.34)
FF/UMEC/VI 200 vs. MF/IND 320	**0.02 (0.0002, 0.80)**
FF/UMEC/VI 100 vs. MF/GLY/IND 80	0.06 (0.0005, 8.15)
MF/GLY/IND 160 vs. MF/GLY/IND 80	1.31 (0.08, 62.71)*
FF/UMEC/VI 200 vs. MF/GLY/IND 80	0.03 (0.0003, 4.74)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	21.94 (0.68, 1362)*
FF/UMEC/VI 200 vs. FF/UMEC/VI 100	0.55 (0.14, 1.89)
FF/UMEC/VI 200 vs. MF/GLY/IND/160	**0.02 (0.0004, 0.85)**

The second named treatment is the baseline intervention. Hazard ratio less than one favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. *HRs are extremely uncertain due to network sparsity and should be interpreted with caution. BUD=budesonide, CrI=Credible Interval, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY=glycopyrronium, HR=hazard ratio, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, UMEC= umeclidinium, VI=vilanterol.

Table 8. Mean and median ranking for individual treatments for severe exacerbations sorted by mean rank (fixed-effect model).

Treatments	Mean Rank	Median Rank	95% CrI
FP/FM 250	3.24	2.0	(1.0, 11.0)
BUD/FM 640	3.49	2.0	(1.0, 10.0)
FF/UMEC/VI 200	3.71	3.0	(1.0, 9.0)

Table 8. Mean and median ranking for individual treatments for severe exacerbations sorted by mean rank (fixed-effect model). *(Continued)*

FF/VI 200	4.42	4.0	(1.0, 10.0)
BUD/FM 320	5.62	6.0	(2.0, 11.0)
FF/VI 100	5.64	5.0	(2.0, 11.0)
FF/UMEC/VI 100	5.64	5.0	(2.0, 11.0)
FP/SAL 250	7.31	8.0	(3.0, 10.0)
MF/IND 160	8.70	9.0	(1.0, 13.0)
MF/GLY/IND 80	10.60	11.0	(3.0, 14.0)
MF/GLY/IND 160	11.36	11.0	(8.0, 14.0)
FP/SAL 500	11.41	12.0	(9.0, 14.0)
FP/SAL 200	11.59	12.0	(6.0, 14.0)
MF/IND 320	12.27	13.0	(8.0, 14.0)

BUD=budesonide, CrI=Credible Interval, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, UMEC= umeclidinium, VI=vilanterol

Table 9. Node-splitting results for moderate to severe exacerbations for grouped treatments.

Overall			**High Risk Subgroup**		
Model	***p***	**Mean LHR (95% CrI)**	**Model**	***p***	**Mean LHR (95% CrI)**
HD-ICS/LABA vs. MD-ICS/LABA			*HD-ICS/LABA vs. MD-ICS/LABA*		
Direct	0.556	-0.100 (-0.318, 0.118)	Direct	0.616	-0.043 (-0.705, 0.639)
Indirect		-0.268 (-0.858, 0.289)	Indirect		-0.250 (-1.361, 0.706)
Network		-0.120 (-0.303, 0.059)	Network		-0.087 (-0.456, 0.236)
MD Triple vs. MD-ICS/LABA			*MD Triple vs. MD-ICS/LABA*		
Direct	0.439	-0.192 (-0.409, 0.020)	Direct	0.505	-0.302 (-0.987, 0.365)
Indirect		0.368 (-1.196, 1.931)	Indirect		-0.574 (-1.654, 0.325)

Table 9. Node-splitting results for moderate to severe exacerbations for grouped treatments. *(Continued)*

Network		-0.177 (-0.376, 0.026)	Network		-0.369 (-0.748, -0.046)
HD Triple vs. MD-ICS/LABA			NA		
Direct	0.574	-0.324 (-0.650, -0.007)	Direct	NA	NA
Indirect		-0.460 (-0.885, -0.039)	Indirect		NA
Network		-0.377 (-0.581, -0.168)	Network		NA
MD Triple vs. HD-ICS/LABA			*MD Triple vs. HD-ICS/LABA*		
Direct	0.313	0.019 (-0.254, 0.341)	Direct	0.803	-0.108 (-0.790, 0.582)
Indirect		-0.244 (-0.704, 0.255)	Indirect		-0.208 (-1.016, 0.892)
Network		-0.059 (-0.255, 0.162)	Network		-0.140 (-0.457, 0.218)
HD Triple vs. HD-ICS/LABA			NA		
Direct	0.413	-0.238 (-0.418, -0.047)	Direct	NA	NA
Indirect		-0.858 (-2.616, 0.627)	Indirect		NA
Network		-0.258 (-0.421, -0.085)	Network		NA
HD Triple vs. MD Triple			NA		
Direct	0.573	-0.221 (-0.526, 0.053)	Direct	NA	NA
Indirect		-0.061 (-0.604, 0.490)	Indirect		NA
Network		-0.199 (-0.430, 0.017)	Network		NA

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LHR: log hazard ratio; MD: medium dose; NA: not applicable.

Table 10. Hazard ratio for moderate to severe exacerbations (fixed-effect model)

	Median HR (95% CrI)		
Comparison	**Overall**	**High Risk**	**Low Risk**
HD-ICS/LABA vs MD-ICS/LABA	0.90 (0.77, 1.04)	0.92 (0.76, 1.12)	0.85 (0.67, 1.08)
MD Triple vs. MD-ICS/LABA	**0.84 (0.71, 0.99)**	**0.80 (0.66, 0.97)**	1.01 (0.72, 1.41)
HD Triple vs MD-ICS/LABA	**0.69 (0.58, 0.82)**	**0.70 (0.56, 0.87)**	0.76 (0.53, 1.08)
MD Triple vs. HD-ICS/LABA	0.93 (0.79, 1.10)	0.87 (0.71, 1.06)	1.19 (0.84, 1.66)
HD Triple vs HD-ICS/LABA	**0.77 (0.67, 0.88)**	**0.76 (0.65, 0.88)**	0.89 (0.62, 1.27)
HD Triple vs MD Triple	0.83 (0.69, 1.00)	0.87 (0.70, 1.08)	0.75 (0.51, 1.09)

The second named treatment is the baseline intervention. Hazard ratio less than one favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; HR: hazard ratio; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 11. Mean and median ranking for moderate to severe exacerbations sorted by mean rank (fixed-effect model).

	Overall			High Risk Subgroup			Low Risk Subgroup		
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**	**Mean Rank**	**Median Rank**	**95% CrI**	**Mean Rank**	**Median Rank**	**95% CrI**
HD Triple	1.02	1.0	(1.0, 1.0)	1.11	1.0	(1.0, 2.0)	1.39	1.0	(1.0, 3.0)
MD Triple	2.21	2.0	(2.0, 3.0)	1.98	2.0	(1.0, 3.0)	3.29	4.0	(1.0, 4.0)
HD-ICS/LABA	2.86	3.0	(2.0, 4.0)	3.13	3.0	(2.0, 4.0)	1.98	2.0	(1.0, 4.0)
MD-ICS/LABA	3.91	4.0	(3.0, 4.0)	3.78	4.0	(3.0, 4.0)	3.33	3.0	(2.0, 4.0)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 12. Thresholds and new optimum treatments for moderate to severe exacerbations for grouped treatments.

	Lower Threshold		Upper Threshold	
Comparison	**New Optimal Treatment**	**Change in lnHR**	**New Optimal Treatment**	**Change in lnHR**
HD-ICS/LABA vs. MD-ICS/LABA	HD-ICS/LABA	-1.84	MD-ICS/LABA	0.77
MD Triple vs. MD-ICS/LABA	MD Triple	-0.56	MD-ICS/LABA	1.47
HD Triple vs. MD-ICS/LABA	N/A	-Inf	MD Triple	1.13
MD Triple vs. HD-ICS/LABA	MD Triple	-0.55	HD-ICS/LABA	2.78
HD Triple vs. HD-ICS/LABA	N/A	-Inf	HD-ICS/LABA	0.34
HD Triple vs. MD Triple	N/A	-Inf	MD Triple	0.60

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; Inf= Infinity; LABA: long-acting beta-2 agonist; lnHR: log hazard ratio; MD: medium dose; N/A; not applicable

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model)

Comparison	**Median HR (95% CrI)**
BUD/FM 320 vs. FP/SAL 250	0.93 (0.63, 1.39)
MF/FM 200 vs. FP/SAL 250	0.99 (0.53, 1.85)
FF/VI 100 vs. FP/SAL 250	0.83 (0.34, 1.88)
FP/FM 250 vs. FP/SAL 250	0.83 (0.27, 2.50)
MF/IND 160 vs. FP/SAL 250	6.13 (0.40, 4476)*
BDP/FM 200 vs. FP/SAL 250	0.29 (0.04, 1.23)
FP/SAL 200 vs. FP/SAL 250	9.04 (0.86, 8275)*
FP/SAL 500 vs. FP/SAL 250	6.92 (0.46, 5048)*
BUD/FM 640 vs. FP/SAL 250	0.79 (0.42, 1.55)
FF/VI 200 vs. FP/SAL 250	0.61 (0.24, 1.47)
MF/IND 320 vs. FP/SAL 250	5.04 (0.33, 3714)*
MF/GLY/IND 80 vs. FP/SAL 250	5.45 (0.36, 4034)*
FF/UMEC/VI 100 vs. FP/SAL 250	0.77 (0.31,1.86)
MF/GLY/IND 160 vs. FP/SAL 250	4.71 (0.31, 3491)*
BDP/FM/G 200 vs. FP/SAL 250	**0.21 (0.03, 0.92)**

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

FF/UMEC/VI 200 vs. FP/SAL 250	0.60 (0.23, 1.46)
FP/SAL 500 + Tio vs. FP/SAL 250	1.64 (0.00000, 747.40)*
MF/FM 200 vs. BUD/FM 320	1.06 (0.51, 2.23)
FF/VI 100 vs. BUD/FM 320	0.88 (0.34, 2.21)
FP/FM 250 vs. BUD/FM 320	0.89 (0.31, 2.49)
MF/IND 160 vs. BUD/FM 320	6.60 (0.41, 4954)*
BDP/FM 200 vs. BUD/FM 320	0.30 (0.05, 1.44)
FP/SAL 200 vs. BUD/FM 320	9.68 (0.89, 8950)*
FP/SAL 500 vs. BUD/FM 320	7.46 (0.47, 5555)*
BUD/FM 640 vs. BUD/FM 320	0.85 (0.51, 1.47)
FF/VI 200 vs. BUD/FM 320	0.65 (0.24, 1.72)
MF/IND 320 vs. BUD/FM 320	5.43 (0.34, 4094)*
MF/GLY/IND 80 vs. BUD/FM 320	5.87 (0.37 4445)*
FF/UMEC/VI 100 vs. BUD/FM 320	0.83 (0.30, 2.17)
MF/GLY/IND 160 vs. BUD/FM 320	5.08 (0.32, 3893)*
BDP/FM/G 200 vs. BUD/FM 320	0.22 (0.03, 1.07)
FF/UMEC/VI 200 vs. BUD/FM 320	0.64 (0.23, 1.69)
FP/SAL 500 + Tio vs. BUD/FM 320	1.75 (0.00000, 805.70)*
FF/VI 100 vs. MF/FM 200	0.82 (0.28, 2.33)
FP/FM 250 vs. MF/FM 200	0.83 (0.23, 2.98)
MF/IND 160 vs. MF/FM 200	6.22 (0.37, 4697)*
BDP/FM 200 vs. MF/FM 200	0.28 (0.04, 1.42)
FP/SAL 200 vs. MF/FM 200	9.14 (0.78, 8495)*
FP/SAL 500 vs. MF/FM 200	7.02 (0.42, 5303)*
BUD/FM 640 vs. MF/FM 200	0.80 (0.32, 1.99)
FF/VI 200 vs. MF/FM 200	0.61 (0.20, 1.80)
MF/IND 320 vs. MF/FM 200	5.11 (0.31, 3891)*
MF/GLY/IND 80 vs. MF/FM 200	5.52 (0.33, 4208)*

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

FF/UMEC/VI 100 vs. MF/FM 200	0.77 (0.26, 2.30)
MF/GLY/IND 160 vs. MF/FM 200	4.77 (0.28, 3694)*
BDP/FM/G 200 vs. MF/FM 200	0.21 (0.03, 1.06)
FF/UMEC/VI 200 vs. MF/FM 200	0.60 (0.20, 1.78)
FP/SAL 500 + Tio vs. MF/FM 200	1.64 (0.00000, 729.20)*
FP/FM 250 vs. FF/VI 100	1.02 (0.25, 4.06)
MF/IND 160 vs. FF/VI 100	7.62 (0.43, 6048.00)*
BDP/FM 200 vs. FF/VI 100	0.35 (0.04, 1.89)
FP/SAL 200 vs. FF/VI 100	11.28 (0.92, 10640)*
FP/SAL 500 vs. FF/VI 100	8.62 (0.49, 6794)*
BUD/FM 640 vs. FF/VI 100	0.97 (0.34, 2.90)
FF/VI 200 vs. FF/VI 100	0.74 (0.53, 1.03)
MF/IND 320 vs. FF/VI 100	6.29 (0.36, 5002)*
MF/GLY/IND 80 vs. FF/VI 100	6.78 (0.38, 5449)*
FF/UMEC/VI 100 vs. FF/VI 100	0.94 (0.68, 1.30)
MF/GLY/IND 160 vs. FF/VI 100	5.86 (0.33, 4673)*
BDP/FM/G 200 vs. FF/VI 100	0.26 (0.03, 1.41)
FF/UMEC/VI 200 vs. FF/VI 100	0.72 (0.51, 1.02)
FP/SAL 500 + Tio vs. FF/VI 100	1.98 (0.00000, 915.90)*
MF/IND 160 vs. FP/FM 250	7.65 (0.38, 6227)*
BDP/FM 200 vs. FP/FM 250	0.34 (0.04, 2.28)
FP/SAL 200 vs. FP/FM 250	11.22 (0.79, 10490)*
FP/SAL 500 vs. FP/FM 250	8.65 (0.44, 6995)*
BUD/FM 640 vs. FP/FM 250	0.96 (0.30, 3.16)
FF/VI 200 vs. FP/FM 250	0.73 (0.17, 3.13)
MF/IND 320 vs. FP/FM 250	6.30 (0.32, 5113)*
MF/GLY/IND 80 vs. FP/FM 250	6.79 (0.34, 5448)*
FF/UMEC/VI 100 vs. FP/FM 250	0.93 (0.23, 3.97)

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

MF/GLY/IND 160 vs. FP/FM 250	5.87 (0.30, 4851)*
BDP/FM/G 200 vs. FP/FM 250	0.25 (0.03, 1.69)
FF/UMEC/VI 200 vs. FP/FM 250	0.71 (0.17, 3.07)
FP/SAL 500 + Tio vs. FP/FM 250	1.97 (0.00000, 950.10)*
BDP/FM 200 vs. MF/IND 160	0.04 (0.0001, 1.06)
FP/SAL 200 vs. MF/IND 160	1.48 (0.38, 8.60)
FP/SAL 500 vs. MF/IND 160	1.13 (0.94, 1.36)
BUD/FM 640 vs. MF/IND 160	0.13 (0.0002, 2.20)
FF/VI 200 vs. MF/IND 160	0.10 (0.0001, 1.76)
MF/IND 320 vs. MF/IND 160	0.83 (0.68, 1.01)
MF/GLY/IND 80 vs. MF/IND 160	0.89 (0.72, 1.10)
FF/UMEC/VI 100 vs. MF/IND 160	0.12 (0.0002, 2.23)
MF/GLY/IND 160 vs. MF/IND 160	**0.77 (0.62, 0.96)**
BDP/FM/G 200 vs. MF/IND 160	**0.03 (0.00004, 0.79)**
FF/UMEC/VI 200 vs. MF/IND 160	0.09 (0.0001, 1.73)
FP/SAL 500 + Tio vs. MF/IND 160	0.37 (0.00000, 2.08)
FP/SAL 200 vs. BDP/FM 200	34.04 (1.97, 33480)*
FP/SAL 500 vs. BDP/FM 200	25.58 (1.08, 21010)*
BUD/FM 640 vs. BDP/FM 200	2.83 (0.55, 19.55)
FF/VI 200 vs. BDP/FM 200	2.13 (0.39, 17.16)
MF/IND 320 vs. BDP/FM 200	18.69 (0.78, 15450)*
MF/GLY/IND 80 vs. BDP/FM 200	20.17 (0.84, 16660)*
FF/UMEC/VI 100 vs. BDP/FM 200	2.70 (0.49, 21.82)
MF/GLY/IND 160 vs. BDP/FM 200	17.39 (0.72, 14470)*
BDP/FM/G 200 vs. BDP/FM 200	**0.74 (0.56, 0.97)**
FF/UMEC/VI 200 vs. BDP/FM 200	2.08 (0.38, 17.12)
FP/SAL 500 + Tio vs. BDP/FM 200	5.82 (0.00000, 3115)*
FP/SAL 500 vs. FP/SAL 200	0.76 (0.13, 2.92)

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

BUD/FM 640 vs. FP/SAL 200	0.09 (0.0001, 1.05)
FF/VI 200 vs. FP/SAL 200	**0.07 (0.0001, 0.82)**
MF/IND 320 vs. FP/SAL 200	0.56 (0.10, 2.16)
MF/GLY/IND 80 vs. FP/SAL 200	0.60 (0.10, 2.35)
FF/UMEC/VI 100 vs. FP/SAL 200	0.08 (0.0001, 1.04)
MF/GLY/IND 160 vs. FP/SAL 200	0.52 (0.09, 2.02)
BDP/FM/G 200 vs. FP/SAL 200	**0.02 (0.00002, 0.38)**
FF/UMEC/VI 200 vs. FP/SAL 200	**0.06 (0.0001, 0.80)**
FP/SAL 500 + Tio vs. FP/SAL 200	0.21 (0.00000, 2.30)
BUD/FM 640 vs. FP/SAL 500	0.11 (0.0002, 1.92)
FF/VI 200 vs. FP/SAL 500	0.09 (0.0001, 1.54)
MF/IND 320 vs. FP/SAL 500	**0.73 (0.60, 0.89)**
MF/GLY/IND 80 vs. FP/SAL 500	**0.79 (0.64, 0.97)**
FF/UMEC/VI 100 vs. FP/SAL 500	0.11 (0.0001, 1.95)
MF/GLY/IND 160 vs. FP/SAL 500	**0.68 (0.55, 0.84)**
BDP/FM/G 200 vs. FP/SAL 500	**0.03 (0.00003, 0.69)**
FF/UMEC/VI 200 vs. FP/SAL 500	0.08 (0.0001, 1.51)
FP/SAL 500 + Tio vs. FP/SAL 500	0.33 (0.00000, 1.84)
FF/VI 200 vs. BUD/FM 640	0.76 (0.25, 2.29)
MF/IND 320 vs. BUD/FM 640	6.42 (0.38, 5053)*
MF/GLY/IND 80 vs. BUD/FM 640	6.95 (0.40, 5493)*
FF/UMEC/VI 100 vs. BUD/FM 640	0.97 (0.31, 2.92)
MF/GLY/IND 160 vs. BUD/FM 640	6.00 (0.35, 4786)*
BDP/FM/G 200 vs. BUD/FM 640	0.26 (0.04, 1.37)
FF/UMEC/VI 200 vs. BUD/FM 640	0.75 (0.24, 2.24)
FP/SAL 500 + Tio vs. BUD/FM 640	2.04 (0.00000, 958.30)*
MF/IND 320 vs. FF/VI 200	8.53 (0.47, 6736)*
MF/GLY/IND 80 vs. FF/VI 200	9.18 (0.51, 7364)*

Table 13. Hazard ratio for moderate to severe exacerbations for individual treatments (fixed-effect model) *(Continued)*

FF/UMEC/VI 100 vs. FF/VI 200	1.27 (0.90, 1.80)
MF/GLY/IND 160 vs. FF/VI 200	7.95 (0.44, 6432)*
BDP/FM/G 200 vs. FF/VI 200	0.34 (0.04, 1.92)
FF/UMEC/VI 200 vs. FF/VI 200	0.98 (0.68, 1.41)
FP/SAL 500 + Tio vs. FF/VI 200	2.68 (0.00000, 1223)*
MF/GLY/IND 80 vs. MF/IND 320	1.08 (0.86, 1.35)
FF/UMEC/VI 100 vs. MF/IND 320	0.15 (0.0002, 2.69)
MF/GLY/IND 160 vs. MF/IND 320	0.93 (0.74, 1.17)
BDP/FM/G 200 vs. MF/IND 320	**0.04 (0.0001, 0.94)**
FF/UMEC/VI 200 vs. MF/IND 320	0.11 (0.0001, 2.09)
FP/SAL 500 + Tio vs. MF/IND 320	0.45 (0.00000, 2.53)
FF/UMEC/VI 100 vs. MF/GLY/IND 80	0.14 (0.0002, 2.50)
MF/GLY/IND 160 vs. MF/GLY/IND 80	0.86 (0.69, 1.09)
BDP/FM/G 200 vs. MF/GLY/IND 80	**0.04 (0.00004, 0.88)**
FF/UMEC/VI 200 vs. MF/GLY/IND 80	0.11 (0.0001, 1.95)
FP/SAL 500 + Tio vs. MF/GLY/IND 80	0.41 (0.00000, 2.33)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	6.25 (0.35, 4959)*
BDP/FM/G 200 vs. FF/UMEC/VI 100	0.27 (0.03, 1.52)
FF/UMEC/VI 200 vs. FF/UMEC/VI 100	0.77 (0.54, 1.10)
FP/SAL 500 + Tio vs. FF/UMEC/VI 100	2.12 (0.00000, 969)*
BDP/FM/G 200 vs. MF/GLY/IND 160	0.04 (0.0001, 1.03)
FF/UMEC/VI 200 vs. MF/GLY/IND 160	0.12 (0.0002, 2.26)
FP/SAL 500 + Tio vs. MF/GLY/IND 160	0.48 (0.00000, 2.70)
FF/UMEC/VI 200 vs. BDP/FM/G 200	2.82 (0.50, 23.33)
FP/SAL 500 + Tio vs. BDP/FM/G 200	7.86 (0.00000, 4308)*
FP/SAL 500 + Tio vs. FF/UMEC/VI 200	2.74 (0.00000, 1260)*

The second named treatment is the baseline intervention. Hazard Ratio less than one favours the first named treatment. Treatment comparisons in bold do not include the “null” effect. *HRs are extremely uncertain due to network sparsity and should be treated with caution. Abbreviations**:** BUD=budesonide, CrI= credible interval, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY=

glycopyrronium, HR=hazard ratio, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Table 14. Mean and median ranking for individual treatments for moderate to severe exacerbations (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
BDP/FM/G 200	1.96	1.0	(1.0, 9.0)
BDP/FM 200	3.51	2.0	(2.0, 11.0)
FF/UMEC/VI 200	5.03	4.0	(1.0, 12.0)
FF/VI 200	5.24	5.0	(1.0, 12.0)
BUD/FM 640	7.42	7.0	(2.0, 16.0)
FF/UMEC/VI 100	7.78	7.0	(3.0, 16.0)
FP/FM 250	7.87	8.0	(1.0, 17.0)
FF/VI 100	8.44	8.0	(4.0, 16.0)
BUD/FM 320	8.91	9.0	(4.0, 16.0)
FP/SAL 500 + Tio	9.00	12.0	(1.0, 18.0)
MF/FM 200	9.32	10.0	(3.0, 17.0)
FP/SAL 250	9.65	10.0	(5.0, 16.0)
MF/GLY/IND 160	12.14	13.0	(3.0, 15.0)
MF/IND 320	12.92	14.0	(4.0, 16.0)
MF/GLY/IND 80	13.87	15.0	(5.0, 17.0)
MF/IND 160	15.21	16.0	(7.0, 18.0)
FP/SAL 200	16.32	18.0	(11.0, 18.0)
FP/SAL 500	16.41	17.0	(8.0, 18.0)

BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, UMEC= umeclidinium, VI=vilanterol.

Table 15. Mean difference for change from baseline in ACQ scores at 3 months

Comparison	Median Mean Difference (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	0.008 (-0.053, 0.069)
MD Triple vs. MD-ICS/LABA	-0.056 (-0.141, 0.029)
HD Triple vs MD-ICS/LABA	**-0.094 (-0.178,-0.011)**

Table 15. Mean difference for change from baseline in ACQ scores at 3 months *(Continued)*

MD Triple vs. HD-ICS/LABA	-0.064 (-0.149, 0.022)
HD Triple vs HD-ICS/LABA	**-0.103 (-0.187, -0.018)**
HD Triple vs MD Triple	-0.039 (-0.111, 0.034)

Mean difference less than zero favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 16. Mean and median ranking for change from baseline in ACQ scores at 3 months sorted by mean rank (fixed-effect model).

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.17	1	(1.00, 2.00)
MD Triple	2.02	2	(1.00, 4.00)
MD-ICS/LABA	3.28	3	(2.00, 4.00)
HD-ICS/LABA	3.52	4	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 17. Node-splitting results for change from baseline in ACQ scores at 6 months

Model	*p*	Mean Difference (95% CrI)
MD Triple vs. MD-ICS/LABA		
Direct	0.472	-0.092 (-0.231, 0.047)
Indirect		0.003 (-0.302, 0.283)
Network		-0.071 (-0.173, 0.026)
HD Triple vs. MD-ICS/LABA		
Direct	0.733	-0.108 (-0.229, 0.016)
Indirect		-0.075 (-0.295, 0.128)
Network		-0.103

Table 17. Node-splitting results for change from baseline in ACQ scores at 6 months *(Continued)*

		(-0.204, -0.015)
MD Triple vs. HD-ICS/LABA		
Direct	0.266	-0.007 (-0.115, 0.101)
Indirect		-0.121 (-0.323, 0.077)
Network		-0.038 (-0.135, 0.050)

Mean difference less than zero favours the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 18. Mean difference for change from baseline in ACQ scores at 6 months

Comparison	Median Mean Difference (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	-0.033 (-0.086, 0.019)
MD Triple vs. MD-ICS/LABA	-0.066 (-0.134, 0.001)
HD Triple vs MD-ICS/LABA	**-0.098 (-0.161, -0.034)**
MD Triple vs. HD-ICS/LABA	-0.033 (-0.095, 0.029)
HD Triple vs HD-ICS/LABA	**-0.064 (-0.121, -0.008)**
HD Triple vs MD Triple	-0.031 (-0.092, 0.029)

Mean difference less than zero favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 19. Mean and median ranking for change from baseline in ACQ scores at 6 months sorted by mean rank (fixed effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.17	1	(1.00, 2.00)
MD Triple	2.02	2	(1.00, 3.00)
HD-ICS/LABA	2.95	3	(2.00, 4.00)
MD-ICS/LABA	3.86	4	(3.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 20. Node-splitting results for change from baseline in ACQ scores at 12 months.

Model	*p*	Mean Difference (95% CrI)
HD Triple vs. MD-ICS/LABA		
Direct	0.946	-0.090 (-0.237, 0.074)
Indirect		-0.080 (-0.335, 0.178)
Network		-0.082 (-0.204, 0.042)

Mean differences less than zero favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 21. Mean difference for change from baseline in ACQ scores at 12 months (fixed-effect model)

Comparison	Median Mean Difference (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	-0.003 (-0.063, 0.057)
MD Triple vs. MD-ICS/LABA	0.024 (-0.066, 0.114)
HD Triple vs MD-ICS/LABA	-0.081 (-0.162, 0.001)
MD Triple vs. HD-ICS/LABA	0.027 (-0.056, 0.111)
HD Triple vs HD-ICS/LABA	**-0.077 (-0.148, -0.007)**
HD Triple vs MD Triple	**-0.105 (-0.199, -0.011)**

Mean difference less than zero favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 22. Mean and median ranks for change from baseline in ACQ scores at 12 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.06	1.0	(1.00, 2.00)
HD-ICS/LABA	2.70	3.0	(2.00, 4.00)
MD-ICS/LABA	2.82	3.0	(2.00, 4.00)
MD Triple	3.43	4.0	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 23. Mean difference for change from baseline in AQLQ scores at 6 months (fixed-effect model)

Comparison	Median Mean Difference (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	-0.056 (-0.138, 0.026)
MD Triple vs. MD-ICS/LABA	0.028 (-0.229, 0.287)
HD Triple vs MD-ICS/LABA	0.108 (-0.088, 0.304)
MD Triple vs. HD-ICS/LABA	0.084 (-0.159, 0.330)
HD Triple vs HD-ICS/LABA	0.164 (-0.013, 0.342)
HD Triple vs MD Triple	0.080 (-0.088, 0.247)

Mean difference less than zero favours the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 24. Mean and median ranking for change from baseline in AQLQ scores at 6 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.35	1.00	(1.00, 3.00)
MD Triple	2.49	2.00	(1.00, 4.00)
MD-ICS/LABA	2.54	3.00	(1.00, 4.00)
HD-ICS/LABA	3.63	4.00	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 25. Node-splitting results for CFB in AQLQ scores at 12 months

Model	*p*	Mean Difference (95% CrI)
HD Triple vs. MD-ICS/LABA		
Direct	0.944	0.060 (-0.247, 0.362)
Indirect		0.073 (-0.324, 0.471)
Network		0.053 (-0.126, 0.258)

Mean differences less than zero favour the first named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 26. Mean difference for change from baseline in AQLQ scores at 12 months (fixed-effect model)

Comparison	Median Mean Difference (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	-0.024 (-0.087, 0.039)
MD Triple vs. MD-ICS/LABA	-0.076 (-0.167, 0.016)
HD Triple vs MD-ICS/LABA	0.045 (-0.041, 0.131)
MD Triple vs. HD-ICS/LABA	-0.052 (-0.135, 0.032)
HD Triple vs HD-ICS/LABA	0.069 (-0.006, 0.144)
HD Triple vs MD Triple	**0.121 (0.025, 0.216)**

Mean difference less than zero favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 27. Mean and median ranking for change from baseline in AQLQ scores at 12 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.20	1	(1.00, 3.00)
MD-ICS/LABA	2.12	2	(1.00, 4.00)
HD-ICS/LABA	2.85	3	(2.00, 4.00)
MD Triple	3.83	4	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 28. Node-splitting results for ACQ responders at 6 months for grouped treatments.

Model	*p*	LORs (95% CrI)
HD-ICS/LABA vs. MD-ICS/LABA		
Direct	0.360	0.080 (-0.142, 0.306)
Indirect		-0.14 (-0.664, 0.373)
Network		0.046 (-0.150, 0.236)
MD Triple vs. MD-ICS/LABA		

Table 28. Node-splitting results for ACQ responders at 6 months for grouped treatments. *(Continued)*

Direct	0.402	0.207 (-0.026, 0.441)
Indirect		0.472 (-0.167, 1.117)
Network		0.228 (0.028, 0.432)
HD Triple vs. MD-ICS/LABA		
Direct	0.720	0.247 (-0.114, 0.612)
Indirect		0.156 (-0.327, 0.620)
Network		0.216 (0.005, 0.425)
MD Triple vs. HD-ICS/LABA		
Direct	0.267	0.089 (-0.218, 0.408)
Indirect		0.343 (-0.058, 0.781)
Network		0.183 (-0.020, 0.394)
HD Triple vs. HD-ICS/LABA		
Direct	0.391	0.185 (-0.006, 0.383)
Indirect		-0.077 (-0.718, 0.584)
Network		0.172 (-0.001, 0.343)
HD Triple vs. MD Triple		
Direct	0.359	-0.061 (-0.305, 0.171)
Indirect		0.158

Table 28. Node-splitting results for ACQ responders at 6 months for grouped treatments. *(Continued)*

	(-0.339, 0.672)
Network	-0.011
	(-0.222, 0.188)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR: log odds ratio; MD: medium dose.

Table 29. Odds ratio for ACQ responders at 6 months (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	1.052 (0.919, 1.203)
MD Triple vs. MD-ICS/LABA	**1.248 (1.086, 1.437)**
HD Triple vs MD-ICS/LABA	**1.246 (1.073, 1.446)**
MD Triple vs. HD-ICS/LABA	**1.187 (1.030, 1.370)**
HD Triple vs HD-ICS/LABA	**1.184 (1.054, 1.331)**
HD Triple vs MD Triple	0.998 (0.861, 1.155)

The second named treatment is the baseline intervention. Odds ratio greater than one favours the first named treatment.Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 30. Mean and median ranking for grouped treatments for ACQ responders at 6 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MD Triple	1.50	1	(1.00, 2.00)
HD Triple	1.52	2	(1.00, 2.00)
HD-ICS/LABA	3.22	3	(3.00, 4.00)
MD-ICS/LABA	3.77	4	(3.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 31. Odds ratio for ACQ responders at 6 months for individual treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
FP/SAL 500 vs. MF/IND 160	0.935 (0.785,1.114)
MF/IND 320 vs. MF/IND 160	0.860 (0.677,1.097)
MF/GLY/IND 80 vs. MF/IND 160	1.140 (0.957,1.360)

Table 31. Odds ratio for ACQ responders at 6 months for individual treatments (fixed-effect model) *(Continued)*

MF/GLY/IND 160 vs. MF/IND 160	1.241 (0.974,1.581)
FP/SAL 500 + Tio vs. MF/IND 160	0.919 (0.732,1.157)
MF/IND 320 vs. FP/SAL 500	1.220 (0.998,1.491)
MF/GLY/IND 80 vs. FP/SAL500	**1.327 (1.124,1.568)**
MF/GLY/IND 160 vs. FP/SAL 500	**1.326 (1.029,1.704)**
FP/SAL 500 + Tio vs. FP/SAL 500	**1.443 (1.087,1.913)**
MF/GLY/IND 80 vs. MF/IND 320	1.088 (0.838,1.412)
MF/GLY/IND 160 vs. MF/IND 320	0.935 (0.785,1.114)
FP/SAL 500 + Tio vs. MF/IND 320	0.860 (0.677,1.097)
MF/GLY/IND 160 vs. MF/GLY/IND 80	1.140 (0.957,1.360)
FP/SAL 500 + Tio vs. MF/GLY/IND 80	1.241 (0.974,1.581)
FP/SAL 500 + Tio vs. MF/GLY/IND 160	0.919 (0.732,1.157)

The second named treatment is the baseline intervention. Odds ratio greater than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI=credible interval, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium.

Table 32. Mean and median ranking for individual treatments for ACQ responders at 6 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median	95% CrI
MF/IND 320	1.78	1	(1.00, 4.00)
MF/GLY/IND 80	2.17	2	(1.00, 5.00)
MF/IND 160	3.44	3	(1.00, 6.00)
MF/GLY/IND 160	3.54	4	(1.00, 6.00)
FP/SAL 500	4.89	5	(3.00, 6.00)
FP/SAL 500 + Tio	5.17	6	(1.00, 6.00)

CrI=credible interval, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium.

Table 33. Node-splitting results for ACQ responders at 12 months for grouped treatments

Model	*p*	LOR (95% CrI)

Table 33. Node-splitting results for ACQ responders at 12 months for grouped treatments *(Continued)*

HD Triple vs. MD-ICS/LABA		
Direct	0.804	0.310 (-0.404, 1.018)
Indirect		0.203 (-0.566, 0.960)
Network		0.263 (-0.172, 0.672)
MD Triple vs. HD-ICS/LABA		
Direct	0.412	-0.129 (-0.775, 0.527)
Indirect		0.228 (-0.599, 1.077)
Network		0.014 (-0.408, 0.469)
HD Triple vs. MD Triple		
Direct	0.752	0.327 (-0.384, 1.033)
Indirect		0.167 (-0.822, 1.143)
Network		0.286 (-0.192, 0.747)

Negative LOR favours the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR log odds ratio; MD: medium dose.

Table 34. Odds ratio for ACQ responders at 12 months for grouped treatments.

Comparison	Odds Ratio (95% CrI)	
	Fixed Effect Model	**Random Effects Model**
HD-ICS/LABA vs MD-ICS/LABA	0.993 (0.839, 1.173)	0.978 (0.736, 1.245)
MD Triple vs. MD-ICS/LABA	0.983 (0.826, 1.169)	0.979 (0.742, 1.280)
HD Triple vs MD-ICS/LABA	**1.306 (1.072, 1.592)**	1.303 (0.959, 1.750)
MD Triple vs. HD-ICS/LABA	0.990 (0.819, 1.199)	1.000 (0.752, 1.382)

Table 34. Odds ratio for ACQ responders at 12 months for grouped treatments. *(Continued)*

HD Triple vs HD-ICS/LABA	**1.316 (1.148, 1.509)**	**1.331 (1.084, 1.690)**
HD Triple vs MD Triple	**1.329 (1.072, 1.647)**	1.332 (0.957, 1.844)

The second named treatment is the baseline intervention. Odds Ratio greater than one favours the treatment named first in the comparisons. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 35. Mean and median ranking for grouped treatments for ACQ responders at 12 months sorted by mean rank

Fixed Effects Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD Triple	1.01	1	(1.00, 1.00)
MD-ICS/LABA	2.88	3	(2.00, 4.00)
HD-ICS/LABA	2.99	3	(2.00, 4.00)
MD Triple	3.11	3	(2.00, 4.00)
Random Effects Model			
Treatments	**Mean Rank**	**Median Rank**	**95% CrI**
HD Triple	1.09	1	(1.00, 2.00)
MD-ICS/LABA	2.81	3	(1.00, 4.00)
MD Triple	3.04	3	(1.00, 4.00)
HD-ICS/LABA	3.07	3	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 36. Odds ratio for ACQ responders at 12 months for individual treatments (fixed-effect model)

Comparison	**Odds Ratio (95% CrI)**
FP/SAL 500 vs. MF/IND 160	0.884 (0.715, 1.093)
MF/IND 320 vs. MF/IND 160	1.053 (0.847, 1.309)
MF/GLY/IND 80 vs. MF/IND 160	0.889 (0.690, 1.146)
MF/GLY/IND 160 vs. MF/IND 160	1.235 (0.950, 1.612)
MF/IND 320 vs. FP/SAL 500	1.192 (0.964, 1.475)
MF/GLY/IND 80 vs. FP/SAL 500	1.006 (0.783, 1.293)
MF/GLY/IND 160 vs. FP/SAL 500	**1.397 (1.078, 1.819)**
MF/GLY/IND 80 vs. MF/IND 320	0.844 (0.654, 1.090)

Table 36. Odds ratio for ACQ responders at 12 months for individual treatments (fixed-effect model) *(Continued)*

MF/GLY/IND 160 vs. MF/IND 320	1.173 (0.901, 1.532)
MF/GLY/IND 160 vs. MF/GLY/IND 80	**1.389 (1.051, 1.838)**

The second named treatment is the baseline intervention. Odds ratio greater than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI=credible interval, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium.

Table 37. Mean and median ranks for individual treatments for ACQ responders at 12 months sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MF/GLY/IND 160	1.19	1	(1.00, 3.00)
MF/IND 320	2.35	2	(1.00, 4.00)
MF/IND 160	2.93	3	(1.00, 5.00)
MF/GLY/IND 80	4.19	4	(2.00, 5.00)
FP/SAL 500	4.33	4	(3.00, 5.00)

CrI=credible interval, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol.

Table 38. Node-splitting results for all-cause SAEs for grouped treatments

Model	*p*	LORs (95% CrI)
HD-ICS/LABA vs. MD-ICS/LABA		
Direct	0.410	-0.005 (-0.364, 0.298)
Indirect		0.388 (-0.612, 1.359)
Network		0.044 (-0.232, 0.298)
MD Triple vs. MD-ICS/LABA		
Direct	0.237	0.166 (-0.258, 0.563)
Indirect		-0.409 (-1.401, 0.485)
Network		0.087

Table 38. Node-splitting results for all-cause SAEs for grouped treatments *(Continued)*

		(-0.250, 0.402)
HD Triple vs. MD-ICS/LABA		
Direct	0.961	0.035 (-0.502, 0.555)
Indirect		0.012 (-0.565, 0.543)
Network		0.039 (-0.293, 0.349)
MD Triple vs. HD-ICS/LABA		
Direct	0.746	0.083 (-0.424, 0.587)
Indirect		-0.038 (-0.656, 0.625)
Network		0.042 (-0.276, 0.368)
HD Triple vs. HD-ICS/LABA		
Direct	0.248	-0.051 (-0.379, 0.267)
Indirect		0.511 (-0.442, 1.523)
Network		-0.005 (-0.282, 0.261)
HD Triple vs. MD Triple		
Direct	0.456	0.013 (-0.390, 0.438)
Indirect		-0.340 (-1.315, 0.547)
Network		-0.050 (-0.381, 0.270)

Negative LOR favours the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR log odds ratio; MD: medium dose.

Table 39. Odds ratios for all-cause SAEs for grouped treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	1.063 (0.853, 1.329)
MD Triple vs. MD-ICS/LABA	1.102 (0.839, 1.446)
HD Triple vs MD-ICS/LABA	1.049 (0.803, 1.372)
MD Triple vs. HD-ICS/LABA	1.037 (0.799, 1.340)
HD Triple vs HD-ICS/LABA	0.986 (0.793, 1.227)
HD Triple vs MD Triple	0.952 (0.727, 1.250)

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons.
CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 40. Mean and median ranking for grouped treatments for all-cause SAEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MD-ICS/LABA	1.90	2	(1.00, 4.00)
HD Triple	2.45	2	(1.00, 4.00)
HD-ICS/LABA	2.65	3	(1.00, 4.00)
MD Triple	3.01	3	(1.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 41. Odds Ratios for all-cause SAEs for individual treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
FF/VI 100 vs. FP/SAL 250	0.781 (0.184, 3.075)
MF/FM 200 vs. FP/SAL 250	0.694 (0.220, 2.042)
MF/IND 160 vs. FP/SAL 250	1.956 (0.934, 4.339)
FP/SAL 200 vs. FP/SAL 250	2.741 (0.897, 9.796)
FP/SAL 500 vs. FP/SAL 250	**1.988 (1.052, 4.036)**
FF/VI 200 vs. FP/SAL 250	0.581 (0.123, 2.567)
MF/FM 400 vs. FP/SAL 250	0.390 (0.034, 3.439)
MF/IND 320 vs. FP/SAL 250	**2.480 (1.195, 5.452)**

Table 41. Odds Ratios for all-cause SAEs for individual treatments (fixed-effect model) *(Continued)*

MF/GLY/IND 80 vs. FP/SAL 250	**2.347 (1.109, 5.275)**
FF/UMEC/VI 100 vs. FP/SAL 250	0.679 (0.144, 3.027)
MF/GLY/IND 160 vs. FP/SAL 250	**2.391 (1.130, 5.357)**
FF/UMEC/VI 200 vs. FP/SAL 250	0.613 (0.129, 2.729)
FP/SAL 500 +Tio vs. FP/SAL 250	**2.827 (1.101, 7.467)**
MF/FM 200 vs. FF/VI 100	0.887 (0.149, 5.342)
MF/IND 160 vs. FF/VI 100	2.525 (0.525, 13.046)
FP/SAL 200 vs. FF/VI 100	3.555 (0.598, 23.952)
FP/SAL 500 vs. FF/VI 100	2.571 (0.563, 12.702)
FF/VI 200 vs. FF/VI 100	0.746 (0.416, 1.314)
MF/FM 400 vs. FF/VI 100	0.499 (0.031, 6.756)
MF/IND 320 vs. FF/VI 100	3.198 (0.669, 16.385)
MF/GLY/IND 80 vs. FF/VI 100	3.032 (0.627, 15.679)
FF/UMEC/VI 100 vs. FF/VI 100	0.872 (0.487, 1.547)
MF/GLY/IND 160 vs. FF/VI 100	3.086 (0.639, 15.980)
FF/UMEC/VI 200 vs. FF/VI 100	0.787 (0.431, 1.413)
FP/SAL 500 +Tio vs. FF/VI 100	3.641 (0.684, 20.535)
MF/IND 160 vs. MF/FM 200	2.842 (0.758, 11.364)
FP/SAL 200 vs. MF/FM 200	4.000 (0.833, 21.872)
FP/SAL 500 vs. MF/FM 200	2.890 (0.816, 11.003)
FF/VI 200 vs. MF/FM 200	0.839 (0.127, 5.448)
MF/FM 400 vs. MF/FM 200	0.569 (0.065, 3.737)
MF/IND 320 vs. MF/FM 200	3.602 (0.966, 14.291)
MF/GLY/IND 80 vs. MF/FM 200	3.408 (0.907, 13.699)
FF/UMEC/VI 100 vs. MF/FM 200	0.982 (0.149, 6.399)
MF/GLY/IND 160 vs. MF/FM 200	3.471 (0.924, 13.957)
FF/UMEC/VI 200 vs. MF/FM 200	0.885 (0.133, 5.777)
FP/SAL 500 +Tio vs. MF/FM 200	4.097 (0.979, 18.243)

Table 41. Odds Ratios for all-cause SAEs for individual treatments (fixed-effect model) *(Continued)*

FP/SAL 200 vs. MD/IND 160	1.396 (0.451, 4.942)
FP/SAL 500 vs. MD/IND 160	1.018 (0.701, 1.479)
FF/VI 200 vs. MD/IND 160	0.294 (0.052, 1.566)
MF/FM 400 vs. MD/IND 160	0.197 (0.016, 2.001)
MF/IND 320 vs. MD/IND 160	1.267 (0.888, 1.814)
MF/GLY/IND 80 vs. MD/IND 160	1.199 (0.807, 1.787)
FF/UMEC/VI 100 vs. MD/IND 160	0.344 (0.061, 1.836)
MF/GLY/IND 160 vs. MD/IND 160	1.221 (0.822, 1.819)
FF/UMEC/VI 200 vs. MD/IND 160	0.310 (0.055, 1.663)
FP/SAL 500 +Tio vs. MD/IND 160	1.442 (0.720, 2.838)
FP/SAL 500 vs. FP/SAL 200	0.731 (0.218, 2.117)
FF/VI 200 vs. FP/SAL 200	0.209 (0.029, 1.365)
MF/FM 400 vs. FP/SAL 200	0.140 (0.009, 1.649)
MF/IND 320 vs. FP/SAL 200	0.909 (0.258, 2.794)
MF/GLY/IND 80 vs. FP/SAL 200	0.860 (0.241, 2.685)
FF/UMEC/VI 100 vs. FP/SAL 200	0.244 (0.033, 1.601)
MF/GLY/IND 160 vs. FP/SAL 200	0.875 (0.245, 2.734)
FF/UMEC/VI 200 vs. FP/SAL 200	0.220 (0.030, 1.450)
FP/SAL 500 +Tio vs. FP/SAL 200	1.028 (0.258, 3.683
FF/VI 200 vs. FP/SAL 500	0.289 (0.053, 1.473)
MF/FM 400 vs. FP/SAL 500	0.194 (0.016, 1.894)
MF/IND 320 vs. FP/SAL 500	1.244 (0.874, 1.776)
MF/GLY/IND 80 vs. FP/SAL 500	1.177 (0.795, 1.750)
FF/UMEC/VI 100 vs. FP/SAL 500	0.338 (0.062, 1.723)
MF/GLY/IND 160 vs. FP/SAL 500	1.199 (0.810, 1.781)
FF/UMEC/VI 200 vs. FP/SAL 500	0.305 (0.056, 1.568)
FP/SAL 500 +Tio vs. FP/SAL 500	1.415 (0.710, 2.783)
MF/FM 400 vs. FF/VI 200	0.668 (0.040, 9.683)

Table 41. Odds Ratios for all-cause SAEs for individual treatments (fixed-effect model) *(Continued)*

MF/IND 320 vs. FF/VI 200	4.305 (0.813, 24.379)
MF/GLY/IND 80 vs. FF/VI 200	4.077 (0.765, 23.295)
FF/UMEC/VI 100 vs. FF/VI 200	1.171 (0.633, 2.166)
MF/GLY/IND 160 vs. FF/VI 200	4.147 (0.778, 23.671)
FF/UMEC/VI 200 vs. FF/VI 200	1.056 (0.562, 1.976)
FP/SAL 500 +Tio vs. FF/VI 200	4.897 (0.838, 30.319)
MF/IND 320 vs. MF/FM 400	6.418 (0.637, 80.971)*
MF/GLY/IND 80 vs. MF/FM 400	6.085 (0.598, 77.060)*
FF/UMEC/VI 100 vs. MF/FM 400	1.750 (0.121, 29.613)
MF/GLY/IND 160 vs. MF/FM 400	6.190 (0.610, 78.360)*
FF/UMEC/VI 200 vs. MF/FM 400	1.578 (0.108, 26.831)
FP/SAL 500 +Tio vs. MF/FM 400	7.299 (0.674, 98.076)*
MF/GLY/IND 80 vs. MF/IND 320	0.947 (0.646, 1.384)
FF/UMEC/VI 100 vs. MF/IND 320	0.272 (0.048, 1.443)
MF/GLY/IND 160 vs. MF/IND 320	0.964 (0.660, 1.408)
FF/UMEC/VI 200 vs. MF/IND 320	0.245 (0.043, 1.306)
FP/SAL 500 +Tio vs. MF/IND 320	1.138 (0.574, 2.214)
FF/UMEC/VI 100 vs. MF/GLY/IND 80	0.287 (0.050, 1.534)
MF/GLY/IND 160 vs. MF/GLY/IND 80	1.018 (0.710, 1.461)
FF/UMEC/VI 200 vs. MF/GLY/IND 80	0.259 (0.045, 1.391)
FP/SAL 500 +Tio vs. MF/GLY/IND 80	1.203 (0.644, 2.194)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	3.544 (0.663, 20.285)
FF/UMEC/VI 200 vs. FF/UMEC/VI 100	0.902 (0.487, 1.662)
FP/SAL 500 +Tio vs. FF/UMEC/VI 100	4.186 (0.714, 25.990)
FF/UMEC/VI 200 vs. MF/GLY/IND 160	0.254 (0.044, 1.368)
FP/SAL 500 +Tio vs. MF/GLY/IND 160	1.182 (0.633, 2.154)
FP/SAL 500 +Tio vs. FF/UMEC/VI 200	0.215 (0.035, 1.268)

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** are do not include the "null" effect. *Hazard ratios are extremely uncertain due to network sparsity

and should be treated with caution. CrI=credible interval, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Table 42. Mean and median ranking for individual treatments for all-cause SAEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MF/FM 400	3.32	1	(1.00, 14.00)
FF/VI 200	3.54	3	(1.00, 11.00)
FF/UMEC/VI 200	3.91	3	(1.00, 12.00)
MF/FM 200	4.33	4	(1.00, 11.00)
FF/UMEC/VI 100	4.63	4	(1.00, 13.00)
FP/SAL 250	5.53	6	(2.00, 8.00)
FF/VI 100	5.54	5	(2.00, 13.00)
MF/IND 160	8.77	9	(4.00, 12.00)
FP/SAL 500	8.99	9	(5.00, 12.00)
MF/GLY/IND 80	10.77	11	(6.00, 14.00)
MF/GLY/IND 160	10.97	11	(6.00, 14.00)
FP/SAL 200	11.26	13	(4.00, 14.00)
MF/IND 320	11.45	12	(7.00, 14.00)
FP/SAL 500 + Tio	11.99	13	(6.00, 14.00)

CrI=credible interval, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Table 43. Node-splitting results for asthma-related SAEs for grouped treatments

Model	*p*	LOR (95% CrI)
HD-ICS/LABA vs. MD-ICS/LABA		
Direct	0.825	0.296 (-0.280, 0.894)
Indirect		0.109 (-1.596, 1.815)
Network		0.259

Table 43. Node-splitting results for asthma-related SAEs for grouped treatments *(Continued)*

		(-0.252, 0.822)
MD Triple vs. MD-ICS/LABA		
Direct	0.442	0.410 (-0.266, 1.093)
Indirect		1.161 (-0.741, 3.063)
Network		0.542 (-0.029, 1.132)
HD Triple vs. MD-ICS/LABA		
Direct	0.410	-0.185 (-1.060, 0.660)
Indirect		0.328 (-0.628, 1.251)
Network		0.053 (-0.531, 0.641)
MD Triple vs. HD-ICS/LABA		
Direct	0.876	0.279 (-0.471, 1.017)
Indirect		0.386 (-0.794, 1.545)
Network		0.284 (-0.275, 0.840)
HD Triple vs. HD-ICS/LABA		
Direct	0.530	-0.161 (-0.652, 0.296)
Indirect		-0.804 (-2.726, 1.179)
Network		-0.212 (-0.655, 0.216)
HD Triple vs. MD Triple		
Direct	0.827	-0.580

Table 43. Node-splitting results for asthma-related SAEs for grouped treatments *(Continued)*

	(-1.374, 0.104)
Indirect	-0.391 (-2.089, 1.219)
Network	-0.493 (-1.092, 0.081)

Negative LOR favours the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR log odds ratio; MD: medium dose.

Table 44. Odds ratio for asthma-related SAEs for grouped treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	1.275 (0.794, 2.073)
MD Triple vs. MD-ICS/LABA	1.711 (0.991, 2.969)
HD Triple vs MD-ICS/LABA	1.047 (0.604, 1.824)
MD Triple vs. HD-ICS/LABA	1.342 (0.819, 2.172)
HD Triple vs HD-ICS/LABA	0.821 (0.556, 1.203)
HD Triple vs MD Triple	0.612 (0.363, 1.034)

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 45. Mean and median ranking for grouped treatments for asthma-related SAEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median	95% CrI
MD-ICS/LABA	1.62	1	(1.00, 3.00)
HD Triple	1.75	2	(1.00, 3.00)
HD-ICS/LABA	2.81	3	(1.00, 4.00)
MD Triple	3.82	4	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 46. Odds ratio for asthma-related SAEs for individual treatments (fixed-effect model).

Comparison	Odds Ratio (95% CrI)
FF/ VI 200 vs. FP/SAL 250	0.451 (0.019, 4.920)
MF/FM 200 vs. FP/SAL 250	0.836 (0.024, 22.820)

Table 46. Odds ratio for asthma-related SAEs for individual treatments (fixed-effect model). *(Continued)*

MF/IND 160 vs. FP/SAL 250	2.724 (0.634, 14.430)
FP/SAL 200 vs. FP/SAL 250	3.846 (0.808, 26.520)
FP/SAL 500 vs. FP/SAL 250	2.926 (0.924, 12.610)
FF/VI 200 vs. FP/SAL 250	0.376 (0.014, 5.295)
MF/FM 400 vs. FP/SAL 250	3.166 (0.028, 889.500)
MF/IND 320 vs. FP/SAL 250	**4.102 (1.003, 21.370)**
MF/GLY/IND 80 vs. FP/SAL 250	**5.028 (1.228, 26.260)**
FF/UMEC/VI 100 vs. FP/SAL 250	0.446 (0.017, 6.139)
MF/GLY/IND 160 vs. FP/SAL 250	3.105 (0.722, 16.610)
FF/UMEC/VI 200 vs. FP/SAL 250	0.239 (0.008, 3.558)
FP/SAL 500 + Tio vs. FP/SAL 250	2.025 (0.182, 18.300)
MF/FM 200 vs. FF/VI 100	1.932 (0.029, 169.300)*
MF/IND 160 vs. FF/VI 100	6.296 (0.358, 218.700)*
FP/SAL 200 vs. FF/VI 100	8.997 (0.478, 337.100)*
FP/SAL 500 vs. FF/VI 100	6.779 (0.440, 210.900)*
FF/VI 200 vs. FF/VI 100	0.852 (0.265, 2.621)
MF/FM 400 vs. FF/VI 100	7.663 (0.036, 4,274.000)*
MF/IND 320 vs. FF/VI 100	9.489 (0.544, 319.600)*
MF/GLY/IND 80 vs. FF/VI 100	11.630 (0.668, 391.800)*
FF/UMEC/VI 100 vs. FF/VI 100	1.005 (0.336, 2.986)
MF/GLY/IND 160 vs. FF/VI 100	7.182 (0.405, 247.500)*
FF/UMEC/VI 200 vs. FF/VI 100	0.548 (0.137, 1.868)
FP/SAL 500 + Tio vs. FF/VI 100	4.602 (0.150, 211.300)*
MF/IND 160 vs. MF/FM 200	3.361 (0.089, 152.900)*
FP/SAL 200 vs. MF/FM 200	4.809 (0.120, 246.900)*
FP/SAL 500 vs. MF/FM 200	3.637 (0.106, 153.300)*
FF/VI 200 vs. MF/FM 200	0.438 (0.004, 33.710)
MF/FM 400 vs. MF/FM 200	3.487 (0.141, 500.800)*

Table 46. Odds ratio for asthma-related SAEs for individual treatments (fixed-effect model). *(Continued)*

MF/IND 320 vs. MF/FM 200	5.069 (0.136, 227.900)*
MF/GLY/IND 80 vs. MF/FM 200	6.216 (0.168, 280.300)*
FF/UMEC/VI 100 vs. MF/FM 200	0.520 (0.005, 39.290)
MF/GLY/IND 160 vs. MF/FM 200	3.813 (0.101, 174.100)*
FF/UMEC/VI 200 vs. MF/FM 200	0.278 (0.003, 22.100)
FP/SAL 500 + Tio vs. MF/FM 200	2.418 (0.042, 145.300)*
FP/SAL 200 vs. MF/IND 160	1.404 (0.278, 8.683)
FP/SAL 500 vs. MF/IND 160	1.086 (0.452, 2.624)
FF/VI 200 vs. MF/IND 160	0.134 (0.003, 2.880)
MF/FM 400 vs. MF/IND 160	1.141 (0.008, 395.800)*
MF/IND 320 vs. MF/IND 160	1.502 (0.673, 3.506)
MF/GLY/IND 80 vs. MF/IND 160	1.837 (0.825, 4.300)
FF/UMEC/VI 100 vs. MF/IND 160	0.158 (0.004, 3.366)
MF/GLY/IND 160 vs. MF/IND 160	1.135 (0.466, 2.821)
FF/UMEC/VI 200 vs. MF/IND 160	0.085 (0.002, 1.946)
FP/SAL 500 + Tio vs. MF/IND 160	0.745 (0.089, 4.096)
FP/SAL 500 vs. FP/SAL 200	0.782 (0.154, 3.019)
FF/VI 200 vs. FP/SAL 200	0.093 (0.002, 2.142)
MF/FM 400 vs. FP/SAL 200	0.797 (0.005, 285.000)*
MF/IND 320 vs. FP/SAL 200	1.076 (0.181, 5.240)
MF/GLY/IND 80 vs. FP/SAL 200	1.313 (0.222, 6.467)
FF/UMEC/VI 100 vs. FP/SAL 200	0.111 (0.003, 2.519)
MF/GLY/IND 160 vs. FP/SAL 200	0.811 (0.132, 4.132)
FF/UMEC/VI 200 vs. FP/SAL 200	0.059 (0.001, 1.446)
FP/SAL 500 + Tio vs. FP/SAL 200	0.515 (0.038, 4.730)
FF/VI 200 vs. FP/SAL 500	0.123 (0.003, 2.364)
MF/FM 400 vs. FP/SAL 500	1.046 (0.007, 339.600)*
MF/IND 320 vs. FP/SAL 500	1.384 (0.633, 3.121)

Table 46. Odds ratio for asthma-related SAEs for individual treatments (fixed-effect model). *(Continued)*

MF/GLY/IND 80 vs. FP/SAL 500	1.690 (0.773, 3.868)
FF/UMEC/VI 100 vs. FP/SAL 500	0.146 (0.004, 2.754)
MF/GLY/IND 160 vs. FP/SAL 500	1.046 (0.437, 2.538)
FF/UMEC/VI 200 vs. FP/SAL 500	0.079 (0.002, 1.591)
FP/SAL 500 + Tio vs. FP/SAL 500	0.688 (0.081, 3.717)
MF/FM 400 vs. FF/VI 200	9.133 (0.039, 5,439.000)*
MF/IND 320 vs. FF/VI 200	11.330 (0.526, 441.100)*
MF/GLY/IND 80 vs. FF/VI 200	13.890 (0.642, 542.400)*
FF/UMEC/VI 100 vs. FF/VI 200	1.181 (0.381, 3.783)
MF/GLY/IND 160 vs. FF/VI 200	8.546 (0.392, 338.100)*
FF/UMEC/VI 200 vs. FF/VI 200	0.645 (0.158, 2.346)
FP/SAL 500 + Tio vs. FF/VI 200	5.441 (0.148, 286.500)*
MF/IND 320 vs. MF/FM 400	1.324 (0.004, 199.100)*
MF/GLY/IND 80 vs. MF/FM 400	1.622 (0.005, 241.900)*
FF/UMEC/VI 100 vs. MF/FM 400	0.130 (0.0002, 29.950)
MF/GLY/IND 160 vs. MF/FM 400	1.002 (0.003, 152.000)*
FF/UMEC/VI 200 vs. MF/FM 400	0.069 (0.0001, 16.970)
FP/SAL 500 + Tio vs. MF/FM 400	0.617 (0.001, 121.300)*
MF/GLY/IND 80 vs. MF/IND 320	1.223 (0.587, 2.576)
FF/UMEC/VI 100 vs. MF/IND 320	0.105 (0.003, 2.221)
MF/GLY/IND 160 vs. MF/IND 320	0.756 (0.328, 1.701)
FF/UMEC/VI 200 vs. MF/IND 320	0.056 (0.001, 1.273)
FP/SAL 500 + Tio vs. MF/IND 320	0.495 (0.060, 2.606)
FF/UMEC/VI 100 vs. MF/GLY/IND 80	0.085 (0.002, 1.815)
MF/GLY/IND 160 vs. MF/GLY/IND 80	0.620 (0.289, 1.274)
FF/UMEC/VI 200 vs. MF/GLY/IND 80	0.046 (0.001, 1.040)
FP/SAL 500 + Tio vs. MF/GLY/IND 80	0.409 (0.053, 1.874)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	7.224 (0.334, 279.900)*

Table 46. Odds ratio for asthma-related SAEs for individual treatments (fixed-effect model). *(Continued)*

FF/UMEC/VI 200 vs. FF/UMEC/VI 100	0.546 (0.138, 1.869)
FP/SAL 500 + Tio vs. FF/UMEC/VI 100	4.605 (0.127, 240.700)*
FF/UMEC/VI 200 vs. MF/GLY/IND 160	0.075 (0.002, 1.725)
FP/SAL 500 + Tio vs. MF/GLY/IND 160	0.660 (0.084, 3.172)
FP/SAL 500 + Tio vs. FF/UMEC/VI 200	8.563 (0.221, 485.500)*

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect.*HRs are extremely uncertain due to network sparsity and should be interpreted with caution. CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Table 47. Mean and median ranking for individual treatments for asthma-related SAEs sorted by mean rank (fixed-effect model).

Treatments	Mean Rank	Median Rank	95% CrI
FF /UMEC/VI 200	2.59	2.0	(1.0, 10.0)
FF/VI 200	3.95	3.0	(1.0, 12.0)
FF/VI 100	4.45	4.0	(1.0, 12.0)
FF/UMEC/VI 100	4.58	4.0	(1.0, 13.0)
FP/SAL 250	5.48	6.0	(1.0, 9.0)
MF/FM 200	5.83	5.0	(1.0, 14.0)
FP/SAL 500 + Tio	7.80	8.0	(1.0, 14.0)
MF/IND 160	8.77	9.0	(3.0, 13.0)
MF/FM 400	9.06	10.0	(1.0, 14.0)
FP/SAL 500	9.28	9.0	(5.0, 13.0)
MF/GLY/IND 160	9.47	10.0	(4.0, 13.0)
FP/SAL 200	10.46	11.0	(4.0, 14.0)
MF/IND 320	11.11	11.0	(6.0, 14.0)
MF/GLY/IND 80	12.17	13.0	(8.0, 14.0)

CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Table 48. Node-splitting results for all-cause AEs for grouped treatments

Model	*p*	LOR

Table 48. Node-splitting results for all-cause AEs for grouped treatments *(Continued)*

		(95% CrI)
HD-ICS/LABA vs. MD-ICS/LABA		
Direct	0.976	-0.007 (-0.146, 0.148)
Indirect		0.002 (-0.413, 0.434)
Network		0.010 (-0.126, 0.147)
MD Triple vs. MD-ICS/LABA		
Direct	0.851	-0.114 (-0.317, 0.096)
Indirect		-0.157 (-0.579, 0.278)
Network		-0.111 (-0.274, 0.045)
HD Triple vs. MD-ICS/LABA		
Direct	0.513	-0.192 (-0.433, 0.057)
Indirect		-0.303 (-0.564, -0.029)
Network		-0.233 (-0.403, -0.083)
MD Triple vs. HD-ICS/LABA		
Direct	0.080	-0.0001 (-0.209, 0.226)
Indirect		-0.298 (-0.573, -0.037)
Network		-0.120 (-0.280, 0.030)
HD Triple vs. HD-ICS/LABA		
Direct	0.844	-0.254

Table 48. Node-splitting results for all-cause AEs for grouped treatments *(Continued)*

		(-0.428, -0.093)
Indirect		-0.212 (-0.662, 0.225)
Network		-0.243 (-0.388, -0.117)
HD Triple vs. MD Triple		
Direct	0.945	-0.107 (-0.286, 0.065)
Indirect		-0.123 (-0.550, 0.304)
Network		-0.122 (-0.283, 0.024)

Negative LOR favours the second named treatment. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR log odds ratio; MD: medium dose.

Table 49. Odds ratio for all-cause AEs for grouped treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	1.000 (0.892, 1.122)
MD Triple vs. MD-ICS/LABA	0.890 (0.776, 1.019)
HD Triple vs MD-ICS/LABA	**0.787 (0.687, 0.902)**
MD Triple vs. HD-ICS/LABA	0.889 (0.780, 1.013)
HD Triple vs HD-ICS/LABA	**0.786 (0.702, 0.881)**
HD Triple vs MD Triple	0.885 (0.777, 1.007)

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 50. Mean and median ranking for grouped treatments for all-cause AEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
HD Triple	1.03	1.0	(1.00, 2.00)
MD Triple	2.05	2.0	(1.00, 3.00)

Table 50. Mean and median ranking for grouped treatments for all-cause AEs sorted by mean rank (fixed-effect model) *(Continued)*

MD-ICS/LABA	3.45	3.0	(2.00, 4.00)
HD-ICS/LABA	3.46	3.0	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
BUD/FM 320 vs. FP/SAL 250	**1.912 (1.048, 3.607)**
FF/VI 100 vs. FP/SAL 250	1.051 (0.770, 1.436)
MF/FM 200 vs. FP/SAL 250	1.058 (0.746, 1.503)
MF/IND 160 vs. FP/SAL 250	0.861 (0.357, 2.065)
FP/FM 250 vs. FP/SAL 250	2.177 (0.935, 5.196)
FP/SAL 200 vs. FP/SAL 250	0.899 (0.442, 1.819)
FP/SAL 500 vs. FP/SAL 250	0.944 (0.398, 2.227)
BUD/FM 640 vs. FP/SAL 250	**2.885 (1.256, 6.663**)
FF/VI 200 vs. FP/SAL 250	0.935 (0.631, 1.385)
MF/FM 400 vs. FP/SAL 250	1.498 (0.565, 4.177)
MF/IND 320 vs. FP/SAL 250	0.775 (0.321, 1.859)
MF/GLY/IND 80 vs. FP/SAL 250	0.773 (0.318, 1.864)
FF/UMEC/VI 100 vs. FP/SAL 250	1.063 (0.701, 1.618)
MF/GLY/IND 160 vs. FP/SAL 250	0.707 (0.291, 1.706)
FF/UMEC/VI 200 vs. FP/SAL 250	0.910 (0.597, 1.391)
FP/SAL 500 + Tio vs. FP/SAL 250	0.703 (0.283, 1.737)
FF/VI 100 vs. BUD/FM 320	0.550 (0.271, 1.083)
MF/FM 200 vs. BUD/FM 320	0.553 (0.269, 1.109)
MF/IND 160 vs. BUD/FM 320	0.449 (0.153, 1.306)
FP/FM 250 vs. BUD/FM 320	1.136 (0.629, 2.065)
FP/SAL 200 vs. BUD/FM 320	0.469 (0.183, 1.189)
FP/SAL 500 vs. BUD/FM 320	0.492 (0.170, 1.413)

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model) *(Continued)*

BUD/FM 640 vs. BUD/FM 320	1.509 (0.851, 2.600)
FF/VI 200 vs. BUD/FM 320	0.488 (0.232, 1.002)
MF/FM 400 vs. BUD/FM 320	0.783 (0.245, 2.575)
MF/IND 320 vs. BUD/FM 320	0.404 (0.137, 1.177)
MF/GLY/IND 80 vs. BUD/FM 320	0.403 (0.136, 1.177)
FF/UMEC/VI 100 vs. BUD/FM 320	0.556 (0.261, 1.157)
MF/GLY/IND 160 vs. BUD/FM 320	0.369 (0.125, 1.078)
FF/UMEC/VI 200 vs. BUD/FM 320	0.476 (0.222, 0.994)
FP/SAL 500 +Tio vs. BUD/FM 320	0.366 (0.122, 1.090)
MF/FM 200 vs. FF/VI 100	1.006 (0.629, 1.609)
MF/IND 160 vs. FF/VI 100	0.818 (0.321, 2.073)
FP/FM 250 vs. FF/VI 100	2.071 (0.842, 5.219)
FP/SAL 200 vs. FF/VI 100	0.855 (0.393, 1.843)
FP/SAL 500 vs. FF/VI 100	0.897 (0.359, 2.230)
BUD/FM 640 vs. FF/VI 100	**2.742 (1.129, 6.708)**
FF/VI 200 vs. FF/VI 100	0.889 (0.698, 1.132)
MF/FM 400 vs. FF/VI 100	1.425 (0.509, 4.163)
MF/IND 320 vs. FF/VI 100	0.737 (0.289, 1.861)
MF/GLY/IND 80 vs. FF/VI 100	0.735 (0.287, 1.864)
FF/UMEC/VI 100 vs. FF/VI 100	1.012 (0.764, 1.338)
MF/GLY/IND 160 vs. FF/VI 100	0.672 (0.263, 1.705)
FF/UMEC/VI 200 vs. FF/VI 100	0.866 (0.651, 1.150)
FP/SAL 500 +Tio vs. FF/VI 100	0.668 (0.255, 1.733)
MF/IND 160 vs. MF/FM 200	0.814 (0.316, 2.085)
FP/FM 250 vs. MF/FM 200	2.057 (0.825, 5.235)
FP/SAL 200 vs. MF/FM 200	0.850 (0.385, 1.860)
FP/SAL 500 vs. MF/FM 200	0.892 (0.352, 2.248)
BUD/FM 640 vs. MF/FM 200	**2.726 (1.105, 6.755)**

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model) *(Continued)*

FF/VI 200 vs. MF/FM 200	0.883 (0.522, 1.497)
MF/FM 400 vs. MF/FM 200	1.415 (0.570, 3.713)
MF/IND 320 vs. MF/FM 200	0.733 (0.284, 1.878)
MF/GLY/IND 80 vs. MF/FM 200	0.731 (0.282, 1.880)
FF/UMEC/VI 100 vs. MF/FM 200	1.005 (0.582, 1.737)
MF/GLY/IND 160 vs. MF/FM 200	0.668 (0.258, 1.723)
FF/UMEC/VI 200 vs. MF/FM 200	0.861 (0.497, 1.491)
FP/SAL 500 +Tio vs. MF/FM 200	0.665 (0.250, 1.751)
FP/FM 250 vs. MF/IND 160	2.534 (0.747, 8.695)
FP/SAL 200 vs. MF/IND 160	1.046 (0.512, 2.130)
FP/SAL 500 vs. MF/IND 160	1.097 (0.918, 1.310)
BUD/FM 640 vs. MF/IND 160	**3.356 (1.002, 11.224)**
FF/VI 200 vs. MF/IND 160	1.086 (0.417, 2.847)
MF/FM 400 vs. MF/IND 160	1.748 (0.470, 6.710)
MF/IND 320 vs. MF/IND 160	0.900 (0.756, 1.073)
MF/GLY/IND 80 vs. MF/IND 160	0.897 (0.735, 1.097)
FF/UMEC/VI 100 vs. MF/IND 160	1.237 (0.469, 3.277)
MF/GLY/IND 160 vs. MF/IND 160	0.822 (0.673, 1.003)
FF/UMEC/VI 200 vs. MF/IND 160	1.058 (0.401, 2.810)
FP/SAL 500 +Tio vs. MF/IND 160	0.817 (0.614, 1.086)
FP/SAL 200 vs. FP/FM 250	0.413 (0.135, 1.241)
FP/SAL 500 vs. FP/FM 250	0.433 (0.128, 1.447)
BUD/FM 640 vs. FP/FM 250	1.326 (0.583, 2.967)
FF/VI 200 vs. FP/FM 250	0.429 (0.165, 1.089)
MF/FM 400 vs. FP/FM 250	0.690 (0.186, 2.603)
MF/IND 320 vs. FP/FM 250	0.355 (0.104, 1.205)
MF/GLY/IND 80 vs. FP/FM 250	0.354 (0.103, 1.204)
FF/UMEC/VI 100 vs. FP/FM 250	0.489 (0.186, 1.251)

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model) *(Continued)*

MF/GLY/IND 160 vs. FP/FM 250	0.324 (0.094, 1.102)
FF/UMEC/VI 200 vs. FP/FM 250	0.418 (0.159, 1.076)
FP/SAL 500 +Tio vs. FP/FM 250	0.322 (0.092, 1.113)
FP/SAL 500 vs. FP/SAL 200	1.049 (0.526, 2.096)
BUD/FM 640 vs. FP/SAL 200	**3.212 (1.079, 9.581)**
FF/VI 200 vs. FP/SAL 200	1.039 (0.465, 2.338)
MF/FM 400 vs. FP/SAL 200	1.671 (0.501, 5.785)
MF/IND 320 vs. FP/SAL 200	0.861 (0.423, 1.758)
MF/GLY/IND 80 vs. FP/SAL 200	0.858 (0.419, 1.768)
FF/UMEC/VI 100 vs. FP/SAL 200	1.184 (0.522, 2.701)
MF/GLY/IND 160 vs. FP/SAL 200	2.701 (0.383, 1.617)
FF/UMEC/VI 200 vs. FP/SAL 200	1.013 (0.446, 2.315)
FP/SAL 500 +Tio vs. FP/SAL 200	0.781 (0.370, 1.652)
BUD/FM 640 vs. FP/SAL 500	3.062 (0.927, 10.102)
FF/VI 200 vs. FP/SAL 500	0.991 (0.387, 2.554)
MF/FM 400 vs. FP/SAL 500	1.594 (0.434, 6.051)
MF/IND 320 vs. FP/SAL 500	**0.821 (0.688, 0.980)**
MF/GLY/IND 80 vs. FP/SAL 500	0.818 (0.669, 1.000)
FF/UMEC/VI 100 vs. FP/SAL 500	1.128 (0.435, 2.936)
MF/GLY/IND 160 vs. FP/SAL 500	**0.750 (0.612, 0.916)**
FF/UMEC/VI 200 vs. FP/SAL 500	0.965 (0.372, 2.522)
FP/SAL 500 +Tio vs. FP/SAL 500	**0.745 (0.560, 0.991)**
FF/VI 200 vs. BUD/FM 640	**0.324 (0.129, 0.814)**
MF/FM 400 vs. BUD/FM 640	0.521 (0.143, 1.947)
MF/IND 320 vs. BUD/FM 640	**0.268 (0.080, 0.898)**
MF/GLY/IND 80 vs. BUD/FM 640	**0.267 (0.080, 0.900)**
FF/UMEC/VI 100 vs. BUD/FM 640	**0.368 (0.145, 0.937)**
MF/GLY/IND 160 vs. BUD/FM 640	**0.245 (0.073, 0.823)**

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model) *(Continued)*

FF/UMEC/VI 200 vs. BUD/FM 640	**0.315 (0.124, 0.803)**
FP/SAL 500 +Tio vs. BUD/FM 640	**0.243 (0.071, 0.832)**
MF/FM 400 vs. FF/VI 200	1.604 (0.558, 4.812)
MF/IND 320 vs. FF/VI 200	0.829 (0.316, 2.159)
MF/GLY/IND 80 vs. FF/VI 200	0.826 (0.314, 2.156)
FF/UMEC/VI 100 vs. FF/VI 200	1.138 (0.858, 1.511)
MF/GLY/IND 160 vs. FF/VI 200	0.756 (0.287, 1.975)
FF/UMEC/VI 200 vs. FF/VI 200	0.974 (0.731, 1.296)
FP/SAL 500 +Tio vs. FF/VI 200	0.752 (0.279, 2.004)
MF/IND 320 vs. MF/FM 400	0.515 (0.134, 1.916)
MF/GLY/IND 80 vs. MF/FM 400	0.514 (0.133, 1.922)
FF/UMEC/VI 100 vs. MF/FM 400	0.710 (0.234, 2.058)
MF/GLY/IND 160 vs. MF/FM 400	0.470 (0.122, 1.761)
FF/UMEC/VI 200 vs. MF/FM 400	0.607 (0.200, 1.767)
FP/SAL 500 +Tio vs. MF/FM 400	0.467 (0.120, 1.778)
MF/GLY/IND 80 vs. MF/IND 320	0.997 (0.817, 1.217)
FF/UMEC/VI 100 vs. MF/IND 320	1.373 (0.522, 3.644)
MF/GLY/IND 160 vs. MF/IND 320	0.912 (0.748, 1.113)
FF/UMEC/VI 200 vs. MF/IND 320	1.175 (0.446, 3.122)
FP/SAL 500 +Tio vs. MF/IND 320	0.907 (0.682, 1.205)
FF/UMEC/VI 100 vs. MF/GLY/IND 80	1.378 (0.521, 3.665)
MF/GLY/IND 160 vs. MF/GLY/IND 80	0.915 (0.771, 1.086)
FF/UMEC/VI 200 vs. MF/GLY/IND 80	1.179 (0.445, 3.146)
FP/SAL 500 +Tio vs. MF/GLY/IND 80	0.910 (0.718, 1.152)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	0.664 (0.249, 1.758)
FF/UMEC/VI 200 vs. FF/UMEC/VI 100	0.856 (0.636, 1.150)
FP/SAL 500 +Tio vs. FF/UMEC/VI 100	0.660 (0.242, 1.784)
FF/UMEC/VI 200 vs. MF/GLY/IND 160	1.288 (0.486, 3.437)

Table 51. Odds ratio for all-cause AEs for individual treatments (fixed-effect model) *(Continued)*

FP/SAL 500 +Tio vs. MF/GLY/IND 160	0.994 (0.784, 1.258)
FP/SAL 500 +Tio vs. FF/UMEC/VI 200	0.772 (0.282, 2.088)

The second named treatment is the baseline intervention. Odds ratio less than one favours the first named treatment. Treatment comparisons **in bold** do not include the "null" effect. BUD: budesonide, CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Table 52. Mean and median ranking for individual treatments for all-cause AEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI
MF/GLY/IND 160	3.78	3	(1.00, 11.00)
FP/SAL 500 +Tio	3.96	3	(1.00, 12.00)
MF/IND 320	5.62	4	(1.00, 13.00)
MF/GLY/IND 80	5.68	4	(1.00, 13.00)
FF/UMEC/VI 200	6.79	7	(1.00, 13.00)
FF/VI 200	7.20	8	(1.00, 13.00)
FP/SAL 200	7.51	7	(1.00, 15.00)
MF/IND 160	7.86	7	(3.00, 15.00)
FP/SAL 250	8.49	9	(2.00, 13.00)
MF/FM 200	9.35	10	(1.00, 14.00)
FP/SAL 500	9.49	9	(5.00, 16.00)
FF/VI 100	9.60	10	(3.00, 14.00)
FF/UMEC/VI 100	9.71	11	(2.00, 15.00)
MF/FM 400	12.23	14	(1.00, 17.00)
BUD/FM 320	14.47	15	(8.00, 16.00)
FP/FM 250	14.95	16	(7.00, 17.00)
BUD/FM 640	16.31	17	(12.00, 17.00)

BUD: budesonide, CrI: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Table 53. Node-splitting results for dropouts due to AEs for grouped treatments

Model	*p*	LOR (95% CrI)
HD-ICS/LABA vs. MD-ICS/LABA		
Direct	**0.003**	-0.027 (-0.646, 0.557)
Indirect		-22.573 (-71.914, -2.303)
Network		-0.141 (-0.797, 0.475)
MD Triple vs. MD-ICS/LABA		
Direct	0.405	-0.652 (-2.291, 0.280)
Indirect		0.301 (-2.064, 2.681)
Network		-0.350 (-1.441, 0.355)
HD Triple vs. MD-ICS/LABA		
Direct	0.840	-0.822 (-2.143, 0.263)
Indirect		-0.683 (-2.060, 0.526)
Network		-0.798 (-1.688, -0.065)
MD Triple vs. HD-ICS/LABA		
Direct	0.117	0.210 (-0.907, 1.247)
Indirect		-1.158 (-2.969, 0.269)
Network		-0.204 (-1.274, 0.487)

Table 53. Node-splitting results for dropouts due to AEs for grouped treatments *(Continued)*

HD Triple vs. HD-ICS/LABA		
Direct	0.402	-0.554 (-1.457, 0.322)
Indirect		-1.509 (-4.439, 0.756)
Network		-0.660 (-1.410, -0.021)
HD Triple vs. MD Triple		
Direct	**0.002**	-0.588 (-1.396, 0.300)
Indirect		23.163 (1.997, 74.056)
Network		-0.446 (-1.195, 0.521)

Negative LOR favours the second named treatment. Comparison **in bold** exhibits evidence of inconsistency**.** CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LOR log odds ratio; MD: medium dose.

Table 54. Odds ratio for drop-outs due to AEs for grouped treatments (fixed-effect model)

Comparison	Odds Ratio (95% CrI)
HD-ICS/LABA vs MD-ICS/LABA	0.911 (0.630, 1.330)
MD Triple vs. MD-ICS/LABA	0.878 (0.531, 1.434)
HD Triple vs MD-ICS/LABA	**0.503 (0.298, 0.837)**
MD Triple vs. HD-ICS/LABA	0.964 (0.602, 1.513)
HD Triple vs HD-ICS/LABA	**0.552 (0.351, 0.849)**
HD Triple vs MD Triple	**0.572 (0.336, 0.976)**

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 55. Mean and median ranking for grouped treatments for drop-outs due to AEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% CrI

Table 55. Mean and median ranking for grouped treatments for drop-outs due to AEs sorted by mean rank (fixed-effect model) *(Continued)*

HD Triple	1.03	1.0	(1.00, 2.00)
MD Triple	2.72	3.0	(2.00, 4.00)
HD-ICS/LABA	2.87	3.0	(2.00, 4.00)
MD-ICS/LABA	3.38	4.0	(2.00, 4.00)

CrI: credible interval; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model).

Comparison	Odds Ratio (95% CrI)
BUD/FM 320 vs. FP/SAL 250	0.998 (0.264, 3.664)
FF/VI 100 vs. FP/SAL 250	0.740 (0.239, 2.146)
MF/FM 200 vs. FP/SAL 250	1.277 (0.435, 4.007)
MF/IND 160 vs. FP/SAL 250	0.432 (0.038, 4.198)
FP/FM 250 vs. FP/SAL 250	0.433 (0.037, 3.724)
FP/SAL 200 vs. FP/SAL 250	**0.036 (0.0002, 0.628)**
FP/SAL 500 vs. FP/SAL 250	0.524 (0.050, 4.655)
BUD/FM 640 vs. FP/SAL 250	1.377 (0.296, 6.523)
FF/VI 200 vs. FP/SAL 250	0.290 (0.059, 1.280)
MF/FM 400 vs. FP/SAL 250	1.136 (0.095, 13.350)
MF/IND 320 vs. FP/SAL 250	0.384 (0.034, 3.745)
MF/GLY/IND 80 vs. FP/SAL 250	0.563 (0.050, 5.421)
FF/UMEC/VI 100 vs. FP/SAL 250	0.162 (0.017, 0.996)
MF/GLY/IND 160 vs. FP/SAL 250	0.281 (0.025, 2.775)
FF/UMEC/VI 200 vs. FP/SAL 250	**0.160 (0.017, 0.992)**
FP/SAL 500 +Tio vs. FP/SAL 250	0.289 (0.017, 3.881)
FF/VI 100 vs. BUD/FM 320	0.741 (0.133, 4.062)
MF/FM 200 vs. BUD/FM 320	1.284 (0.237, 7.314)
MF/IND 160 vs. BUD/FM 320	0.431 (0.027, 5.990)
FP/FM 250 vs. BUD/FM 320	0.445 (0.053, 2.405)

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model). *(Continued)*

FP/SAL 200 vs. BUD/FM 320	**0.035 (0.0001, 0.857)**
FP/SAL 500 vs. BUD/FM 320	0.522 (0.035, 6.650)
BUD/FM 640 vs. BUD/FM 320	1.367 (0.643, 3.291)
FF/VI 200 vs. BUD/FM 320	0.289 (0.037, 2.102)
MF/FM 400 vs. BUD/FM 320	1.139 (0.070, 18.780)
MF/IND 320 vs. BUD/FM 320	0.382 (0.024,5.286)
MF/GLY/IND 80 vs. BUD/FM 320	0.560 (0.036, 7.725)
FF/UMEC/VI 100 vs. BUD/FM 320	0.159 (0.012, 1.547)
MF/GLY/IND 160 vs. BUD/FM 320	0.281 (0.018, 3.944)
FF/UMEC/VI 200 vs. BUD/FM 320	0.159 (0.012, 1.540)
FP/SAL 500 +Tio vs. BUD/FM 320	0.287 (0.013, 5.302)
MF/FM 200 vs. FF/VI 100	1.733 (0.380, 8.567)
MF/IND 160 vs. FF/VI 100	0.584 (0.041, 7.346)
FP/FM 250 vs. FF/VI 100	0.585 (0.040, 6.765)
FP/SAL 200 vs. FF/VI 100	0.048 (0.0002, 1.082)
FP/SAL 500 vs. FF/VI 100	0.709 (0.053, 8.184)
BUD/FM 640 vs. FF/VI 100	1.871 (0.288, 12.670)
FF/VI 200 vs. FF/VI 100	0.396 (0.123, 1.090)
MF/FM 400 vs. FF/VI 100	1.542 (0.105, 23.090)
MF/IND 320 vs. FF/VI 100	0.519 (0.036, 6.544)
MF/GLY/IND 80 vs. FF/VI 100	0.761 (0.054, 9.456)
FF/UMEC/VI 100 vs. FF/VI 100	**0.224 (0.031, 0.927)**
MF/GLY/IND 160 vs. FF/VI 100	0.381 (0.026, 4.827)
FF/UMEC/VI 200 vs. FF/VI 100	**0.223 (0.031, 0.924)**
FP/SAL 500 +Tio vs. FF/VI 100	0.391 (0.019, 6.641)
MF/IND 160 vs. MF/FM 200	0.335 (0.023, 4.179)
FP/FM 250 vs. MF/FM 200	0.337 (0.023, 3.791)
FP/SAL 200 vs. MF/FM 200	**0.027 (0.0001, 0.608)**

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model). *(Continued)*

FP/SAL 500 vs. MF/FM 200	0.406 (0.030, 4.673)
BUD/FM 640 vs. MF/FM 200	1.072 (0.158, 7.145)
FF/VI 200 vs. MF/FM 200	0.224 (0.032, 1.427)
MF/FM 400 vs. MF/FM 200	0.884 (0.093, 8.140)
MF/IND 320 vs. MF/FM 200	0.297 (0.020, 3.727)
MF/GLY/IND 80 vs. MF/FM 200	0.435 (0.030, 5.363)
FF/UMEC/VI 100 vs. MF/FM 200	0.125 (0.010, 1.049)
MF/GLY/IND 160 vs. MF/FM 200	0.218 (0.015, 2.755)
FF/UMEC/VI 200 vs. MF/FM 200	0.124 (0.011, 1.048)
FP/SAL 500 +Tio vs. MF/FM 200	0.224 (0.011, 3.779)
FP/FM 250 vs. MF/IND 160	1.001 (0.037, 26.680)
FP/SAL 200 vs. MF/IND 160	0.082 (0.0003, 2.170)
FP/SAL 500 vs. MF/IND 160	1.206 (0.654, 2.247)
BUD/FM 640 vs. MF/IND 160	3.217 (0.208, 56.650)*
FF/VI 200 vs. MF/IND 160	0.667 (0.042, 11.580)
MF/FM 400 vs. MF/IND 160	2.659 (0.091, 84.700)*
MF/IND 320 vs. MF/IND 160	0.888 (0.455, 1.712)
MF/GLY/IND 80 vs. MF/IND 160	1.299 (0.712, 2.405)
FF/UMEC/VI 100 vs. MF/IND 160	0.366 (0.016, 7.836)
MF/GLY/IND 160 vs. MF/IND 160	0.653 (0.319, 1.311)
FF/UMEC/VI 200 vs. MF/IND 160	0.365 (0.016, 7.867)
FP/SAL 500 +Tio vs. MF/IND 160	0.684 (0.131, 2.794)
FP/SAL 200 vs. FP/FM 250	0.079 (0.0003, 3.709)
FP/SAL 500 vs. FP/FM 250	1.207 (0.048, 30.870)
BUD/FM 640 vs. FP/FM 250	3.139 (0.482, 30.040)
FF/VI 200 vs. FP/FM 250	0.668 (0.045, 11.700)
MF/FM 400 vs. FP/FM 250	2.653 (0.099, 84.660)*
MF/IND 320 vs. FP/FM 250	0.888 (0.033, 23.970)

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model). *(Continued)*

MF/GLY/IND 80 vs. FP/FM 250	1.305 (0.049, 35.030)
FF/UMEC/VI 100 vs. FP/FM 250	0.367 (0.017, 7.834)
MF/GLY/IND 160 vs. FP/FM 250	0.654 (0.024, 17.880)
FF/UMEC/VI 200 vs. FP/FM 250	0.365 (0.017, 7.886)
FP/SAL 500 +Tio vs. FP/FM 250	0.672 (0.019, 22.980)
FP/SAL 500 vs. FP/SAL 200	14.560 (0.595, 3358)*
BUD/FM 640 vs. FP/SAL 200	39.890 (1.448, 9944)*
FF/VI 200 vs. FP/SAL 200	8.274 (0.295, 2017)*
MF/FM 400 vs. FP/SAL 200	34.560 (0.684, 11170)*
MF/IND 320 vs. FP/SAL 200	10.740 (0.410, 2534)*
MF/GLY/IND 80 vs. FP/SAL 200	15.800 (0.606, 3707)*
FF/UMEC/VI 100 vs. FP/SAL 200	4.603 (0.116, 1234)*
MF/GLY/IND 160 vs. FP/SAL 200	7.914 (0.297, 1863)*
FF/UMEC/VI 200 vs. FP/SAL 200	4.583 (0.115, 1239)*
FP/SAL 500 +Tio vs. FP/SAL 200	8.346 (0.227, 2184)*
BUD/FM 640 vs. FP/SAL 500	2.655 (0.186, 44.82)
FF/VI 200 vs. FP/SAL 500	0.550 (0.038, 9.071)
MF/FM 400 vs. FP/SAL 500	2.201 (0.080, 66.500)*
MF/IND 320 vs. FP/SAL 500	0.737 (0.386, 1.380)
MF/GLY/IND 80 vs. FP/SAL 500	1.076 (0.604, 1.933)
FF/UMEC/VI 100 vs. FP/SAL 500	0.302 (0.014, 6.159)
MF/GLY/IND 160 vs. FP/SAL 500	0.542 (0.270, 1.059)
FF/UMEC/VI 200 vs. FP/SAL 500	0.303 (0.014, 6.152)
FP/SAL 500 +Tio vs. FP/SAL 500	0.567 (0.110, 2.288)
FF/VI 200 vs. BUD/FM 640	0.208 (0.023, 1.777)
MF/FM 400 vs. BUD/FM 640	0.820 (0.045, 15.230)
MF/IND 320 vs. BUD/FM 640	0.275 (0.015, 4.245)
MF/GLY/IND 80 vs. BUD/FM 640	0.404 (0.023, 6.212)

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model). *(Continued)*

FF/UMEC/VI 100 vs. BUD/FM 640	0.115 (0.008, 1.276)
MF/GLY/IND 160 vs. BUD/FM 640	0.202 (0.011, 3.165)
FF/UMEC/VI 200 vs. BUD/FM 640	0.114 (0.008, 1.270)
FP/SAL 500 +Tio vs. BUD/FM 640	0.208 (0.008, 4.223)
MF/FM 400 vs. FF/VI 200	3.941 (0.222, 73.760)*
MF/IND 320 vs. FF/VI 200	1.333 (0.076, 21.060)
MF/GLY/IND 80 vs. FF/VI 200	1.950 (0.112, 30.490)
FF/UMEC/VI 100 vs. FF/VI 200	0.565 (0.071, 2.938)
MF/GLY/IND 160 vs. FF/VI 200	0.978 (0.055, 15.580)
FF/UMEC/VI 200 vs. FF/VI 200	0.565 (0.071, 2.935)
FP/SAL 500 +Tio vs. FF/VI 200	1.002 (0.040, 21.050)
MF/IND 320 vs. MF/FM 400	0.333 (0.011, 9.713)
MF/GLY/IND 80 vs. MF/FM 400	0.488 (0.016, 14.170)
FF/UMEC/VI 100 vs. MF/FM 400	0.139 (0.005, 3.022)
MF/GLY/IND 160 vs. MF/FM 400	0.244 (0.008, 7.258)
FF/UMEC/VI 200 vs. MF/FM 400	0.138 (0.005, 3.057)
FP/SAL 500 +Tio vs. MF/FM 400	0.251 (0.006, 9.248)
MF/GLY/IND 80 vs. MF/IND 320	1.463 (0.788, 2.773)
FF/UMEC/VI 100 vs. MF/IND 320	0.412 (0.018, 8.829)
MF/GLY/IND 160 vs. MF/IND 320	0.736 (0.354, 1.502)
FF/UMEC/VI 200 vs. MF/IND 320	0.412 (0.018, 8.908)
FP/SAL 500 +Tio vs. MF/IND 320	0.771 (0.147, 3.188)
FF/UMEC/VI 100 vs. MF/GLY/IND 80	0.281 (0.012, 6.043)
MF/GLY/IND 160 vs. MF/GLY/IND 80	0.504 (0.260, 0.937)
FF/UMEC/VI 200 vs. MF/GLY/IND 80	0.281 (0.012, 6.009)
FP/SAL 500 +Tio 5 vs. MF/GLY/IND 80	0.529 (0.109, 1.941)
MF/GLY/IND 160 vs. FF/UMEC/VI 100	1.787 (0.081, 41.780)
FF/UMEC/VI 200 vs. FF/UMEC/VI 100	1.000 (0.107, 9.359)

Table 56. Odds ratio for dropouts due to AEs for individual treatments (fixed-effect model). *(Continued)*

FP/SAL 500 +Tio vs. FF/UMEC/VI 100	1.831 (0.062, 54.540)*
FF/UMEC/VI 200 vs. MF/GLY/IND 160	0.560 (0.024, 12.210)
FP/SAL 500 +Tio vs. MF/GLY/IND 160	1.052 (0.210, 4.076)
FP/SAL 500 +Tio vs. FF/UMEC/VI 200	1.837 (0.062, 54.250)*

The second named treatment is the baseline intervention. Odds ratio less than one favours the treatment named first in the comparisons. Treatment comparisons **in bold** do not include the "null" effect. *ORs are extremely uncertain due to network sparsity and should be interpreted with caution. BUD: budesonide,Crl: credible interval, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, OR: odds ratio, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Table 57. Mean and median ranking for individual treatments for dropouts due to AEs sorted by mean rank (fixed-effect model)

Treatments	Mean Rank	Median Rank	95% Credible Interval
FP/SAL 200	2.27	1.0	(1.0, 10.0)
FF/UMEC/VI 200	4.73	3.0	(1.0, 13.0)
FF/UMEC/VI 100	4.74	3.0	(1.0, 13.0)
MF/GLY/IND 160	5.88	5.0	(1.0, 13.0)
FF/VI 200	6.72	6.0	(2.0, 14.0)
FP/SAL 500 +Tio	6.81	6.0	(1.0, 17.0)
MF/IND 320	7.82	7.0	(2.0, 15.0)
FP/FM 250	8.45	8.0	(1.0, 17.0)
MF/IND 160	8.71	8.0	(3.0, 16.0)
FP/SAL 500	10.18	10.0	(4.0, 17.0)
MF/GLY/IND 80	10.77	10.0	(5.0, 17.0)
FF/VI 100	11.16	12.0	(5.0, 17.0)
MF/FM 400	12.29	14.0	(2.0, 17.0)
BUD/FM 320	12.30	13.0	(5.0, 17.0)
FP/SAL 250	12.69	13.0	(7.0, 17.0)
MF/FM 200	13.63	14.0	(6.0, 17.0)
BUD/FM 640	13.85	15.0	(6.0, 17.0)

BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

APPENDICES

Appendix 1. Database search strategies

Database/search platform/date of last search	Search strategy	Results
Airways Register (via Cochrane Register of Studies) Date of most recent search: 1 December 2020	#1 MESH DESCRIPTOR Asthma EXPLODE ALL AND INSEGMENT #2 asthma*:ti,ab AND INSEGMENT #3 #1 OR #2 #4 MESH DESCRIPTOR Formoterol Fumarate AND INSEGMENT #5 MESH DESCRIPTOR Salmeterol Xinafoate AND INSEGMENT #6 formoterol:ti,ab AND INSEGMENT #7 salmeterol:ti,ab AND INSEGMENT #8 indacaterol:ti,ab AND INSEGMENT #9 vilanterol:ti,ab AND INSEGMENT #10 #4 OR #5 OR #6 OR #7 OR #8 OR #9 #11 MESH DESCRIPTOR Budesonide AND INSEGMENT #12 MESH DESCRIPTOR Fluticasone AND INSEGMENT #13 MESH DESCRIPTOR Beclomethasone AND INSEGMENT #14 budesonide:ti,ab AND INSEGMENT #15 fluticasone:ti,ab AND INSEGMENT #16 mometasone:ti,ab AND INSEGMENT #17 beclomethasone:ti,ab AND INSEGMENT #18 ciclesonide:ti,ab AND INSEGMENT #19 (inhal* NEAR3 (steroid* or corticosteroid* or glucocorticoid*)):ti,ab AND INSEGMENT #20 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 #21 MESH DESCRIPTOR Budesonide, Formoterol Fumarate Drug Combination AND INSEGMENT #22 MESH DESCRIPTOR Mometasone Furoate, Formoterol Fumarate Drug Combination AND INSEGMENT #23 MESH DESCRIPTOR Fluticasone-Salmeterol Drug Combination AND INSEGMENT #24 #21 OR #22 OR #23 #25 #3 AND #10 AND #20 #26 #3 AND #24 #27 #25 OR #26 #28 (2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020):yr AND INSEGMENT #29 #27 AND #28 #30 INREGISTER #31 #29 AND #30	Dec 2020=915
CENTRAL (via Cochrane Register of Studies) Date of most recent search: 1 December 2020	#1 MESH DESCRIPTOR Asthma EXPLODE ALL AND CENTRAL:TARGET #2 asthma*:ti,ab AND CENTRAL:TARGET #3 #1 OR #2 AND CENTRAL:TARGET #4 MESH DESCRIPTOR Formoterol Fumarate AND CENTRAL:TARGET #5 MESH DESCRIPTOR Salmeterol Xinafoate AND CENTRAL:TARGET #6 formoterol:ti,ab AND CENTRAL:TARGET #7 salmeterol:ti,ab AND CENTRAL:TARGET #8 indacaterol:ti,ab AND CENTRAL:TARGET #9 vilanterol:ti,ab AND CENTRAL:TARGET #10 #4 OR #5 OR #6 OR #7 OR #8 OR #9 AND CENTRAL:TARGET #11 MESH DESCRIPTOR Budesonide AND CENTRAL:TARGET #12 MESH DESCRIPTOR Fluticasone AND CENTRAL:TARGET	Dec 2020=1665

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	#13 MESH DESCRIPTOR Beclomethasone AND CENTRAL:TARGET #14 budesonide:ti,ab AND CENTRAL:TARGET #15 fluticasone:ti,ab AND CENTRAL:TARGET #16 mometasone:ti,ab AND CENTRAL:TARGET #17 beclomethasone:ti,ab AND CENTRAL:TARGET #18 ciclesonide:ti,ab AND CENTRAL:TARGET #19 (inhal* NEAR3 (steroid* or corticosteroid* or glucocorticoid*)):ti,ab AND CENTRAL:TARGET #20 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 AND CENTRAL:TARGET #21 MESH DESCRIPTOR Budesonide, Formoterol Fumarate Drug Combination AND CENTRAL:TARGET #22 MESH DESCRIPTOR Mometasone Furoate, Formoterol Fumarate Drug Combination AND CENTRAL:TARGET #23 MESH DESCRIPTOR Fluticasone-Salmeterol Drug Combination AND CENTRAL:TARGET #24 #21 OR #22 OR #23 AND CENTRAL:TARGET #25 #3 AND #10 AND #20 AND CENTRAL:TARGET #26 #3 AND #24 AND CENTRAL:TARGET #27 #25 OR #26 AND CENTRAL:TARGET #28 (2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014 or 2015 or 2016 or 2017 or 2018 or 2019 or 2020):yr AND CENTRAL:TARGET #29 #27 AND #28 AND CENTRAL:TARGET	
MEDLINE (Ovid) ALL Date of most recent search: 1 December 2020	1 exp Asthma/ 2 asthma$.tw. 3 1 or 2 4 Formoterol Fumarate/ 5 Salmeterol Xinafoate/ 6 formoterol.tw. 7 salmeterol.tw. 8 indacaterol.mp. 9 vilanterol.mp. 10 or/4-9 11 Budesonide/ 12 Fluticasone/ 13 Mometasone Furoate/ 14 Beclomethasone/ 15 budesonide.tw. 16 fluticasone.tw. 17 mometasone.tw. 18 beclomethasone.tw. 19 ciclesonide.mp. 20 (inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw. 21 or/11-20 22 Budesonide, Formoterol Fumarate Drug Combination/ 23 Mometasone Furoate, Formoterol Fumarate Drug Combination/ 24 Fluticasone-Salmeterol Drug Combination/ 25 or/22-24 26 3 and 10 and 21 27 3 and 25 28 26 or 27 29 (controlled clinical trial or randomized controlled trial).pt. 30 (randomized or randomised).ab,ti. 31 placebo.ab,ti. 32 dt.fs. 33 randomly.ab,ti. 34 trial.ab,ti. 35 groups.ab,ti. 36 or/29-35 37 Animals/	Dec 2020=993

(Continued)

	38 Humans/ 39 37 not (37 and 38) 40 36 not 39 41 28 and 40 42 limit 41 to yr="2008 -Current"	
Embase (Ovid) Date of most recent search: 1 December 2020	1 exp asthma/ 2 asthma$.tw. 3 1 or 2 4 formoterol fumarate/ 5 salmeterol xinafoate/ 6 formoterol.tw. 7 salmeterol.tw. 8 indacaterol.mp. 9 vilanterol.mp. 10 or/4-9 11 budesonide/ 12 fluticasone/ 13 mometasone furoate/ 14 beclometasone/ 15 budesonide.tw. 16 fluticasone.tw. 17 mometasone.tw. 18 beclomethasone.tw. 19 ciclesonide.mp. 20 (inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw. 21 or/11-20 22 budesonide plus formoterol/ 23 formoterol fumarate plus mometasone furoate/ 24 exp fluticasone propionate plus salmeterol/ 25 or/22-24 26 3 and 10 and 21 27 3 and 25 28 26 or 27 29 Randomized Controlled Trial/ 30 randomization/ 31 controlled clinical trial/ 32 Double Blind Procedure/ 33 Single Blind Procedure/ 34 Crossover Procedure/ 35 (clinica$ adj3 trial$).tw. 36 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw. 37 exp Placebo/ 38 placebo$.ti,ab. 39 random$.ti,ab. 40 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 41 (crossover$ or cross-over$).ti,ab. 42 or/29-41 43 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 44 human/ or normal human/ or human cell/ 45 43 and 44 46 43 not 45 47 42 not 46 48 28 and 47 49 limit 48 to yr="2008 -Current"	Dec 2020=1758
Global Health (Ovid)	1 exp asthma/ 2 asthma$.tw. 3 1 or 2	Dec 2020=32

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Date of most recent search: 1 December 2020	4 formoterol.tw. 5 salmeterol.tw. 6 indacaterol.mp. 7 vilanterol.mp. 8 4 or 5 or 6 or 7 9 exp corticoids/ 10 budesonide.tw. 11 fluticasone.tw. 12 mometasone.tw. 13 beclomethasone.tw. 14 ciclesonide.mp. 15 (inhal$ adj3 (steroid$ or corticosteroid$ or glucocorticoid$)).tw. 16 or/9-15 17 3 and 8 and 16 18 randomized controlled trials/ 19 (randomized or randomised).ab,ti. 20 placebo.ab,ti. 21 randomly.ab,ti. 22 trial.ab,ti. 23 or/18-22 24 17 and 23 25 limit 24 to yr="2008 -Current"	
ClinicalTrials.gov Date of most recent search: 1 December 2020	Study type: Interventional Condition: asthma Intervention: (formoterol OR salmeterol OR indacaterol OR vilanterol) AND (budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide)	Dec 2020=270

Appendix 2. Data table for studies included for severe exacerbations

Dichotomous Data

Study	Treatment	N	n of participants with the event
Bernstein 2015* (low risk group)	MD-ICS/LABA	346	0
	HD-ICS/LABA	346	0
Kerstjens 2012 (high risk group)	HD-ICS/LABA	456	20
	HD Triple	457	16
Lee 2020 (low risk group)	MD-ICS/LABA	407	7
	HD-ICS/LABA	406	5
	MD Triple	406	7
	HD Triple	408	4
Mansfield 2017 (low risk group)	MD-ICS/LABA	174	2

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	HD-ICS/LABA	44	0
Peters 2008 (low risk group)	MD-ICS/LABA	132	2
	HD-ICS/LABA	443	2
Stempel 2016 (high risk group)	MD-ICS/LABA	580	1
	HD-ICS/LABA	982	14
van Zyl-Smit 2020 (high risk group)	MD-ICS/LABA	437	1
	HD-ICS/LABA	887	5

Log-Hazards Data

Study	Treatment	lnHR	lnSE
Kerstjens 2020† (high risk group)	MD-ICS/LABA	0.637	0.439
	MD Triple		
Kerstjens 2020† (high risk group)	HD-ICS/LABA	0	0.503
	HD Triple		

* Study was excluded from the NMA, as it contributed no evidence to the network. † Both entries from Kerstjens 2020 are from a single study but are included in the NMA as independent studies because it was not possible to calculate a covariance matrix for the reported correlated the data. HD: high dose; ICS: inhaled corticosteroids; lnHR: log hazard ratio; lnSE: log standard error; LABA: long-acting beta-2 agonist; MD: medium dose.

Appendix 3. Model fit parameters

	Fixed-Effect Model	Random-Effects Model
Severe exacerbations- group (18 DPs)		
DIC	72.92	74.38
Total Residual Deviance, Mean	19.95	18.27
Between-study SD, Median (95% CrI)	--	0.30 (0.02, 0.94)
Severe exacerbations- high risk subgroup (6 DPs)		
DIC	26.54	28.77
Total Residual Deviance, Mean†	5.26	4.03
Between-study SD, Median (95% CrI)	--	0.263 (0.011, 0.977)

(Continued)

Severe exacerbations- low risk subgroup (12 DPs)		
DIC	39.86	46.19
Total Residual Deviance, Mean†	11.06	10.01
Between-study SD, Median (95% CrI)	--	0.314 (0.016, 1.05)
Severe exacerbations- individual treatment (36 DPs)		
DIC	95.97	97.45
Total Residual Deviance, Mean	33.86	33.92
Between-study SD, Median (95% CrI)	--	0.13 (0.01, 0.77)
Moderate to severe exacerbations- group (24 DPs)		
DIC	32.56	34.19
Total Residual Deviance, Mean	19.49	19.39
Between-study SD, Median (95% CrI)	--	0.063 (0.003, 0.243)
Moderate to severe exacerbations- high risk subgroup (12 DPs)		
DIC	17.55	19.26
Total Residual Deviance, Mean†	9.55	10.13
Between-study SD, Median (95% CrI)	--	0.080 (0.003, 0.411)
Moderate to severe exacerbations- low risk subgroup (12 DPs)		
DIC	18.33	19.24
Total Residual Deviance, Mean†	10.35	10.08
Between-study SD, Median (95% CrI)	--	0.18 (0.01, 0.67)
Moderate to severe exacerbations- individual treatment (36 DPs)		
DIC	224.90	231.30
Total Residual Deviance, Mean	33.86	33.92
Between-study SD, Median (95% CrI)	--	0.13 (0.01, 0.77)
Change from baseline in ACQ scores at 3 months-group (10 DPs)		

(Continued)

DIC	15.23	16.62
Total Residual Deviance, Mean	8.24	8.59
Between-study SD, Median (95% CrI)	--	0.032 (0.001, 0.108)
Change from baseline in ACQ scores at 6 months-group (16 DPs)		
DIC	26.68	27.48
Total Residual Deviance, Mean	17.78	15.51
Between-study SD, Median (95% CrI)	--	0.040 (0.002, 0.128)
Change from baseline in ACQ scores at 12 months-group (14 DPs)		
DIC	24.90	24.11
Total Residual Deviance, Mean	16.91	13.36
Between-study SD, Median (95% CrI)	--	0.061 (0.006, 0.130)
Change from baseline in AQLQ scores at 6 months-group (8 DPs)		
DIC	15.69	15.64
Total Residual Deviance, Mean	8.69	8.07
Between-study SD, Median (95% CrI)	--	0.132 (0.006, 0.270)
Change from baseline in AQLQ scores at 12 months - group (10 DPs)		
DIC	17.85	18.32
Total Residual Deviance, Mean	10.86	9.71
Between-study SD, Median (95% CrI)	--	0.073 (0.004, 0.219)
ACQ responders at 6 months – group (18 DPs)		
DIC	31.45	31.65
Total Residual Deviance, Mean	21.43	19.94
Between-study SD, Median (95% CrI)	--	0.038 (0.002, 0.190)
ACQ responders at 6 months - individual treatment (11 DPs)		
DIC	18.75	19.09

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Total Residual Deviance, Mean	10.75	10.54
Between-study SD, Median (95% CrI)	--	0.035 (0.002, 0.258)
ACQ responders at 12 months - group (12 DPs)		
DIC	26.70	25.06
Total Residual Deviance, Mean	18.69	14.70
Between-study SD, Median (95% CrI)	--	0.092 (0.003, 0.371)
ACQ responders at 12 months - individual treatment (8 DPs)		
DIC	17.51	16.92
Total Residual Deviance, Mean	11.51	9.83
Between-study SD, Median (95% CrI)	--	0.071 (0.003, 0.513)
All-cause SAEs - group (30 DPs)		
DIC	46.04	46.59
Total Residual Deviance, Mean	30.04	29.73
Between-study SD, Median (95% CrI)	--	0.033 (0.002, 0.228)
All-cause SAEs - individual treatment (28 DPs)		
DIC	49.67	49.67
Total Residual Deviance, Mean	26.27	26.14
Between-study SD, Median (95% CrI)	--	0.038 (0.002, 0.300)
Asthma-related SAEs - group (26 DPs)		
DIC	33.38	33.59
Total Residual Deviance, Mean	19.20	19.22
Between-study SD, Median (95% CrI)	--	0.034 (0.002, 0.252)
Asthma-related SAEs- individual treatment (26 DPs)		
DIC	123.60	123.80
Total Residual Deviance, Mean	22.80	22.86
Between-study SD,	--	0.08 (0.004, 0.634)

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Median (95% CrI)		
All-cause AEs - group (28 DPs)		
DIC	40.88	41.66
Total Residual Deviance, Mean	25.87	25.67
Between-study SD, Median (95% CrI)	--	0.024 (0.002, 0.123)
All-cause AEs - individual treatment (32 DPs)		
DIC	57.73	58.34
Total Residual Deviance, Mean	29.65	28.54
Between-study SD, Median (95% CrI)	--	0.027 (0.002, 0.170)
Dropouts due to AEs - group (28 DPs)		
DIC	49.64	49.66
Total Residual Deviance, Mean	34.31	33.22
Between-study SD, Median (95% CrI)	--	0.058 (0.003, 0.603)
Dropouts due to AEs - individual treatment (34 DPs)		
DIC	170.10	170.50
Total Residual Deviance, Mean	33.79	33.82
Between-study SD, Median (95% CrI)	--	0.091 (0.005, 0.812)

ACQ: Asthma Control Questionnaire, AE: adverse event, AQLQ: Asthma Quality of Life Questionnaire, CrI: credible interval; DIC: deviance information criterion; DP: data point, SAE: serious adverse event, SD: standard deviation.

Appendix 4. Data table for studies included for severe exacerbations for individual treatments

Dichotomous Data

Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2015*	FF/VI 100/25 qd	346	0
	FF/VI 200/25 qd	346	0
Bodzenta-Lukaszyk 2012	BUD/FM 320/12 bid	139	1

(Continued)

	FP/FM 250/10 bid	140	0
Busse 2008	FP/SAL 250/50 bid	404	2
	BUD/FM 320/12 bid	422	1
Lee 2020	FF/VI 100/25 qd	407	7
	FF/VI 200/25 qd	406	5
	FF/UMEC/VI 100/62.5/25 qd	406	7
	FF/UMEC/VI 200/62.5/25 qd	408	4
Mansfield 2017	FP/SAL 250/50 bid	41	0
	FP/SAL 200/12.5 bid	133	2
	FP/SAL 500/50 bid	44	0
Peters 2008	BUD/FM 320/12 bid	132	2
	BUD/FM 640/18 bid	443	2
Stempel 2016	FP/SAL 250/50 bid	580	1
	FP/SAL 500/50 bid	982	14
van Zyl-Smit 2020	MF/IND 160/150 qd	437	1
	FP/SAL 500/50 bid	444	2
	MF/IND 320/150 qd	443	3
Woodcock 2013	FP/SAL 250/50 bid	403	2
	FF/VI 100/25 qd	403	1

Log-Hazards Data

Study	Treatment	lnHR	lnSE
Kerstjens 2020†	MF/IND 160/150 qd	0.637	0.439
	MF/GLY/IND 80/50/150 qd		
Kerstjens 2020†	FP/SAL 500/50 bid	0	0.503
	MF/GLY/IND 160/50/150 qd		

* Study was excluded from the NMA, as it contributed no evidence to the network. † Both entries from Kerstjens 2020 are from a single study but are included in the NMA as independent studies because it was not possible to calculate a covariance matrix for the reported correlated the data. bid= twice daily, BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, lnHR= log hazard ratio, lnSE= log standard error, MF=mometasone furoate, qd= once daily, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Appendix 5. Data table for studies included for moderate to severe exacerbations

Dichotomous Data			
Study	**Treatment**	**N**	**n of participants with the event**
Bernstein 2015 (low risk group)	MD-ICS/LABA	346	3
	HD-ICS/LABA	346	4
Gessner 2020 (high risk group)	MD Triple	474	4
	HD Triple	951	4
Kerstjens 2012 (high risk group)	HD-ICS/LABA	454	149
	HD Triple	454	122
Kerstjens 2020 (high risk group)	MD-ICS/LABA	607	166
	HD-ICS/LABA	1223	324
	MD Triple	616	151
	HD Triple	615	134
Lee 2020 (low risk group)	MD-ICS/LABA	407	77
	HD-ICS/LABA	406	57
	MD Triple	406	72
	HD Triple	408	57
Mansfield 2017 (low risk group)	MD-ICS/LABA	174	8
	HD-ICS/LABA	44	2
Peters 2008 (low risk group)	MD-ICS/LABA	132	19
	HD-ICS/LABA	443	54
van Zyl-Smit 2020	MD-ICS/LABA	437	43
	HD-ICS/LABA	887	89
Virchow 2019a (high risk group)	MD-ICS/LABA	575	119
	MD Triple	573	90
Virchow 2019b (high risk group)	HD-ICS/LABA	570	138
	HD Triple	859	166

HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Appendix 6. Data table for studies included for moderate to severe exacerbations for individual treatments

Dichotomous Data			
Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2011	FP/SAL 250/50 bid	351	20
	MF/FM 200/10 bid	371	21
Bernstein 2015	FF/VI 100/25 qd	346	3
	FF/VI 200/25 qd	346	4
Bodzenta-Lukaszyk 2012	BUD/FM 320/12 bid	139	2
	FP/FM 250/10 bid	140	1
Busse 2008	FP/SAL 250/50 bid	404	50
	BUD/FM 320/12 bid	422	49
Cukier 2013	BUD/FM 320/12 bid	99	6
	FP/FM 250/10 bid	97	6
Gessner 2020	MF/GLY/IND 80/50/150 qd	474	4
	MF/GLY/IND 160/50/150 qd	476	2
	FP/SAL 500/50 bid + Tio 5 qd	475	2
Kerstjens 2020	MF/IND 160/150 qd	607	166
	FP/SAL 500/50 bid	612	182
	MF/IND 320/150 qd	611	142
	MF/GLY/IND 80/50/150 qd	616	151
	MF/GLY/IND 160/50/150 qd	615	134
Lee 2020	FF/VI 100/25 qd	407	77
	FF/VI 200/25 qd	406	57
	FF/UMEC/VI 100/62.5/25 qd	406	72
	FF/UMEC/VI 200/62.5/25 qd	408	57
Mansfield 2017	FP/SAL 250/50 bid	41	0

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	FP/SAL 200/12.5 bid	133	8
	FP/SAL 500/50 bid	44	2
Papi 2007	FP/SAL 250/50 bid	113	6
	BDP/FM 200/12 bid	115	2
Peters 2008	BUD/FM 320/12 bid	132	19
	BUD/FM 640/18 bid	443	54
van Zyl-Smit 2020	MF/IND 160/150 qd	437	43
	FP/SAL 500/50 bid	444	53
	MF/IND 320/150 qd	443	36
Virchow 2019a	BDP/FM 200/12 bid	575	119
	BDP/FM/G 200/12/20 bid	573	90
Woodcock 2013	FP/SAL 250/50 bid	403	12
	FF/VI 100/25 qd	403	10

bid= twice daily, BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, qd= once daily, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Appendix 7. Data table for studies included for the change from baseline in ACQ scores at 3 months

Study	Treatment	N	Mean CFB	SD
Gessner 2020	MD Triple	436	-1.043	0.940
	HD Triple	869	-1.060	0.938
Lee 2020	MD-ICS/LABA	379	-0.579	0.701
	HD-ICS/LABA	382	-0.607	0.723
	MD Triple	389	-0.643	0.71
	HD Triple	385	-0.699	0.667
van Zyl-Smit 2020	MD-ICS/LABA	414	-0.923	0.834
	HD-ICS/LABA	848	-0.880	0.844
Weinstein 2010	MD-ICS/LABA	205	-0.590	0.630
	HD-ICS/LABA	222	-0.580	0.626

ACQ: Asthma Control Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SD: standard deviation.

Appendix 8. Data table for studies included for change from baseline in ACQ scores at 6 months

Study	Treatment	N	Mean CFB	SD
Gessner 2020	MD Triple	437	-1.080	0.962
	HD Triple	888	-1.111	0.960
Kerstjens 2012a	HD-ICS/LABA	222	-0.580	1.058
	HD Triple	237	-0.705	1.047
Kerstjens 2012b	HD-ICS/LABA	232	-0.390	1.036
	HD Triple	216	-0.589	1.029
Kerstjens 2020	MD-ICS/LABA	598	-0.886	0.954
	HD-ICS/LABA	1195	-0.972	0.968
	MD Triple	595	-0.957	0.976
	HD Triple	607	-0.958	1.010
Lee 2020	MD-ICS/LABA	371	-0.637	0.732
	HD-ICS/LABA	374	-0.720	0.696
	MD Triple	385	-0.749	0.746
	HD Triple	376	-0.775	0.640
van Zyl-Smit 2020	MD-ICS/LABA	407	-1.035	0.706
	HD-ICS/LABA	817	-1.003	0.715

ACQ: Asthma Control Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; LD: low dose; MD: medium dose; SD: standard deviation.

Appendix 9. Data table for studies included for change from baseline in ACQ scores at 12 months

Study	Treatment	N	Mean CFB	SD
Kerstjens 2012a	HD-ICS/LABA	222	-0.593	1.073
	HD Triple	237	-0.714	1.062
Kerstjens 2012b	HD-ICS/LABA	232	-0.441	1.036

(Continued)

	HD Triple	216	-0.573	1.043
Kerstjens 2020	MD-ICS/LABA	598	-0.955	0.978
	HD-ICS/LABA	1195	-1.054	0.981
	MD Triple	595	-0.965	0.976
	HD Triple	607	-1.094	1.010
Lee 2020	MD-ICS/LABA	84	-0.781	0.660
	HD-ICS/LABA	88	-0.687	0.653
	MD Triple	89	-0.809	0.782
	HD Triple	90	-0.771	0.617
van Zyl-Smit 2020	MD-ICS/LABA	397	-1.114	0.709
	HD-ICS/LABA	790	-1.066	0.707

ACQ: Asthma Control Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SD: standard deviation.

Appendix 10. Data table for studies included for change from baseline in AQLQ scores at 6 months

Study	Treatment	N	Mean CFB	SD
Gessner 2020	MD Triple	474	0.710	1.524
	HD Triple	952	0.790	1.505
Kerstjens 2012a	HD-ICS/LABA	222	0.484	1.415
	HD Triple	237	0.525	1.401
Kerstjens 2012b	HD-ICS/LABA	232	0.169	1.325
	HD Triple	216	0.447	1.337
van Zyl-Smit 2020	MD-ICS/LABA	407	0.767	0.660
	HD-ICS/LABA	816	0.712	0.749

AQLQ: Asthma Quality of Life Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SD: standard deviation.

Appendix 11. Data table for studies included for change from baseline in AQLQ scores at 12 months

Study	Treatment	N	Mean CFB	SD
Kerstjens 2012a	HD-ICS/LABA	222	0.509	1.415
	HD Triple	237	0.547	1.416
Kerstjens 2012b	HD-ICS/LABA	232	0.245	1.356
	HD Triple	216	0.485	1.352
Kerstjens 2020	MD-ICS/LABA	536	0.810	0.833
	HD-ICS/LABA	1093	0.830	0.841
	MD Triple	535	0.760	0.833
	HD Triple	552	0.870	0.822
van Zyl-Smit 2020	MD-ICS/LABA	397	0.861	0.773
	HD-ICS/LABA	789	0.792	0.769

AQLQ: Asthma Quality of Life Questionnaire; CFB: change from baseline; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SD: standard deviation.

Appendix 12. Data table for studies included for ACQ responders at 6 months

Study	Treatment	N	Responders
Gessner 2020	MD Triple	447	393
	HD Triple	901	762
Kerstjens 2012	HD-ICS/LABA	454	213
	HD Triple	453	244
Kerstjens 2020	MD-ICS/LABA	559	395
	HD-ICS/LABA	1124	796
	MD Triple	559	401
	HD Triple	566	403
Lee 2020	MD-ICS/LABA	396	205
	HD-ICS/LABA	397	231
	MD Triple	400	247
	HD Triple	395	251

(Continued)

van Zyl-Smit 2020	MD-ICS/LABA	407	310
	HD-ICS/LABA	817	622
Virchow 2019a	MD-ICS/LABA	574	291
	MD Triple	575	317
Virchow 2019b	HD-ICS/LABA	571	319
	HD Triple	858	530

ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SD: standard deviation.

Appendix 13. Data table for studies included for ACQ responders at 6 months for individual interventions

Study	**Treatment** (dose in micrograms)	**N**	**Responders**
Gessner 2020	MF/GLY/IND 80/50/150 qd	447	393
	MF/GLY/IND 160/50/150 qd	454	387
	SAL/FP 50/500 bid +Tio 5 qd	447	375
Kerstjens 2020	MF/IND 160/150 qd	559	395
	FP/SAL 500/50 bid	562	379
	MF/IND 320/150 qd	562	417
	MF/GLY/IND 80/50/150 qd	559	401
	MF/GLY/IND 160/50/150 qd	566	403
van Zyl-Smit 2020	MF/IND 160/150 qd	407	310
	FP/SAL 500/50 bid	410	311
	MF/IND 320/150 qd	407	311
Kerstjens 2012*	HD-ICS/LABA	454	213
	HD-ICS/LABA+Tio5	453	244
Lee 2020*	FF/VI 100/25 qd	396	205
	FF/VI 200/25 qd	397	231
	FF/UMEC/VI 100/62.5/25 qd	400	247
	FF/UMEC/VI 200/62.5/25 qd	395	251

(Continued)

Virchow 2019a*	BDP/FM 200/12 bid	574	291
	BDP/FM/GLY 200/12/20 bid	575	317

* These studies were disconnected from the main network and not included in the analysis for this outcome. ACQ= Asthma Control Questionnaire, BDP= beclomethasone dipropionate, bid= twice daily, BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, HDICSLABA= high-dose inhaled corticosteroids/long-acting beta2 agonist, IND=indacaterol, MF=mometasone furoate, qd= once daily, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Appendix 14. Data table for studies included for ACQ responders at 12 months for grouped interventions

Study	Treatment	N	Responders
Kerstjens 2012	HD-ICS/LABA	454	205
	HD Triple	453	263
Kerstjens 2020	MD-ICS/LABA	536	392
	HD-ICS/LABA	1094	824
	MD Triple	537	391
	HD Triple	552	435
van Zyl-Smit 2020	MD-ICS/LABA	397	326
	HD-ICS/LABA	790	612
Virchow 2019a	MD-ICS/LABA	574	340
	MD Triple	575	350
Virchow 2019b	HD-ICS/LABA	571	332
	HD Triple	858	524

ACQ: Asthma Control Questionnaire; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Appendix 15. Data table for studies included for ACQ responders at 12 months for individual interventions

Study	**Treatment** (dose in micrograms)	N	Responders
Kerstjens 2020	MF/IND 160/150 qd	536	392
	FP/SAL 500/50 bid	547	398
	MF/IND 320/150 qd	547	426
	MF/GLY/IND 80/50/150 qd	537	391

(Continued)

	MF/GLY/IND 160/50/150 qd	552	435
van Zyl-Smit 2020	MF/IND 160/150 qd	397	326
	FP/SAL 500/50 bid	405	313
	MF/IND 320/150 qd	385	299
Kerstjens 2012*	HD-ICS/LABA	454	205
	HDICSLABA+Tio5	453	263
Virchow 2019*	BDP/FM 200/12 bid	574	340
	BDP/FM 400/12 bid	571	332
	BDP/FM /GLY 200/12/20 bid	575	350
	BDP/FM 400/12 bid +Tio 5 qd	287	168
	BDP/FM /GLY 400/12/20 bid	571	356

* These studies were disconnected from the main network and not included in the analysis for this outcome. ACQ= Asthma Control Questionnaire, BDP= beclomethasone dipropionate, bid= twice daily, BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, HD-ICS/LABA= high-dose inhaled corticosteroids/long-acting beta2 agonist, IND=indacaterol, MF=mometasone furoate, qd=once daily, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Appendix 16. Data table for studies included for all-cause SAEs for grouped interventions

Study	Treatment	N	n of participants with the event
Bernstein 2015	MD-ICS/LABA	346	4
	HD-ICS/LABA	346	1
Gessner 2020	MD Triple	474	14
	HD Triple	951	37
Kerstjens 2012a	HD-ICS/LABA	222	15
	HD Triple	237	18
Kerstjens 2012b	HD-ICS/LABA	234	25
	HD Triple	219	19
Kerstjens 2020	MD-ICS/LABA	608	38
	HD-ICS/LABA	1231	91
	MD Triple	617	49

(Continued)

	HD Triple	616	46
Lee 2020	MD-ICS/LABA	407	25
	HD-ICS/LABA	406	21
	MD Triple	406	23
	HD Triple	408	21
Mansfield 2017	MD-ICS/LABA	174	15
	HD-ICS/LABA	44	3
Peters 2008	MD-ICS/LABA	132	12
	HD-ICS/LABA	443	21
Stempel 2016	MD-ICS/LABA	580	10
	HD-ICS/LABA	982	34
van Zyl-Smit 2020	MD-ICS/LABA	437	20
	HD-ICS/LABA	887	42
Virchow 2019a	MD-ICS/LABA	574	22
	MD Triple	576	28
Virchow 2019b	HD-ICS/LABA	573	33
	HD Triple	858	43
Weinstein 2010	MD-ICS/LABA	233	3
	HD-ICS/LABA	255	2

HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SAE: serious adverse event.

Appendix 17. Data table for studies included for all-cause SAEs for individual interventions

Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2011	FP/SAL 250/50 bid	351	8
	MF/FM 200/10 bid	371	6
Bernstein 2015	FF/VI 100/25 qd	346	4
	FF/VI 200/25 qd	346	1

(Continued)

Gessner 2020	MF/GLY/IND 80/50/150 qd	474	14
	MF/GLY/IND 160/50/150 qd	476	18
	SAL/FP 50/500 µg bid HD +Tio 5 qd	475	19
Kerstjens 2020	MF/IND 160/150 qd	608	38
	FP/SAL 500/50 bid	618	39
	MF/IND 320/150 qd	613	52
	MF/GLY/IND 80/50/150 qd	617	49
	MF/GLY/IND 160/50/150 qd	616	46
Lee 2020	FF/VI 100/25 qd	407	25
	FF/VI 200/25 qd	406	21
	FF/UMEC/VI 100/62.5/25 qd	406	23
	FF/UMEC/VI 200/62.5/25 qd	408	21
Mansfield 2017	FP/SAL 250/50 bid	41	2
	FP/SAL 200/12.5 bid	133	13
	FP/SAL 500/50 bid	44	3
Stempel 2016	FP/SAL 250/50 bid	580	10
	FP/SAL 500/50 bid	982	34
van Zyl-Smit 2020	MF/IND 160/150 qd	437	20
	FP/SAL 500/50 bid	444	21
	MF/IND 320/150 qd	443	21
Weinstein 2010	MF/FM 200/10 bid	233	3
	MF/FM 400/10 bid	255	2
Woodcock 2013	FP/SAL 250/50 bid	403	5
	FF/VI 100/25 qd	403	4
Bodzenta-Lukaszyk 2012*	BUD/FM 400/12 bid	139	2
	FP/FM 250/10 bid	140	1
Cukier 2013*	BUD/FM 400/12 bid	99	3
	FP/FM 250/12 bid	97	2

(Continued)

Kerstjens 2012a*	HD-ICS/LABA	222	15
	HD-ICS/LABA+Tio5	237	18
Kerstjens 2012a*	HD-ICS/LABA	234	25
	HD-ICS/LABA+Tio5	219	19
Peters 2008*	BUD/FM 320/9 bid	132	12
	BUD/FM 640/18 bid	443	21
Virchow 2019a*	BDP/FM/GLY 200/12/20 bid	576	28
	BDP/FM 200/12 bid	574	22
Virchow 2019b*	BDP/FM/GLY 400/12/20 bid	571	28
	BDP/FM 400/12 bid	573	33
	BDP/FM 400/12 bid +Tio 5 qd	287	15

* These studies were disconnected from the main network and not included in the analysis for this outcome. BDP= beclomethasone dipropionate, bid= twice daily, BUD=budesonide, FF=fluticasone furoate, FM=formoterol, FP=fluticasone propionate, GLY= glycopyrronium, IND=indacaterol, MF=mometasone furoate, qd=once daily, SAE= serious adverse event, SAL=salmeterol, Tio=tiotropium, UMEC= umeclidinium, VI=vilanterol.

Appendix 18. Data table for studies included for asthma-related SAEs for grouped interventions

Study	Treatment	N	n of participants with the event
Gessner 2020	MD Triple	474	4
	HD Triple	951	4
Kerstjens 2012a	HD-ICS/LABA	222	10
	HD Triple	237	9
Kerstjens 2012b	HD-ICS/LABA	234	11
	HD Triple	219	8
Kerstjens 2020	MD-ICS/LABA	608	8
	HD-ICS/LABA	1231	21
	MD Triple	617	15
	HD Triple	616	9
Lee 2020	MD-ICS/LABA	407	7

(Continued)

	HD-ICS/LABA	406	6
	MD Triple	406	7
	HD Triple	408	4
Mansfield 2017	MD-ICS/LABA	174	9
	HD-ICS/LABA	44	2
Stempel 2016	MD-ICS/LABA	580	2
	HD-ICS/LABA	982	11
van Zyl-Smit 2020	MD-ICS/LABA	437	2
	HD-ICS/LABA	887	5
Virchow 2019a	MD-ICS/LABA	574	4
	MD Triple	576	7
Virchow 2019b	HD-ICS/LABA	573	11
	HD Triple	858	17
Weinstein 2010	MD-ICS/LABA	233	0
	HD-ICS/LABA	255	1

HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose; SAE: serious adverse event.

Appendix 19. Data table for studies included for asthma-related SAEs for individual interventions

Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2011	FP/SAL 250/50 bid	351	1
	MF/FM 200/10 bid	371	1
Gessner 2020	MF/GLY/IND 80/50/150 qd	474	4
	MF/GLY/IND 160/50/150 qd	476	3
	SAL/FP 50/500 µg bid HD +Tio 5 qd	475	2
Kerstjens 2020	MF/IND 160/150 qd	608	8
	FP/SAL 500/50 bid	618	9
	MF/IND 320/150 qd	613	12

(Continued)

	MF/GLY/IND 80/50/150 qd	617	15
	MF/GLY/IND 160/50/150 qd	616	9
Lee 2020	FF/VI 100/25 qd	407	7
	FF/VI 200/25 qd	406	6
	FF/UMEC/VI 100/62.5/25 qd	406	7
	FF/UMEC/VI 200/62.5/25 qd	408	4
Mansfield 2017	FP/SAL 250/50 bid	41	1
	FP/SAL 200/12.5 bid	133	8
	FP/SAL 500/50 bid	44	2
Stempel 2016	FP/SAL 250/50 bid	580	2
	FP/SAL 500/50 bid	982	11
van Zyl-Smit 2020	MF/IND 160/150 qd	437	2
	FP/SAL 500/50 bid	444	2
	MF/IND 320/150 qd	443	3
Weinstein 2010	MF/FM 200/10 bid	234	0
	MF/FM 400/10 bid	256	1
Woodcock 2013	FP/SAL 250/50 bid	403	2
	FF/VI 100/25 qd	403	1
Kerstjens 2012a*	HD-ICS/LABA	222	10
	HD-ICS/LABA +Tio5	237	9
Kerstjens 2012b*	HD-ICS/LABA	234	11
	HD-ICS/LABA +Tio5	219	8
Virchow 2019a*	BDP/FM/GLY 200/12/20 bid	576	7
	BDP/FM 200/12 bid	574	4
Virchow 2019b*	BDP/FM /GLY 400/12/20 bid	571	11
	BDP/FM 400/12 bid	573	11
	BDP/FM 400/12 bid + Tio 5 qd	287	6

* These studies were disconnected from the main network and not included in the analysis for this outcome. BDP: beclomethasone dipropionate, bid: twice daily, BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, qd: once daily, SAE: serious adverse event; SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Appendix 20. Data table for studies included for all-cause AEs for grouped interventions

Study	Treatment	N	n of participants with the event
Bernstein 2015	MD-ICS/LABA	346	54
	HD-ICS/LABA	346	52
Gessner 2020	MD Triple	474	252
	HD Triple	952	494
Kerstjens 2012a	HD-ICS/LABA	222	148
	HD Triple	237	136
Kerstjens 2012b	HD-ICS/LABA	234	171
	HD Triple	219	134
Kerstjens 2020	MD-ICS/LABA	608	392
	HD-ICS/LABA	1231	796
	MD Triple	617	387
	HD Triple	616	367
Lee 2020	MD-ICS/LABA	407	136
	HD-ICS/LABA	406	122
	MD Triple	406	135
	HD Triple	408	122
Mansfield 2017	MD-ICS/LABA	174	90
	HD-ICS/LABA	44	23
Peters 2008	MD-ICS/LABA	132	111
	HD-ICS/LABA	443	394
van Zyl-Smit 2020	MD-ICS/LABA	437	233
	HD-ICS/LABA	887	467
Virchow 2019a	MD-ICS/LABA	574	455

(Continued)

	MD Triple	576	431
Virchow 2019b	HD-ICS/LABA	573	443
	HD Triple	858	620
Weinstein 2010	MD-ICS/LABA	233	8
	HD-ICS/LABA	255	12

AE: adverse event; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Appendix 21. Data table for studies included for all-cause AEs for individual interventions

Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2011	FP/SAL 250/50 bid	351	77
	MF/FM 200/10 bid	371	85
Bernstein 2015	FF/VI 100/25 qd	346	54
	FF/VI 200/25 qd	346	52
Bodzenta-Lukaszyk 2012	BUD/FM 320/9 bid	139	26
	FP/FM 250/12 bid	140	29
Busse 2018	FP/SAL 250/50 bid	391	17
	BUD/FM 320/9 bid	389	31
Gessner 2020	MF/GLY/IND 80/50/150 qd	474	252
	MF/GLY/IND 160/50/150 qd	476	249
	SAL/FP 50/500 µg bid HD +Tio 5 qd	476	245
Kerstjens 2020	MF/IND 160/150 qd	608	392
	FP/SAL 500/50 bid	618	419
	MF/IND 320/150 qd	613	377
	MF/GLY/IND 80/50/150 qd	617	387
	MF/GLY/IND 160/50/150 qd	616	367
Lee 2020	FF/VI 100/25 qd	407	136
	FF/VI 200/25 qd	406	122

(Continued)

	FF/UMEC/VI 100/62.5/25 qd	406	135
	FF/UMEC/VI 200/62.5/25 qd	408	122
Mansfield 2017	FP/SAL 250/50 bid	41	22
	FP/SAL 200/12.5 bid	133	68
	FP/SAL 500/50 bid	44	23
Peters 2008	BUD/FM 320/9 bid	132	111
	BUD/FM 640/18 bid	443	394
van Zyl-Smit 2020	MF/IND 160/150 qd	437	233
	FP/SAL 500/50 bid	444	239
	MF/IND 320/150 qd	443	228
Weinstein 2010	MF/FM 200/10 bid	233	8
	MF/FM 400/10 bid	255	12
Woodcock 2013	FP/SAL 250/50 bid	403	106
	FF/VI 100/25 qd	403	110
Kerstjens 2012a*	HD-ICS/LABA	222	148
	HD-ICS/LABA + Tio 5	237	136
Kerstjens 2012b*	HD-ICS/LABA	234	171
	HD-ICS/LABA + Tio 5	219	134
Virchow 2019a*	BDP/FM/GLY 200/12/20 bid	576	431
	BDP/ FM 200/12 bid	574	455
Virchow 2019b*	BDP/FM/GLY 400/12/20 bid	571	410
	BDP/ FM 400/12 bid	573	443
	BDP/ FM 400/12 bid +Tio 5 qd	287	210

* These studies were disconnected from the main network and not included in the analysis for this outcome. AE: adverse event, bid: twice daily, BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, qd: once daily, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

Appendix 22. Data table for studies for dropouts due to AEs for grouped interventions

Study	Treatment	N	n of participants with the event
Bernstein 2015	MD-ICS/LABA	346	3
	HD-ICS/LABA	346	3
Gessner 2020	MD Triple	474	5
	HD Triple	951	6
Kerstjens 2012a	HD-ICS/LABA	222	6
	HD Triple	237	6
Kerstjens 2012b	HD-ICS/LABA	234	8
	HD Triple	219	2
Kerstjens 2020	MD-ICS/LABA	617	19
	HD-ICS/LABA	1236	38
	MD Triple	620	24
	HD Triple	619	12
Lee 2020	MD-ICS/LABA	407	9
	HD-ICS/LABA	406	2
	MD Triple	406	2
	HD Triple	408	2
Mansfield 2017	MD-ICS/LABA	174	2
	HD-ICS/LABA	44	1
Peters 2008	MD-ICS/LABA	132	8
	HD-ICS/LABA	443	35
van Zyl-Smit 2020	MD-ICS/LABA	439	0
	HD-ICS/LABA	891	2
Virchow 2019a	MD-ICS/LABA	576	5
	MD Triple	579	0
Virchow 2019b	HD-ICS/LABA	576	7
	HD Triple	861	5
Weinstein 2010	MD-ICS/LABA	233	2

(Continued)

	HD-ICS/LABA	255	2

AE: adverse event; HD: high dose; ICS: inhaled corticosteroids; LABA: long-acting beta-2 agonist; MD: medium dose.

Appendix 23. Data table for studies included for dropouts due to AEs for individual interventions

Study	**Treatment** (dose in micrograms)	**N**	**n of participants with the event**
Bernstein 2011	FP/SAL 250/50 bid	351	6
	MF/FM 200/10 bid	371	8
Bernstein 2015	BUD/FM 320/9 bid	346	3
	FF/VI 200/25 qd	346	3
Bodzenta-Lukaszyk 2012	BUD/FM 320/9 bid	139	3
	FP/FM 250/12 bid	140	1
Busse 2008	FP/SAL 250/50 bid	391	5
	BUD/FM 320/9 bid	389	5
Cukier 2013	BUD/FM 320/9 bid	99	1
	FP/FM 250/ 12 bid	97	1
Gessner 2020	MF/GLY/IND 80/50/150 qd	474	5
	MF/GLY/IND 160/50/150 qd	476	3
	SAL/FP 50/500 bid +Tio 5 qd	475	3
Kerstjens 2020	MF/IND 160/150 qd	617	19
	FP/SAL 500/50 bid	618	21
	MF/IND 320/150 qd	618	17
	MF/GLY/IND 80/50/150 qd	620	24
	MF/GLY/IND 160/50/150 qd	619	12
Lee 2020	FF/VI 100/25 qd	407	9
	FF/VI 200/25 qd	406	2
	FF/UMEC/VI 100/62.5/25 qd	406	2
	FF/UMEC/VI 200/62.5/25 qd	408	2

(Continued)

Mansfield 2017	FP/SAL 250/50 bid	41	2
	FP/SAL 200/12.5 bid	133	0
	FP/SAL 500/50 bid	44	1
Peters 2008	BUD/FM 320/9 bid	132	8
	BUD/FM 640/18 bid	443	35
van Zyl-Smit 2020	MF/IND 160/150 qd	439	0
	FP/SAL 500/50 bid	446	2
	MF/IND 320/150 qd	445	0
Weinstein 2010	MF/FM 200/10 bid	233	2
	MF/FM 400/10 bid	255	2
Woodcock 2013	FP/SAL 250/50 bid	403	8
	FF/VI 100/25 qd	403	6
Kerstjens 2012a*	HD-ICS/LABA	222	6
	HD-ICS/LABA +Tio 5 qd	237	6
Kerstjens 2012a*	HD-ICS/LABA	234	8
	HD-ICS/LABA +Tio 5 qd	219	2
Virchow 2019a*	BDP/FM/GLY 200/12/20 bid	579	0
	BDP/FM 200/12 bid	576	5
Virchow 2019b*	BDP/FM/GLY 400/12/20 bid	573	3
	BDP/FM 400/12 bid	576	7
	BDP/FM 400/12 bid +Tio 5 qd	288	2

* These studies were disconnected from the main network and not included in the analysis for this outcome. AE: adverse event, BDP: beclomethasone dipropionate, bid: twice daily, BUD: budesonide, FF: fluticasone furoate, FM: formoterol, FP: fluticasone propionate, GLY: glycopyrronium, IND: indacaterol, MF: mometasone furoate, qd: once daily, SAL: salmeterol, Tio: tiotropium, UMEC: umeclidinium, VI: vilanterol.

HISTORY

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CONTRIBUTIONS OF AUTHORS

Y. Oba: extracted data, assessed studies for methodological quality, constructed figures and tables for pairwise meta-analyses and otherwise constructed the review.

T Maduke: extracted data and assessed studies for methodological quality.

S Anwer: conducted the network meta-analyses, constructed tables and figures, and drafted the network meta-analysis results.

T Patel: extracted data and assessed studies for methodological quality.

S Dias: provided guidance and supervision of the network meta-analyses and their presentation and interpretation and drafted the network meta-analysis results.

All review authors contributed to the writing of the review and approved the final version of the document.

Contributions of editorial team

Sally Spencer (Coordinating Editor) edited the review; advised on methodology, interpretation and content; approved the review prior to publication.

Rebecca Fortescue (Coordinating Editor): Checked data entry prior to write-up of full review.

Milo Puhan (Contact Editor): edited the review; advised on methodology, interpretation and content.

Emma Dennett (Deputy Coordinating Editor): advised on methodology, interpretation and content; edited the review.

Emma Jackson (Managing Editor): coordinated the editorial process; conducted peer review; edited the review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

DECLARATIONS OF INTEREST

Y. Oba: has provided consultation and received honoraria from Genentech unrelated to the current review.

T Patel: none known.

S Anwer: none known.

T Maduke: none known.

S Dias: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We conducted subgroup analyses for exacerbation outcomes separating studies requiring or not requiring a history of asthma exacerbation in the previous year to assess intransitivity in the NMAs.
- We did not perform a subgroup analysis on publication status as it was homogenous across the included studies.
- We used the GeMTC package in R as well as OpenBUGS for the NMAs
- We used a normal prior (0,0.01) for relative treatment effects in some outcomes in the NMAs in order to make the models more stable.
- We used informative, empirically derived prior distributions for the between-study heterogeneity parameter for the adverse event outcomes NMAs (Turner 2015) and semi-informative half-normal prior distributions for the between-study heterogeneity parameter in severe exacerbations NMAs (Röver 2021).
- We used the node-splitting model (van Valkenhoef 2016) to assess inconsistency between direct and indirect estimates instead of an inconsistency model (Dias 2013b; Dias 2013c) in the NMAs. This is a more sensitive method to detect inconsistency.