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Long-acting muscarinic antagonists vs. long-acting β_2 agonists in COPD exacerbations: a systematic review and meta-analysis

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Study carried out at the Universidade Federal de Santa Catarina, Florianópolis (SC), at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), and at Hospital Alemão Oswaldo Cruz, São Paulo (SP) Brasil.

ABSTRACT

Objective: To determine whether long-acting muscarinic antagonists (LAMAs) provide superior therapeutic effects over long-acting β_2 agonists (LABAs) for preventing COPD exacerbations. **Methods:** This was a systematic review and meta-analysis of randomized clinical trials involving patients with stable, moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria, treated with a LAMA (i.e., tiotropium bromide, aclidinium, or glycopyrronium), followed for at least 12 weeks and compared with controls using a LABA in isolation or in combination with a corticosteroid. **Results:** A total of 2,622 studies were analyzed for possible inclusion on the basis of their title and abstract; 9 studies (17,120 participants) were included in the analysis. In comparison with LABAs, LAMAs led to a greater decrease in the exacerbation rate ratio (relative risk [RR] = 0.88; 95% CI: 0.84-0.93]; a lower proportion of patients who experienced at least one exacerbation (RR = 0.90; 95% CI: 0.87-0.94; $p < 0.00001$); a lower risk of exacerbation-related hospitalizations (RR = 0.78; 95% CI: 0.69-0.87; $p < 0.0001$); and a lower number of serious adverse events (RR = 0.81; 95% CI: 0.67-0.96; $p = 0.0002$). The overall quality of evidence was moderate for all outcomes. **Conclusions:** The major findings of this systematic review and meta-analysis were that LAMAs significantly reduced the exacerbation rate (exacerbation episodes/year), as well as the number of exacerbation episodes, of hospitalizations, and of serious adverse events.

Keywords: Pulmonary disease, chronic obstructive; Muscarinic antagonists; Adrenergic beta-agonists; Bronchodilator agents; Aerosol/therapeutic use; Disease management.

INTRODUCTION

COPD is a common preventable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response to noxious particles or gases.[1] According to the World Health Organization, COPD is the fourth leading cause of death worldwide,[2] and its burden is projected to increase in the coming decades due to the aging of the population worldwide and the continuous exposure to risk factors.[3] COPD is the fifth leading cause of hospitalization.[4] Most information comes from high-income countries, but it is known that almost 90% of COPD deaths occur in low- and middle-income countries.[2] In Latin America, the prevalence of COPD in 2005 was the highest among those over 60 years of age, ranging from 7.8% in Mexico City to 19.7% in Montevideo, Uruguay.[5] In Brazil, the prevalence rate of COPD was 15.6% in 2010,[5] with 33,000 deaths per year.[6]

The clinical presentation of COPD is progressive loss of lung function, worsening of quality of life, and increasing severity of the symptoms. In addition to chronic impairment, this disease can progress with periods of acute decline by exacerbations, defined as acute events characterized by the worsening of the respiratory symptoms of the patient beyond normal day-to-day variations, which leads to a change in medication.[7] COPD exacerbations are major contributors to deterioration of lung function, worsening of quality of life, increases in health care costs, need for hospitalization, and risk of death.[7,8] Therefore, decreasing the exacerbation rate is an important therapeutic goal for COPD patients. Therapy with a long-acting muscarinic antagonist (LAMA) or a long-acting β_2 agonist (LABA) is recommended as the first-line maintenance therapy for patients with moderate to very severe COPD.[1] These medications were primarily introduced to provide symptomatic control. On the basis of their efficacy in recent clinical trials against placebo, they are now recommended for preventing exacerbations in patients with moderate to severe COPD.[9-11] Current treatment guidelines,[1] however, do not specify whether a LAMA or a LABA should be the preferred agent.

In a meta-analysis performed by Chong et al. in 2012,[12] a LAMA (tiotropium) reduced the number of patients experiencing one or more exacerbations when compared with the use of various LABA formulations. Since that review, new formulations of LAMAs and LABAs have been introduced,[13-15] and larger trials comparing LAMAs with LABAs have been recently published.[16,17]

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Furthermore, the lack of summary statistics in order to measure the ratio of exacerbations per year and the need for updating the quality of evidence justify the interest in and the relevance of the present review, whose objective was to determine whether LAMAs are superior to LABAs in preventing COPD exacerbations.

METHODS

This review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA)[18] guidelines and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; Protocol no. CRD42015024682). The construction of the population, intervention, control, and outcome in the present study were, respectively, COPD patients, LAMAs, LABAs, and COPD exacerbations. No research ethics committee approval was needed for the present systematic review.

The study inclusion criteria were as follows: randomized clinical trials (RCTs) involving patients with stable, moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria,[1] treated with a LAMA (i.e., tiotropium bromide, aclidinium bromide, or glycopyrronium), who were followed for at least 12 weeks and compared with controls using a LABA in isolation (i.e., salmeterol, formoterol, or vilanterol) or as fixed-dose combinations of LABAs and inhaled corticosteroids (i.e., formoterol/budesonide, formoterol/mometasone, or salmeterol/fluticasone). No language or timeframe restrictions were included. The study exclusion criteria were observational studies, studies with no information regarding the severity of COPD, and studies performed with generic drugs. The literature search strategy included the terms "COPD", "LAMA", "LABA", and the derivative terms shown in Appendix 1 (all of the appendices in the present study are available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=54).

We used the following databases in order to retrieve the RCTs: PubMed; EMBASE; Cochrane Library; LILACS; Cumulative Index of Nursing and Allied Health Literature; Web Of Science; Scopus; Grey Literature Report; and the Brazilian *Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia/Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* Thesis Bank. In addition, we searched proceedings of conferences and workshops (abstracts). Authors of unpublished abstracts were contacted. We also consulted the online ClinicalTrials.gov registry and results database. The searches were performed between April and May of 2015.

Data collection and analysis

Study selection

After the preliminary search results were obtained, we eliminated duplicate citations and the remaining citations were screened in two steps. In the first step, the title and the abstract of each article were examined, and citations not meeting the inclusion criteria were discarded. In the second step, we obtained full-text copies of the remaining citations. Two of the authors independently assessed all of the studies retrieved during the search and listed all eligible RCTs. Differences and uncertainties regarding the inclusion list were resolved by discussion to reach a consensus. A third reviewer was consulted when a consensus was not achieved.

Data extraction and management

Two reviewers extracted the data independently. A third reviewer helped in cases of disagreement. Data extraction included the name of the first author; year of publication; study design; number of participants; mean age and gender of the participants in each group; diagnostic criteria; drug and dosage for each study group; and outcome measures. The primary outcome measures were COPD exacerbation rate in each group, exacerbation rate ratio, and proportions of patients who experienced at least one exacerbation during the study period. The secondary outcome measures included the number of hospitalizations due to COPD exacerbations, mortality, and the number of serious adverse events.

Assessment of risk of bias

We assessed the risk of bias of the included studies using the Cochrane Risk of Bias Tool.[19]

Data synthesis

In the binomial data analysis, an event was considered present if a patient had at least one exacerbation during the course of the RCT. Summary data were reported as relative risk (RR) and 95% CI. Wherever the rate ratio was reported, log transformation was performed before the rate ratios were analyzed and combined across studies using the generic inverse variance method. An approximate standard error of the log rate ratio was calculated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0.[19] The number needed to treat (NNT) to prevent one event was calculated using the risk difference between groups. The data were analyzed with the Review Manager software, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, UK). Trials were pooled using a fixed effects model to ensure that larger trials would have adequate weight in the overall treatment effect.

Assessment of heterogeneity

For pooled effects, we tested heterogeneity using the *I2* statistics.[19] Values of 25%, 50%, and 75%, respectively, are representative of low, moderate, and high heterogeneity.

Subgroup analysis and heterogeneity investigation

We evaluated the studies by stratifying them into studies including only patients with frequent exacerbations and studies in which the presence of

frequent exacerbations was not an inclusion criterion. We also evaluated low vs. high risk of bias using the Cochrane Risk of Bias Tool.[19]

Sensitivity analysis

The sensitivity analysis was performed with RCTs in which the comparator group included a combination of inhaled corticosteroids and LABA, those including ultra-long-acting drugs, and those with a follow-up time of 48 weeks or less.

Quality of evidence

The quality of the evidence was measured for the primary outcomes using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[20]

RESULTS

Search results

A total of 2,622 studies were analyzed by title and abstract for possible inclusion, leading to the exclusion of 2,609 studies. Thus, 13 RCTs met the inclusion criteria and were selected for the full-text phase. Four of these studies[21-24] were excluded, 9 studies remaining for the final quantitative analysis[16,17,25-31] (Figure 1). A total of 17,120 participants were included, and the main characteristics of this population are described in Table 1. Table 2 shows the types of analyses, specified treatment groups, and follow-up times. Three studies[16,17,30] included only patients with frequent exacerbations, defined as a documented history of at least one exacerbation leading to treatment with systemic glucocorticosteroids or antibiotics, or hospitalizations within the previous year.[17] All studies excluded patients with asthma, other related previous medical conditions, and COPD exacerbations within the past 4 weeks. Four studies[25,27,28,30] had both symptom-based and event-based definitions of COPD exacerbation.[32] Three studies[17,26,29] applied only a symptom-based definition, and the remaining 2 applied only an event-based definition.[16,31] Age (range: 61.8-65.0 years), proportion of male patients (range: 65-84%), and mean baseline FEV_1 in percentage of the predicted value (range: 37.7-54.5%) were comparable across the studies. Two studies[27,28] were open label for the LAMA treatment arm, which compromises blinding in this group.

Interventions

All studies compared LAMAs directly with a LABA formulation. Tiotropium HandiHaler® (18 µg; Boehringer Ingelheim, Ingelheim, Germany) was used as LAMA in all but one study,[31] which used aclidinium HandiHaler® (400 µg; Boehringer Ingelheim). As for LABAs, salmeterol (50 µg) and formoterol (12 µg), both delivered by metered dose or dry power inhalers, were used in 6 studies,[16,25-27,30,31] and an ultra-long indacaterol (150 µg) formulation was used in 3 studies.[17,28,29] A combined LABA/inhaled corticosteroid formulation was used in 1 study[16] (salmeterol, 50 µg + fluticasone propionate, 500 µg) delivered by Diskus/Accuhaler® (GlaxoSmithKline, Bretford, UK).

Risk of bias in the included studies

The methodological quality of the included studies was assessed by the Cochrane Risk of Bias Tool,[19] as shown in Figure 2. To investigate publication bias, a contour-enhanced funnel plot (Appendix 2) and analyses using Harbord's and Peter's tests were carried out.

Effect of the interventions

Primary outcomes

- Exacerbation rate ratio

The exacerbation rates with the use of LAMAs were lower than those with the use of a LABA alone (RR = 0.88; 95% CI: 0.84-0.93), as estimated by the fixed effects model. The number of randomized participants was 14,488 from 6 RCTs. Heterogeneity among the studies was low ($I2$ = 48%; Figure 3). A random effects model was applied and revealed no change in heterogeneity and negligible change in the treatment effect.

A subgroup analysis based on the history of frequent exacerbations and follow-up time of at least 48 weeks was performed, showing no change in the treatment effect (RR = 0.86; 95% CI: 0.81-0.91; Figure 3). However, heterogeneity was high ($I2$ = 74%) due to the study using an inhaled corticosteroid.[16] Those studies that included patients with or without frequent exacerbations had a similar RR (0.86) and a larger and nonsignificant 95% CI (0.73-1.02), as estimated by the fixed effects model (Figure 3). Subgroup analysis of the studies stratified by low and high risk of bias showed a smaller treatment effect in the group with a high risk of bias (Figure 3).

- Number of participants who experienced at least one exacerbation

Patients treated with LAMAs had a lower risk of exacerbation than those treated with LABAs (RR = 0.90; 95% CI: 0.87-0.94; p < 0.00001), as estimated by the fixed effects model, with no evidence of heterogeneity (I^2 = 0%; Figure 4). The subgroup analysis based on a history of frequent exacerbations is shown in Figure 4. In the subgroup of patients without frequent exacerbations (RR = 0.92; 95% CI: 0.81-1.04; p = 0.19),[25-29,31] the exacerbation rate was not significantly different between LAMAs and LABAs. In the subgroup analysis of those studies that included patients with frequent exacerbations,[16,17,30] the exacerbation rate was significantly different among the groups favoring LAMAs (RR = 0.90; 95% CI: 0.86-0.94; p < 0.00001). The overall NNT with LAMAs to prevent one exacerbation was 29, and this number was reduced to 24 when only patients with frequent exacerbations were considered.

Secondary outcomes

- Hospitalizations

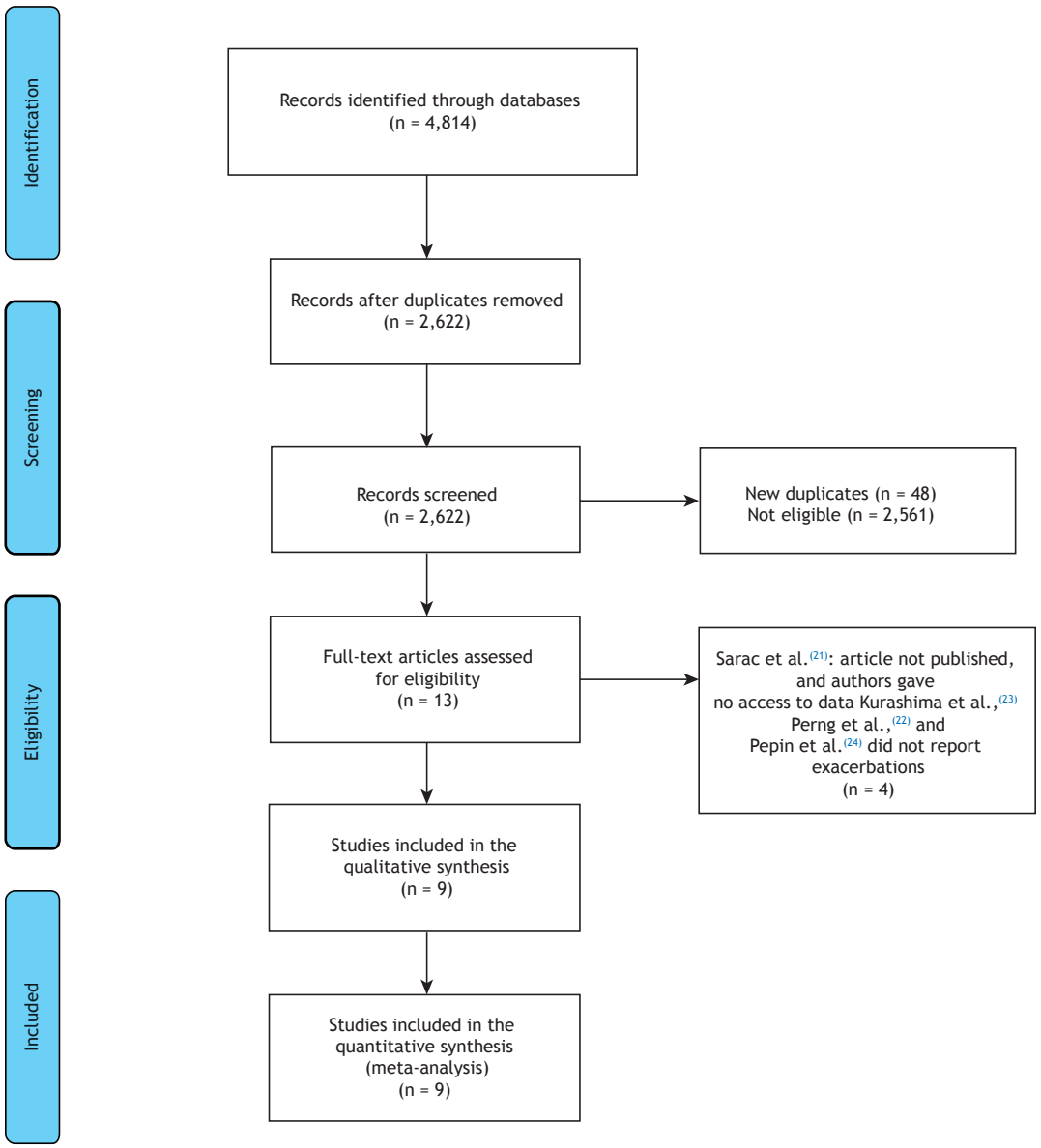

Figure 1. Flow chart of the article selection process in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[18]

Six studies,[16,17,26,27,30,31] involving 13,899 participants reported the number of patients who had had at least one hospitalization related to a COPD exacerbation. The patients treated with LAMAs had a lower risk of hospitalization when compared with those treated with LABA (RR = 0.78; 95% CI: 0.69-0.87; p < 0.0001; Figure 5). The *I2* statistic showed low heterogeneity (42%), which was completely explained when we considered only those studies that included patients with frequent exacerbations.[16,17,30]

- Mortality

Eight studies, involving 16,746 participants reported the number of deaths in each group.[16,17,25,26,28-31] None of the events were reportedly related to the medications under investigation. The number of deaths did not differ significantly between the treatment groups (RR = 1.00; 95% CI: 0.79-1.27; Figure 5).

- Serious adverse events

Five trials involving 13,738 participants reported serious adverse effects.[16,17,28,30,31] The risk of severe adverse effects was significantly lower in the patients using LAMAs than in those using LABAs (RR = 0.91, 95% CI: 0.84-0.97; p = 0.0007; Figure 5). The major reported severe adverse effects were respiratory complications, such as COPD worsening and pneumonia, and cardiac disorders.

- Publication bias

Analyses using Harbord's and Peter's tests (p = 0.4716 and p = 0.2585, respectively) and a contour-enhanced

Table 1. Characteristics of the selected studies.[a]

First author	Year	Male, %		Age, years		Smoking history, years		COPD duration, years		FEV_1%		FEV_1/FVC%	
		LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA	LAMA	LABA
Brusasco et al.[25]	2003	77.4	75.0	63.8 (8.0)	64.1 (8.5)	44.1 (22.9)	44.8 (24.1)	9.0 (7.3)	9.9 (8.0)	39.2 (11.6)	37.7 (11.7)	43.7 (9.7)	42.3 (9.5)
Briggs et al.[26]	2005	65	68	64.2 (8.6)	64.6 (7.8)	55.6 (29.6)	56.1 (27.9)	9.4 (6.5)	9.4 (6.8)	37.7 (11.9)	37.7 (12.2)	43.7 (10.0)	43 (9.7)
Buhl et al.[29]	2011	67	70	63.4 (8.3)	63.6 (8.6)	41.8 (19.8)	43.2 (20.9)	7.0 (6.0)	7.0 (6.3)	54.3 (12.8)	54.6 (12.8)	51.2 (9.4)	51.0 (9.4)
Decramer et al.[17]	2013	76	78	64	64	43.2 (23.9)	42.8 (23.8)	6.6 (5.4)	7.0 (5.7)	40.7 (6.1)	40.2 (6.0)	46.5 (9.8)	46.0 (9.7)
Donohue et al.[28]	2002	74	75	64.5 (7.9)	64.6 (8.1)	47 (25)	48 (26)	9.2 (7.8)	10.4 (8.2)	ND	ND	43.6 (9.8)	42.0 (9.5)
Vogelmeier et al.[27]	2008	79.2	75.7	63.4 (9.5)	61.8 (8.8)	38.6 (19.3)	35.4 (18.0)	6.9 (6.3)	7.0 (6.0)	51.6 (11.2)	51.6 (10.6)	54.4 (9.6)	54.6 (10.2)
Vogelmeier et al.[30]	2013	74.4	74.9	62.9 (9.0)	62.8 (9.0)	38.8 (20.0)	37.8 (19.2)	8.0 (6.7)	7.9 (6.5)	49.2 (13.3)	49.4 (13.1)	52.5 (10.8)	52.4 (11.2)
Singh et al.[31]	2014	66.5	66.4	63.1 (8.2)	63.4 (7.8)	NI	NI	NI	NI	53.6 (13.0)	54.5 (13.2)	NI	NI
Wedzicha et al.[16]	2008	84	81	65	64	39.5	41.3	ND	ND	39.4	39.1	ND	ND

LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2 agonist; ND: not done; and NI: not informed. [a]Values expressed as mean (SD), except where otherwise indicated.

Table 2. Study interventions.

First author	Year	Participants, n		Type of analysis	Intervention	Control	Follow-up time, weeks
		LAMA	LABA		LAMA	LABA	
Brusasco et al.[25]	2003	402	405	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	24
Briggs et al.[26]	2005	308	300	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	12
Buhl et al.[29]	2011	799	794	ITT	Tiotropium, 18 µg	Indacaterol, 150 µg	12
Decramer et al.[17]	2013	1,689	1,693	Per protocol	Tiotropium, 18 µg	Indacaterol, 150 µg	52
Donohue et al.[28]	2010	415	416	ITT	Tiotropium, 18 µg	Indacaterol, 150 µg	26
Vogelmeier et al.[27]	2014	385	384	ITT	Aclidinium, 400 µg	Formoterol, 12 µg	24
Vogelmeier et al.[30]	2008	221	210	ITT	Tiotropium, 18 µg	Formoterol, 12 µg	24
Singh et al.[31]	2013	3,707	3,669	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg	52
Wedzicha et al.[16]	2008	665	658	ITT	Tiotropium, 18 µg	Salmeterol, 50 µg + fluticasone propionate, 500 µg	104

LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2 agonist; and ITT: intention to treat

funnel plot (Appendix 2) provided no evidence of publication bias.

- GRADE

The evaluation using GRADE included three outcomes: exacerbation rate, number of people experiencing one or more exacerbations, and number/duration of hospitalizations. The overall quality of evidence was moderate for all outcomes (Appendix 3).

DISCUSSION

The present systematic review and meta-analysis revealed a 12% reduction in the exacerbation rate in patients on LAMA treatment when compared with those on LABA treatment, as well as a 10% reduction in the number of patients that experienced at least one exacerbation episode during the follow-up period. Treatment with LAMAs significantly reduced the number of hospitalizations due to COPD exacerbations (resulting in a decrease of 22% in RR), as well as resulting in a significant decrease (9%) in the RR of severe adverse effects. However, LAMA treatment did not significantly alter mortality.

The results of the present meta-analysis relied on head-to-head RCTs. Although a previous review evaluated these two treatments for COPD,[12] it neither reported on exacerbation rates nor on publication bias, and the treatment effect in a subgroup of patients with frequent exacerbations was not considered. The studies included in the present review had a large number of events, a large sample size, a low risk of bias, and low heterogeneity, leading to high consistency and precision of our findings.

Exacerbations and hospitalizations are important outcomes[20] that are critical for decision-making. The evidence summarized in the present review indicates that LAMA therapy provides significant advantages

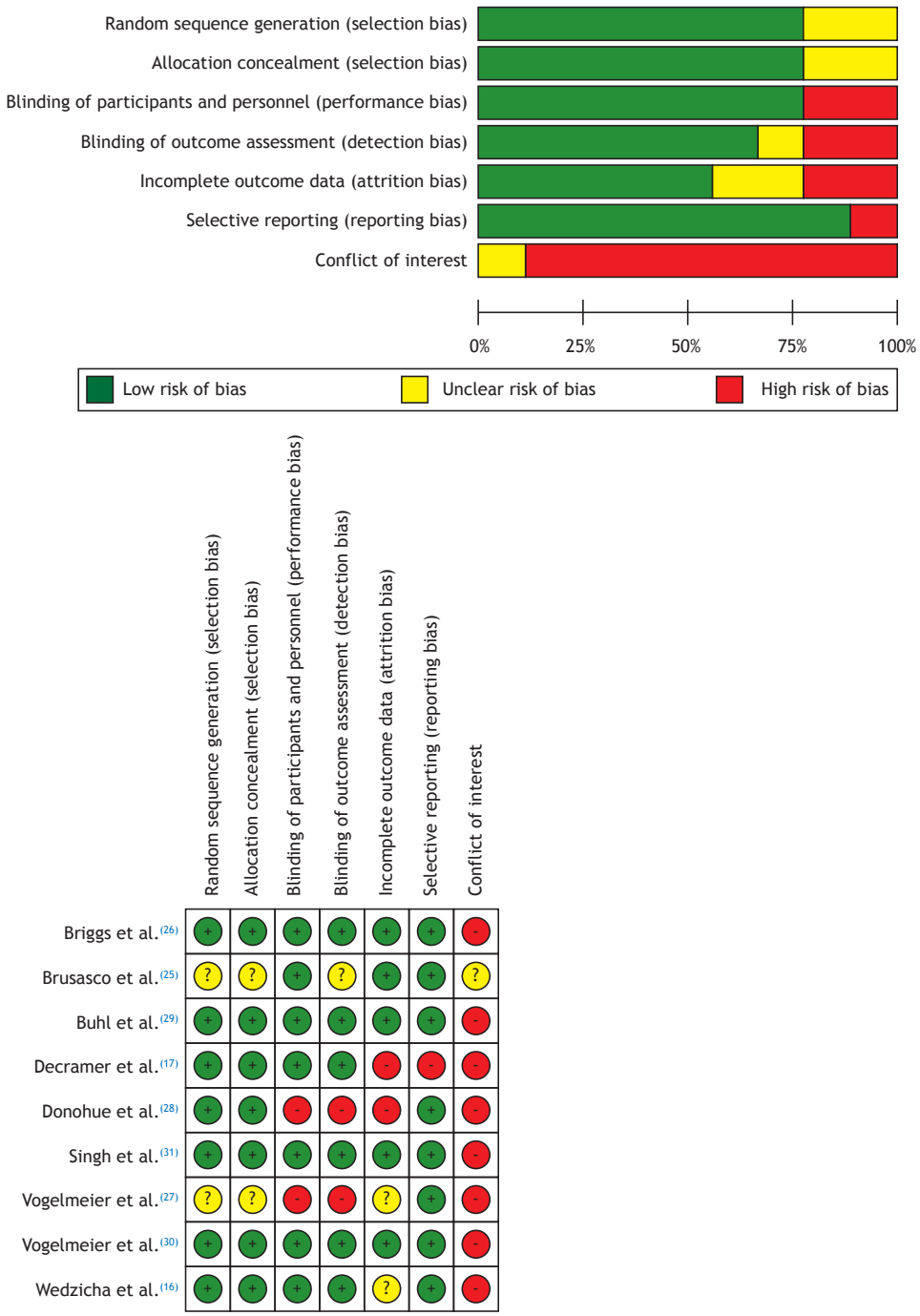

Figure 2. Risk of biases in the included studies.

when compared with LABA therapy; however, the size of the effect is likely to be a source of ongoing debate. The minimal clinically important difference for the exacerbation rate is suggested to be 22%,[33] but the lack of a uniform definition of exacerbation, the lack of severity grading, and the underreporting of exacerbations make it difficult to establish a valid minimal clinically important difference.[34]

Due to seasonal variation, evaluating the frequency of exacerbations requires follow-up periods of at least 1 year.[35] In the long term, patients with previous frequent exacerbations have a high probability of suffering from frequent exacerbations in the future.[36,37] The present review included studies involving patients with a low probability of exacerbations and follow-up times shorter than 1 year. Therefore, this can explain

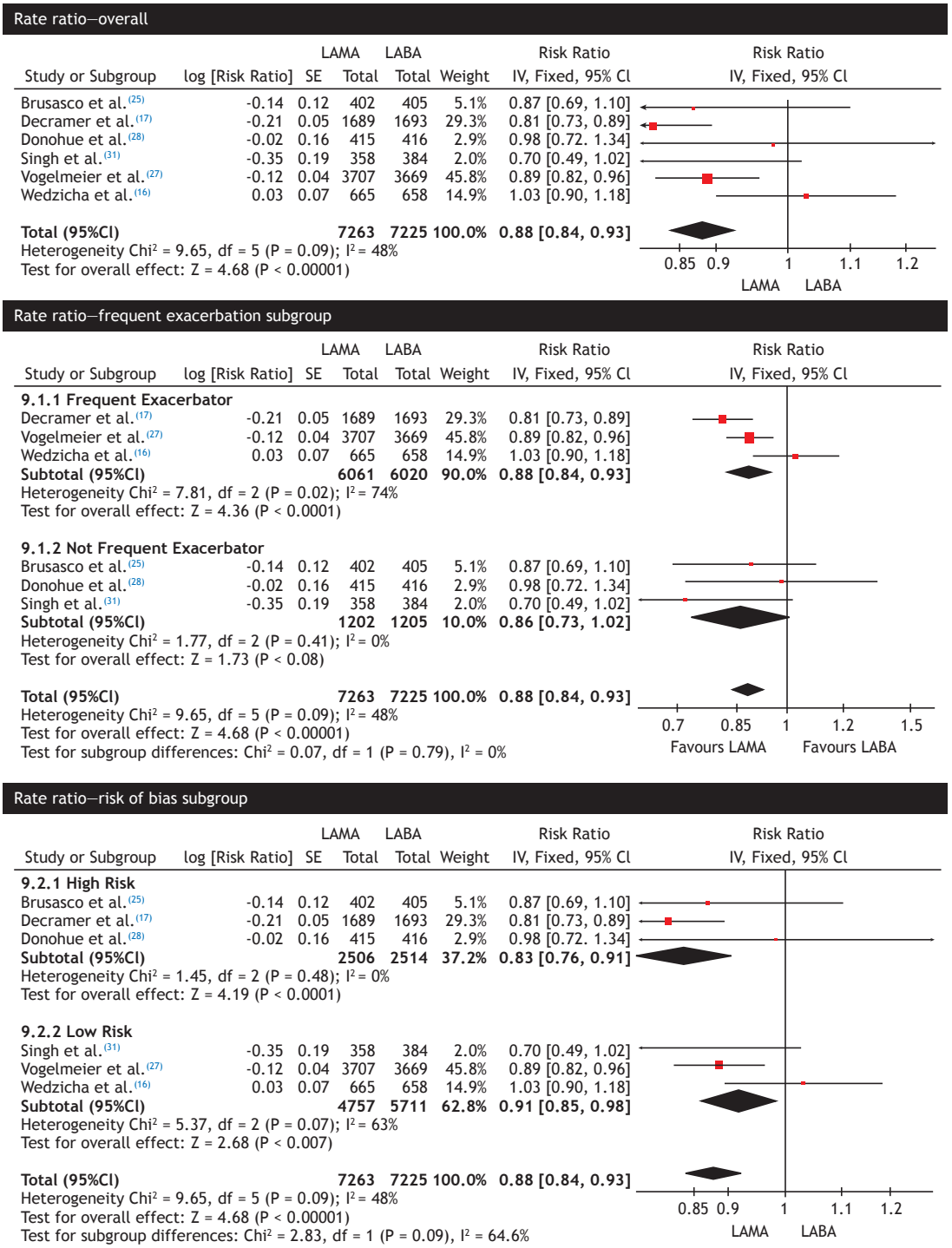

Figure 3. Rate ratio—overall and subgroups.

why the estimated treatment effect was not significant in the subgroup analysis of studies that included COPD patients with infrequent exacerbations.

Inhaled corticosteroids alone or in combination with LABAs reduce airway inflammation (detected by endobronchial biopsy),[38,39] leading to a reduction in the risk of exacerbations.[40] One of the studies included in the analysis compared a LAMA with a LABA in combination with an inhaled corticosteroid.[16] The inclusion of that study in the data synthesis compromised the results of the rate ratio of exacerbations regarding heterogeneity. However, the compromise in the overall effect after excluding that study was small, with a reduction of 0.2 in the rate ratio and of 0.1 in the number of exacerbations, which made the authors decide to keep the study in the analysis.

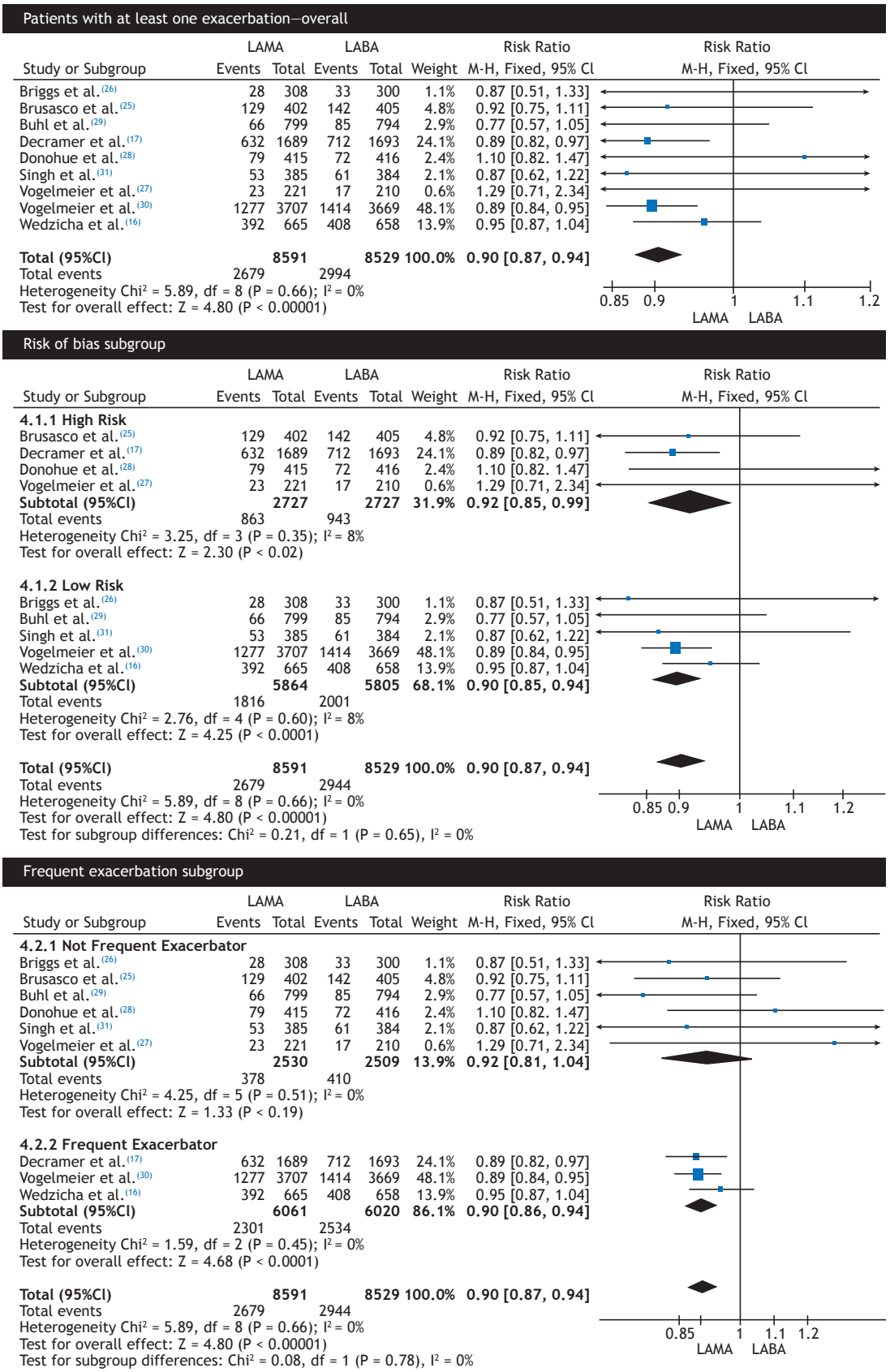

Figure 4. Proportion of patients with at least one exacerbation and subgroups.

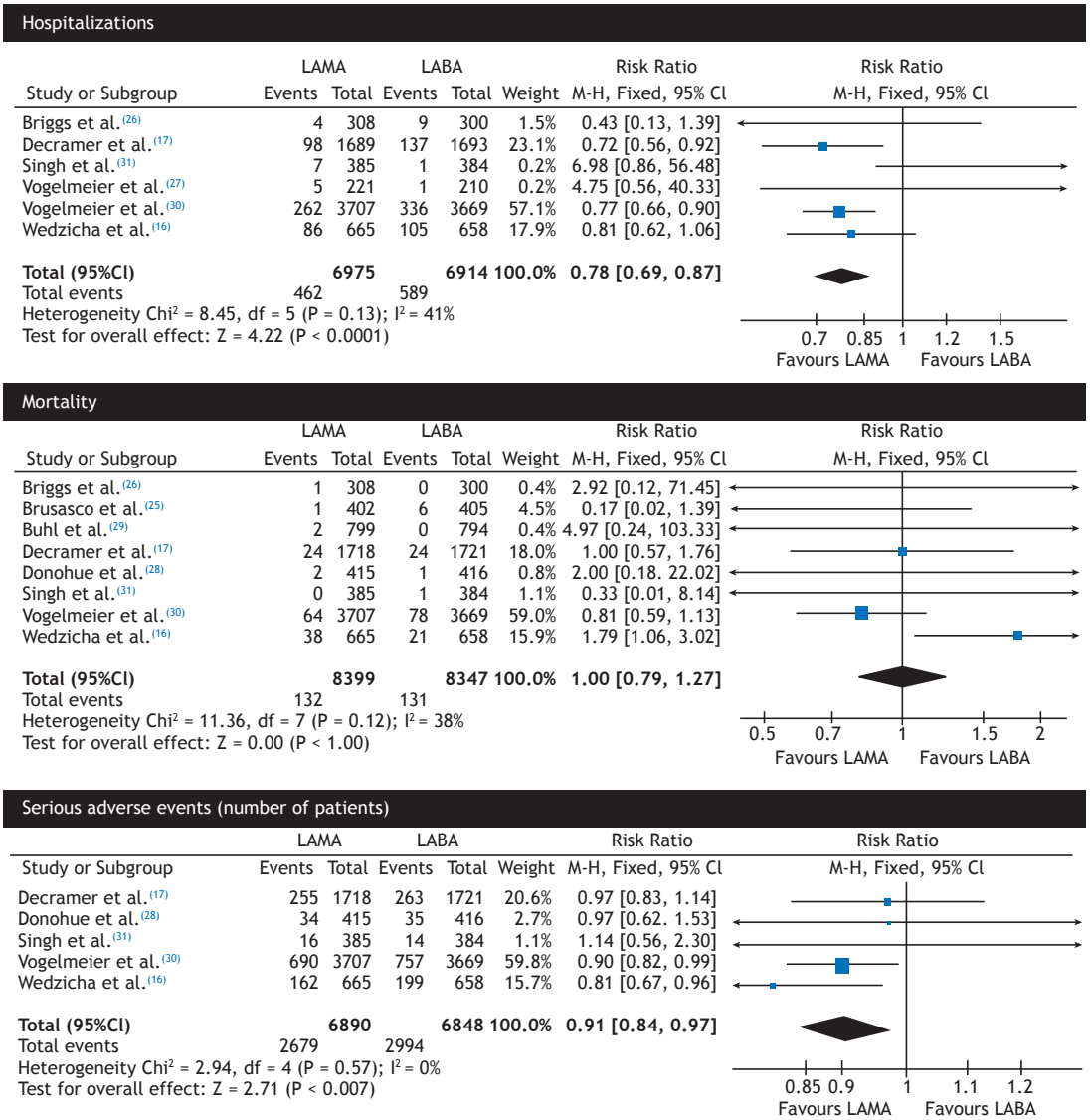

Figure 5. Secondary outcomes.

The definitions of exacerbation and exacerbation severity need to be standardized. There is a symptom-based definition that uses a complex of worsening respiratory symptoms to define exacerbation, and there is an event-based definition that requires a therapeutic intervention or a change in health care utilization.[32] The latter approach has more objective and more easily measured parameters, but it can lead to underreporting of mild exacerbation episodes,[34,41,42] which can be a source of bias, since not all of the studies included symptom diaries to report exacerbations. Blinded adjudication of exacerbation events by an adjudication committee can help classify COPD exacerbations.[43] The RCTs included here did not employ blinded adjudication, making the information reliant on individual investigators, which can be uncertain.

Exacerbation rates can be influenced by a small minority of patients who experience multiple exacerbation events. The summary statistic is the rate ratio. The best statistical approach for evaluating this ratio is a weighted approach that adjusts the ratio for asymmetry in the follow-up time, producing an unbiased estimate.[44] The authors of the studies covered by the present review used a weighted statistical approach of the exacerbation rates,[16,17,28,30] which increases the reliability of this finding.

The evaluation of outcomes in the GRADE system included exacerbation rate (moderate quality), number of people experiencing one or more exacerbations (moderate quality), and hospitalizations (moderate quality). We did not further downgrade the risk of bias, because most of the RCTs were at a low risk for that (as assessed by to the Cochrane Risk of Bias Tool), although there was some confusion in some small RCTs regarding randomization, allocation concealment, and attrition bias.

The findings of the present review are in agreement with those of a previous review[12] reporting that

LAMAs reduced the number of patients experiencing an exacerbation with a similar estimated effect. However, the exacerbation rate was not reported, whereas the present review demonstrated that the LAMA treatment reduced the exacerbation rate. Heterogeneity was found within this outcome, but it could be explained.

Considering that COPD is a chronic and prevalent disease,[5,6] decisions about which medication should be recommended must take into consideration the relatively large NNT to prevent one exacerbation. Furthermore, studies focusing on cost effectiveness are needed to guide the decision-making process in public health care systems.

The major findings of this systematic review and meta-analysis were that LAMAs, when compared with LABAs, significantly reduced the number of COPD patients experiencing exacerbation episodes, as well as the number of exacerbations per year, of exacerbation-related hospitalizations, and of severe adverse effects.

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