ORIGINAL ARTICLE
ASTHMA

ICS-formoterol reliever *versus* ICS and short-acting β_2-agonist reliever in asthma: a systematic review and meta-analysis

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ABSTRACT

Background: The Global Initiative for Asthma recommends as-needed inhaled corticosteroid (ICS)-formoterol as an alternative to maintenance ICS plus short-acting β_2-agonist (SABA) reliever at step 2 of its stepwise treatment algorithm. Our aim was to assess the efficacy and safety of these two treatment regimens, with a focus on prevention of severe exacerbation.

Methods: We performed a systematic review and meta-analysis of all randomised controlled trials (RCTs) comparing as-needed ICS-formoterol with maintenance ICS plus SABA. MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and Clinicaltrials.gov were searched from database inception to 12 December 2019. The primary outcome was time to first severe exacerbation. RCTs were excluded if they used as-needed budesonide-formoterol as part of a maintenance and reliever regimen, or did not report on severe exacerbations. The review is registered with PROSPERO (identifier number CRD42020154680).

Results: Four RCTs (n=8065 participants) were included in the analysis. As-needed ICS-formoterol was associated with a prolonged time to first severe exacerbation (hazard ratio 0.85, 95% CI 0.73–1.00; p=0.048) and reduced daily ICS dose (mean difference −177.3 µg, 95% CI −182.2–−172.4 µg). Asthma symptom control was worse in the as-needed group (Asthma Control Questionnaire-5 mean difference 0.12, 95% CI 0.09–0.14), although this did not meet the minimal clinically important difference of 0.50 units. There was no significant difference in serious adverse events (OR 1.07, 95% CI 0.84–1.36).

Conclusion: As-needed ICS-formoterol offers a therapeutic alternative to maintenance low-dose ICS plus SABA in asthma and may be the preferred option when prevention of severe exacerbation is the primary aim of treatment.

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As-needed low-dose ICS-formoterol prolongs time to first severe asthma exacerbation compared to maintenance ICS/SABA reliever and represents an alternative for patients, particularly when severe exacerbation prevention is the primary treatment aim https://bit.ly/3mpHVKc

Cite this article as: Hatter L, Bruce P, Braithwaite I, *et al.* ICS-formoterol reliever *versus* ICS and short-acting β_2-agonist reliever in asthma: a systematic review and meta-analysis. *ERJ Open Res* 2021; 7: 00701-2020 [https://doi.org/10.1183/23120541.00701-2020].

This article has supplementary material available from openres.ersjournals.com.

Received: 27 Sept 2020 | Accepted: 21 Oct 2020

Introduction

The Global Initiative for Asthma (GINA) recommends inhaled corticosteroid (ICS)-formoterol as the preferred reliever across the spectrum of asthma severity in adults and adolescents [1]. At step 1 of the GINA stepwise treatment algorithm, this recommendation is supported by data from two randomised controlled trials (RCTs), which demonstrated that as-needed combination low-dose budesonide-formoterol reduced the risk of severe exacerbations by ⩾60% compared to short-acting β_2-agonist (SABA) reliever therapy in mild asthma [2, 3]. At steps 3 and 4, this recommendation is supported by evidence that in patients taking maintenance ICS with a long-acting β_2-agonist (LABA), the use of ICS-formoterol reliever rather than SABA reliever reduced the risk of severe exacerbations by 32% [4]. At steps 4 and 5, this recommendation is supported by evidence that in patients taking budesonide-formoterol maintenance and reliever therapy, the risk of a severe exacerbation is reduced by 23% compared with maintenance ICS/LABA at double the equivalent ICS dose, plus SABA reliever [4].

The one step where GINA suggests equipoise between treatments is at step 2, with low-dose as-needed ICS-formoterol now recommended as an alternative to maintenance low-dose ICS plus SABA reliever [1]. This update was first made in 2019 following publication of two large double-blind RCTs, which demonstrated noninferiority for severe exacerbations between the two regimens [2, 5, 6, 7]. Two real-world RCTs have since reported that as-needed budesonide-formoterol reduced the risk of a severe exacerbation compared with maintenance budesonide plus SABA reliever in patients with mild to moderate asthma [3, 8].

Undertaking a systematic review to identify additional studies and combining all available results in a summary data meta-analysis has the potential to improve the precision of the estimates of the treatment effects for the comparison between these two regimens. The aim was to compare the efficacy and safety of as-needed budesonide-formoterol with maintenance ICS plus SABA reliever in adults and children with mild to moderate asthma. The primary focus was on severe exacerbation prevention as an important clinical and public health outcome [9], and in recognition of the zero-tolerance approach to severe exacerbations that has been advocated [10].

Methods

Search strategy and selection criteria

This systematic review and meta-analysis is registered with PROSPERO (identifier number CRD42020154680) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [11]. Two reviewers (LH and PB) searched MEDLINE (Ovid), Embase (Ovid), the Cochrane Central Register of Controlled Trials and Clinicaltrials.gov from database inception to 12 December 2019. Full search strategies can be found in supplementary figure S1. Results were enhanced through forward–backward citation tracking of relevant publications.

RCTs comparing as-needed ICS-formoterol with maintenance ICS plus SABA reliever in adults and/or children with mild to moderate asthma were eligible for inclusion. RCTs were excluded if they used as-needed budesonide-formoterol as part of a maintenance and reliever regimen, or did not report on severe exacerbations. Non-RCTs and studies without full-text publications were excluded. No language restrictions were built into our literature search.

Two reviewers (LH and PB) independently screened the titles, abstracts and full-text publications against the eligibility criteria. Full-text publications that met the inclusion criteria were included in the meta-analysis. Disagreements were resolved through discussion within the review team.

Data analysis

The primary outcome was time to first severe exacerbation. Secondary outcomes included rate ratio (RR) of severe exacerbation; risk of at least one severe exacerbation, emergency department (ED) visit, hospital admission, combined ED visit or hospital admission, serious adverse events (SAE) and death; mean daily ICS dose; Asthma Control Questionnaire (ACQ)-5 scores; and forced expiratory volume in 1 s (FEV_1). Mean number of daily formoterol-adjusted β_2-agonist actuations was a *post hoc* outcome variable.

Data on the primary and secondary outcomes were extracted into tables (supplementary tables S3–S7). This was done independently by three reviewers (LH, PB and RB). Missing data relevant to the meta-analysis were obtained from study authors on request. All data were cross-checked and verified by the same three reviewers prior to inclusion in the meta-analysis.

Three reviewers (JF, LH and PB) independently assessed risk of bias using the Cochrane Collaboration risk of bias tool for RCTs [12].

Inverse variance weighted meta-analysis was used for the hazard ratio (HR) for time to first severe exacerbation, the rate ratio of number of severe exacerbations, the odds ratio for risk of at least one severe exacerbation, odds ratio for risk of at least one SAE, mean difference for investigational product ICS dose, mean difference in the

number of β_2-agonist actuations, ACQ-5 and FEV_1. Peto's method (Peto's odds ratio (POR)) was used for estimation of the risk of at least one ED visit, hospital admission, ED visit or hospital admission, and death.

The meta-analyses of the hazard ratios for time to first severe exacerbation, and the rate ratios for number of severe exacerbations used the logarithm-transformed estimates of hazard and rate and their confidence intervals to estimate the variance, on the logarithm scale, for the estimates. The variances were estimated by dividing the difference between the upper and lower confidence bounds by 3.92, and squaring the results. Back-transformation by exponentiation gives estimates back on the scale of rate ratios and hazard ratios. The risk of at least one exacerbation, SAE, ED visit, hospitalisation, combined ED visit or hospitalisation, and death used the reported counts of events and nonevents. For ICS dose, the reported counts and mean±SD by study arm were used. For the β_2-agonist actuations, the mean±SD by study arm were used, with the data standardised in formoterol equivalents, based on actuations equivalent to formoterol at a dose of 6 µg having bronchodilator bioequivalence with terbutaline at a dose of 500 µg and salbutamol at 200 µg, when administered repeatedly in acute severe asthma [13–15]. For ACQ-5 and FEV_1 the study estimates of mean differences and confidence intervals were used. The variances were estimated by the difference between the upper and lower confidence bounds, divided by 3.92 and squared. Homogeneity statistics were calculated for each analysis as well as an estimate of the I-squared (I^2) statistic. Fixed-effects pooled estimates were calculated. Meta-analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

Certainty of evidence for each outcome was assessed independently by two reviewers (LH and PB) using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) domains: risk of bias, imprecision, inconsistency, indirectness and publication bias (supplementary figure S2).

Results

The literature search yielded 1947 results (figure 1). Following removal of duplicates, 1540 references were screened against the eligibility criteria, of which 1536 were excluded. Four RCTs (8065 participants) comparing as-needed budesonide-formoterol (4023 participants) with maintenance ICS plus SABA reliever (4042 participants) in adults (n=4) and adolescents aged ⩾12 years (n=2) were included in the meta-analysis (table 1) [2, 3, 5, 8]. No studies examined the use of as-needed ICS-formoterol in children aged ⩽11 years. All studies compared as-needed budesonide-formoterol *via* dry-powder inhaler (DPI) with maintenance budesonide DPI plus SABA reliever (either salbutamol pressurised metered-dose inhaler [8] or terbutaline DPI) [2, 3, 5].

Key differences between the studies (table 1 and supplementary table S1) included the larger size and double-blind, placebo-controlled design of the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 studies [2, 5]. By comparison, the PeRsonalised Asthma Combination Therapy with an Inhaled Corticosteroid And fast-onset Long-acting β-agonist (PRACTICAL) and the Novel Symbicort Turbuhaler Asthma Reliever Therapy (Novel START) trials were smaller and used an open-label, real-world design [3, 8]. In all four studies, participants were receiving step 1 [2, 3, 5, 8] or 2 [2, 5, 8] treatment at study entry, although some participants enrolled in PRACTICAL were on step 3 therapy at baseline. PRACTICAL was the only fully independently funded study.

All studies were deemed to be at low risk of bias (supplementary figure S3).

As-needed budesonide-formoterol was associated with a prolonged time to first severe exacerbation (HR 0.85, 95% CI 0.73–1.00; p=0.048) (table 2 and figure 2).

As-needed budesonide-formoterol reduced the rate ratio of severe exacerbations (RR 0.85, 95% CI 0.72–1.00) (figure 3a) and the risk of at least one severe exacerbation (OR 0.86, 95% CI 0.73–1.01) (figure 3b). Quantitative heterogeneity was evident in these analyses with the two larger studies showing less of a difference between the two treatment groups.

There were fewer ED visits in the as-needed budesonide-formoterol group (POR 0.65, 95% CI 0.43–0.98). There was no difference in hospitalisations (POR 0.85, 95% CI 0.49–1.49) or the combination of ED visits or hospitalisations (POR 0.73, 0.52–1.04) (figure 4). The datasets contributing to these variables had few or no events.

There was no difference between the two groups in the number of participants experiencing at least one SAE (OR 1.07, 95% CI 0.84–1.36) or deaths (POR 0.52, 95% CI 0.10–2.57). Of the six reported deaths, one was asthma-related and occurred in the maintenance ICS group.

The ICS dose taken was lower in the as-needed budesonide-formoterol group across all four studies (mean difference −177.3 µg, 95% CI −182.2–−172.4 µg), with evidence of heterogeneity (I^2 98.8).

The number of formoterol-adjusted β_2-agonist-containing actuations per day was higher in the as-needed budesonide-formoterol group across all four studies (mean difference 0.08, 95% CI 0.05–0.10), with evidence of heterogeneity (I^2 94.2).

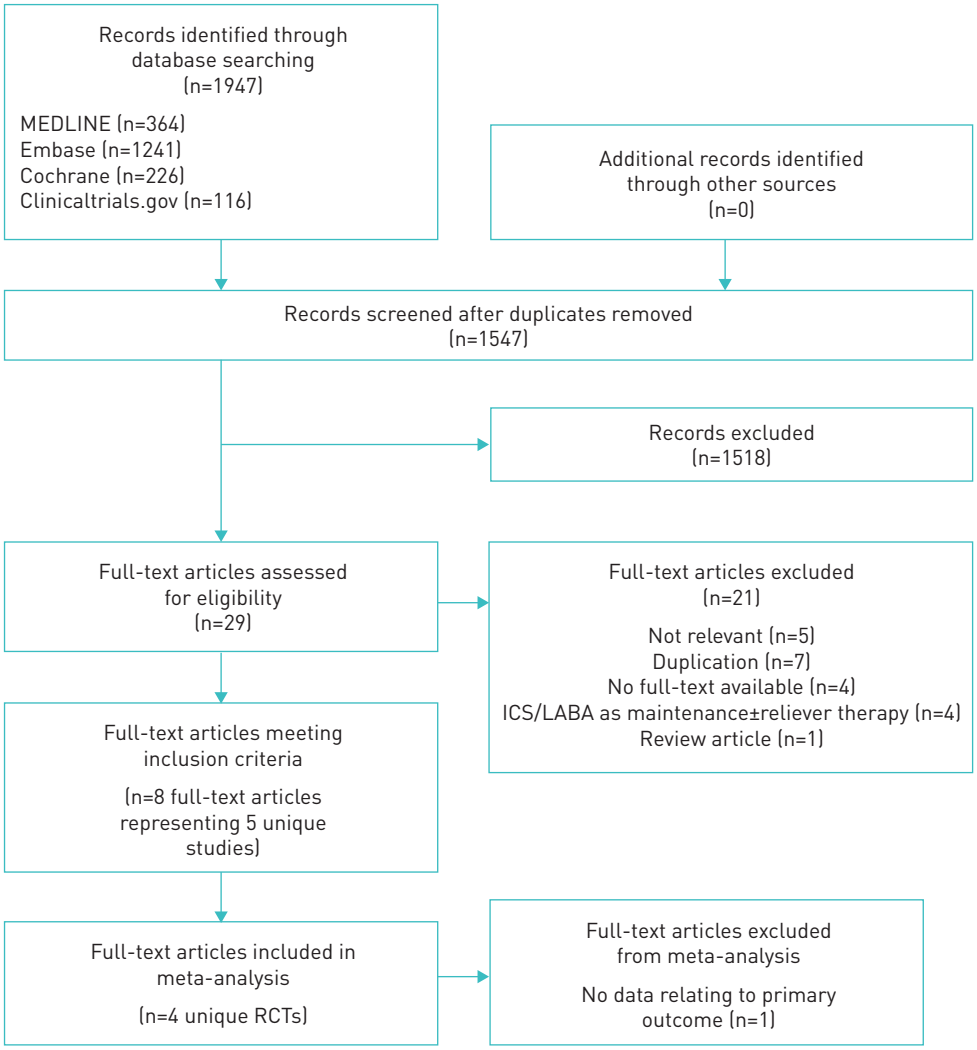

FIGURE 1 Flow diagram of literature search and screening process. ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; RCT: randomised controlled trial.

The ACQ-5 score was higher in the as-needed budesonide-formoterol group (mean difference 0.12, 95% CI 0.09–0.14). The FEV_1 was lower in the as-needed budesonide-formoterol group (mean difference −27.4 mL, 95% CI −40.7–−14.1 mL). There was evidence of heterogeneity (I^2 74.8) with the two SYGMA studies having a larger and negative effect on FEV_1, favouring ICS maintenance.

Discussion

This meta-analysis has shown modest evidence of a statistically significant 15% reduction in the hazard ratio for a first severe exacerbation with as-needed budesonide-formoterol compared with maintenance budesonide plus SABA reliever in adults and adolescents with mild to moderate asthma. We propose that this difference is clinically important, although acknowledge there is no agreed standard for what constitutes a minimal clinically importance difference (MCID) in exacerbation risk. Similar estimates of a 15% reduction in the rate ratio of severe exacerbations and a 14% reduction in the risk of at least one severe exacerbation were noted, together with a 35% reduction in risk of at least one ED visit. In contrast, the maintenance ICS regimen was associated with a greater level of asthma symptom control and higher lung function, although the differences were well below the MCID for these measures [16, 17].

The primary outcome of time to first severe exacerbation was chosen as it minimises the effect of changes to the randomised treatment (such as the introduction of additional medication) and participant withdrawal [9, 18], which occurred in the Novel START study following a first severe exacerbation. Severe exacerbation was similarly defined in all studies, based on the American Thoracic Society/European Respiratory Society criteria [9]. The Novel START study definition included the "prescription" of oral

TABLE 1 Characteristics of included studies

Study, first author (year)	Design	Duration	Sites	Population	Participants (intervention *versus* control) [#] n	Primary outcome (analysis)	Intervention	Control
SYGMA 1 O'Byrne (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	261 sites, 18 countries	Adults and adolescents (⩾12 years)	2559 (1277 *versus* 1282)	Mean percentage of electronically recorded weeks with well-controlled asthma per patient (noninferiority)[¶]	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
SYGMA 2 Bateman (2018)	RCT, parallel-group, double-blind placebo-controlled	52 weeks	350 sites, 25 countries	Adults and adolescents (⩾12 years)	4176 (2089 *versus* 2087)	Annualised rate of severe exacerbations (non-inferiority)[+]	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed plus twice-daily placebo	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 500 µg (Turbuhaler) as needed
Novel start Beasley (2019)	RCT, parallel-group, open-label, real-world	52 weeks	16 sites, 4 countries	Adults (⩾18 years)	425 (220 *versus* 225)	Annualised rate of asthma exacerbations (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as-needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus albuterol 100 µg (Ventolin pMDI) two inhalations as needed
PRACTICAL Hardy (2019)	RCT, parallel-group, open-label, real-world	52 weeks	15 sites, 1 country	Adults and adolescents (⩾18 years)	885 (437 *versus* 448)	Number of severe exacerbations per patient per year (superiority)	Budesonide-formoterol 200/6 µg (Symbicort Turbuhaler, AstraZeneca) one inhalation as needed	Budesonide 200 µg (Pulmicort Turbuhaler, AstraZeneca) twice daily plus terbutaline 250 µg (Bricanyl Turbuhaler, AstraZeneca) two inhalations as needed

This table does not include details of additional trial arms, which were present in the SYGMA 1 and Novel START studies. All information derived from published trial protocols (including trial registries), manuscripts and supplementary material. RCT: randomised controlled trial; pMDI: pressurised metered-dose inhaler. [#]: intervention refers to as-needed budesonide-formoterol, control refers to maintenance budesonide plus short-acting β_2-agonist (SABA) reliever. Participant numbers refer to as-needed inhaled corticosteroid (ICS)-formoterol and maintenance ICS plus SABA arms only; numbers for SABA only arms in SYGMA 1 and Novel START not included; [¶]: superiority analysis for as-needed budesonide-formoterol *versus* SABA (primary), and noninferiority analysis for as-needed budesonide-formoterol *versus* maintenance budesonide plus SABA (secondary); [+]: initially superiority.

TABLE 2 Summary of findings and certainty of evidence

	Reference	Budesonide-formoterol		Maintenance budesonide		Pooled fixed effect (95% CI)	I^2 (95% CI)	Certainty of evidence
		Event	Participants	Event	Participants			
Severe asthma exacerbations								
Time to first severe exacerbation	[2,3,5,8]	294	4023	342	4042	HR 0.85 (0.73–1.00)	60.7 (0.0–86.9)	Moderate
Number of severe exacerbations	[2,3,5,8]	351	4023	399	4042	RR 0.85 (0.72–1.00)	49.5 (0–83.3)	Moderate
Risk of at least one severe exacerbation	[2,3,5,8]	294	4023	342	4042	OR 0.86 (0.73–1.01)	53.5 (0–84.6)	Moderate
ED visits with systemic glucocorticoid use#	[2,3,5,8]	36	4023	56	4042	POR 0.65 (0.43–0.98)	0.0 (0–76.1)	Moderate
Hospital admissions#	[2,3,5,8]	23	4023	27	4042	POR 0.85 (0.49–1.49)	0.0 (0.0–89.1)	Low
ED visit or hospital admissions#	[2,3,5,8]	55	4023	75	4042	POR 0.73 (0.52–1.04)	0.0 (0–82.7)	Moderate
Serious adverse events								
Risk of at least one SAE	[2,3,5,8]	140	4028	131	4044	OR 1.07 (0.84–1.36)	30.1 (0–74.6)	Very low
Deaths	[2,3,5,8]	2	4028	4	4044	POR 0.52 (0.10–2.57)	0.0 (0–84.5)	Very low
Inhaled medication use								
ICS dose	[2,3,5,8]	NA	3641	NA	3649	MD −177.3 (−182.2–−172.4)	98.8 (98.2–99.2)	Moderate
β_2-agonist daily actuations¶	[2,3,5,8]	NA	3640	NA	3645	MD 0.08 (0.05–0.10)	94.2 (88.8–97.2)	Low
Asthma symptom control and lung function+								
ACQ-5 score	[2,3,5,8]	NA	4023	NA	4042	MD 0.12 (0.09–0.14)	42.5 (0–80.7)	High
FEV_1§	[2,3,5,8]	NA	4023	NA	4042	MD −27.4 (−40.7–−14.1)	74.8 (29.9–90.9)	Low

Data are presented as n, unless otherwise stated. ED: emergency department; SAE: serious adverse event; ICS: inhaled corticosteroid; ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s; HR: hazard ratio; RR: rate ratio; POR: Peto odds ratio; NA: not applicable; MD: mean difference. #: data displayed are for the risk of at least one event; ¶: for the meta-analysis, daily β_2-agonist-containing actuations were standardised to formoterol 6 µg=salbutamol 200 µg=terbutaline 500 µg. Data for daily β_2-agonist-containing actuations from the SYGMA 1 and SYGMA 2 studies were provided by the study authors, on request; +: numbers of participants in ACQ-5 and FEV_1 represent total numbers of participants in each arm; it is not possible to determine exact numbers as individual analyses used mixed linear models to measure continuous and repeated measures; §: SYGMA 1 and SYGMA 2 reported pre-bronchodilator FEV_1 measurements; Novel-START and PRACTICAL reported on-treatment FEV_1 measurements.

corticosteroids, whereas the other studies measured "use". It is unlikely this difference would affect the validity of the meta-analysis, based on the assumption that the ratios of severe exacerbations do not depend on individual definitions.

There was evidence of heterogeneity in the findings for the primary outcome variable between the four RCTs. Much of this can be explained by the difference in study design, with the results of the two open-label studies having a greater treatment effect (favouring as-needed budesonide-formoterol) than the two large double-blind studies. By removing the need to take a placebo inhaler every day, the open-label design allowed the use of budesonide-formoterol as a single medication with no requirement for a regular inhaler. This enabled patient behaviour to be closer to that seen in real life and may enhance the generalisability of these findings to clinical practice.

A number of secondary outcomes that showed no evidence of a significant difference between the two groups, such as the number of deaths and hospital admissions, were limited by the small number of events. However, the significant 35% reduction in ED visits with as-needed budesonide-formoterol suggests this regimen may provide protection against the most severe exacerbations associated with greater mortality risk [19].

A reduction in the daily dose of ICS was observed in the as-needed budesonide-formoterol group in all four studies. Although there was evidence of heterogeneity in this analysis, the estimates for all four studies were in the same direction. This supports the idea that timing of ICS administration, driven by symptom-directed bronchodilator use, may be of greater importance for preventing severe exacerbations than total ICS dose

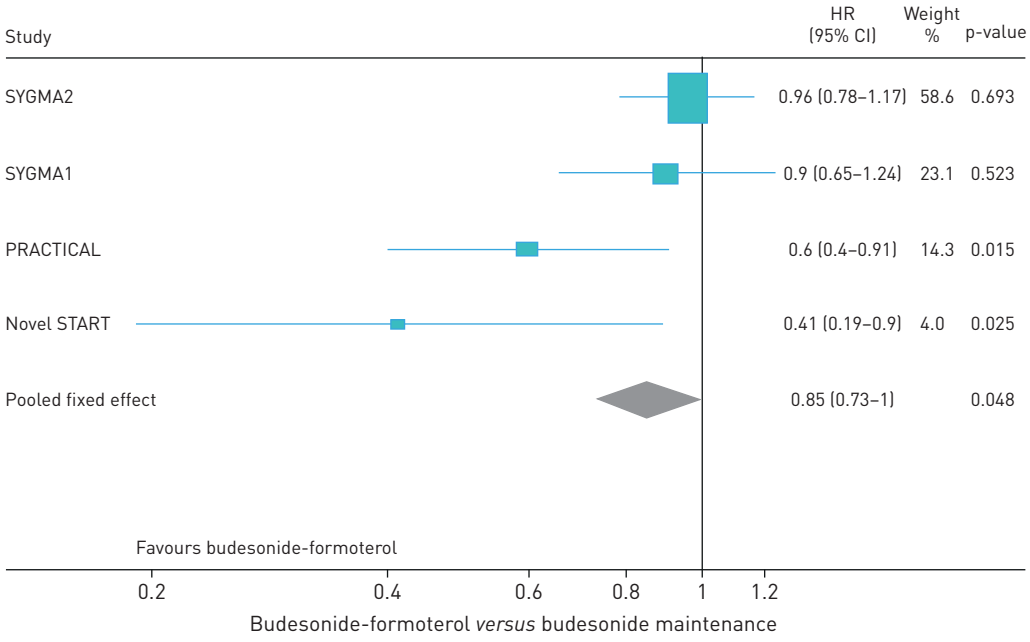

FIGURE 2 Pooled fixed effect for the hazard ratio of time to first severe exacerbation.

received. The ability of participants taking as-needed budesonide-formoterol to increase their dose in response to worsening symptoms may lead to resolution of an exacerbation before it becomes severe. Conversely, participants on maintenance ICS are restricted to fixed twice-daily dosing, which may result in under-dosing of ICS during exacerbations, and a greater dose than is required during periods of excellent symptom control. Patient unease over unnecessary medication use was highlighted in a substudy of 306 participants enrolled in the PRACTICAL trial, in which 47% of participants believed there was no need to take a preventer inhaler every day when well, and 40% were concerned about taking too much medication [20].

Mean adherence to prescribed maintenance ICS in the four studies was considerably higher than in clinical practice (56–79% *versus* <50%) [21, 22]. This was probably due in part to the motivational influence of electronic inhaler monitors and frequent study visits on participant behaviour (Hawthorne effect) [23], which occurred in both the double-blind and open-label trials. As adherence influences outcomes, it is possible that the efficacy of maintenance ICS was greater in the trials than might be expected in clinical practice.

β_2-agonist use is also relevant to the comparative clinical efficacy of the two regimens. In all four studies, participants taking as-needed budesonide-formoterol required a greater number of formoterol-adjusted β_2-agonist actuations per day than participants using a SABA reliever. Although reliever use was low in both groups, and the mean difference of 0.08 per day was small, it is likely that a component of the increased efficacy of budesonide-formoterol reliever compared with SABA may be due to the greater bronchodilator dose of formoterol. When added to ICS/LABA maintenance therapy, formoterol reduces the rate of severe exacerbations by 22% compared with terbutaline at similar bronchodilator doses [24].

The mean ACQ-5 score was 0.12 units lower with maintenance ICS across the four studies, indicating better symptom control. This difference is likely due to the intrinsic characteristic of as-needed therapy, in which inhaler use is largely symptom-driven. Of note, participants in the double-blind studies were only permitted to use their as-needed medications for symptom relief, whereas prophylactic use was allowed in the open-label studies. An important clinical consideration is that the 0.12-unit difference in the ACQ-5 score was below the MCID of 0.50 units [16]. A related point is that the inclusion of subjects with mild asthma means there is likely to be a floor effect, as it would be difficult for those with well-controlled asthma at baseline to achieve the required 0.50-unit change. It is therefore probable that although the magnitude of the overall difference is not clinically important, for some people the use of maintenance ICS will result in a clinically important improvement in symptom control.

FEV_1 was measured differently in the double-blind (pre-bronchodilator FEV_1) and open-label (on-treatment FEV_1) studies, which may account for some of the heterogeneity in this analysis. The FEV_1 was higher in the maintenance ICS group in all four studies, with a mean difference of −27.4 mL, which is below the MCID of 230 mL [17].

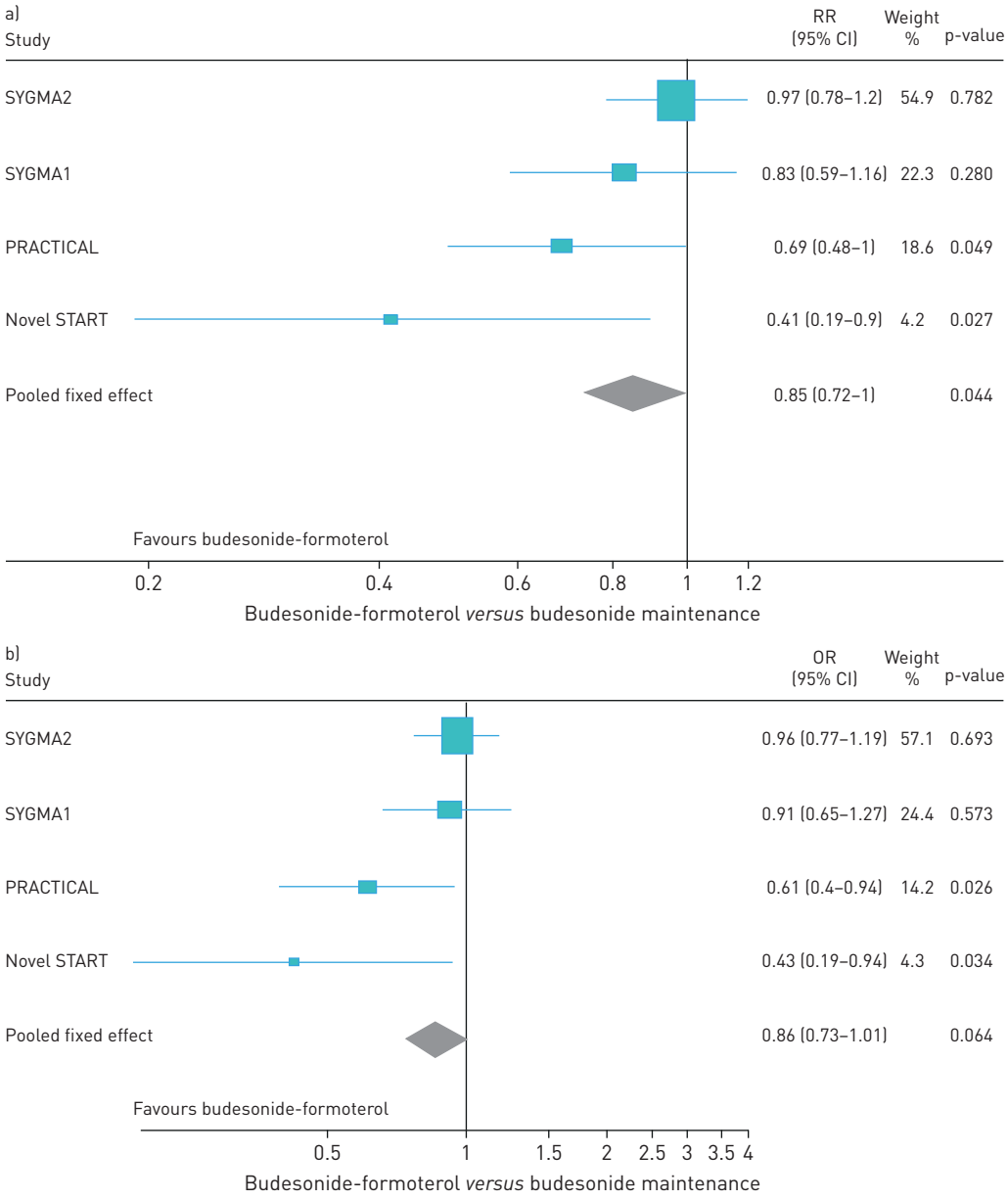

FIGURE 3 Pooled fixed effect of a) rate ratio (RR) of severe exacerbations, and b) odds ratio for relative risk of severe exacerbations.

Exhaled nitric oxide fraction (F_{eNO}), a biomarker of type-2 airway inflammation, was only measured in the two open-label studies [3, 8] and not included in the meta-analysis. In steroid-naïve participants, a reduction in F_{eNO} was observed with as-needed budesonide-formoterol, providing evidence of an anti-inflammatory effect of ICS when taken on a purely as-needed basis. A greater benefit was observed with maintenance ICS, although the magnitude of the difference was of uncertain clinical importance [25]. This data was derived from 1-year studies, and the longer-term effects of these regimens on airways inflammation will be important to determine.

It is worthwhile considering the results of this meta-analysis in line with the GINA 2020 report, which reconfirms ICS-formoterol as a therapeutic alternative to maintenance ICS plus SABA at step 2. When deciding between the two treatments, GINA ascribes particular importance to preventing severe exacerbations and minimising the need for daily ICS [1]. Our findings suggest that as-needed ICS-formoterol is superior on both counts.

A separate consideration is to whom these results apply. The observation that in all four studies the mean ACQ did not meet the cut point for well-controlled asthma (<0.75 units) [16] at the end of 12 months'

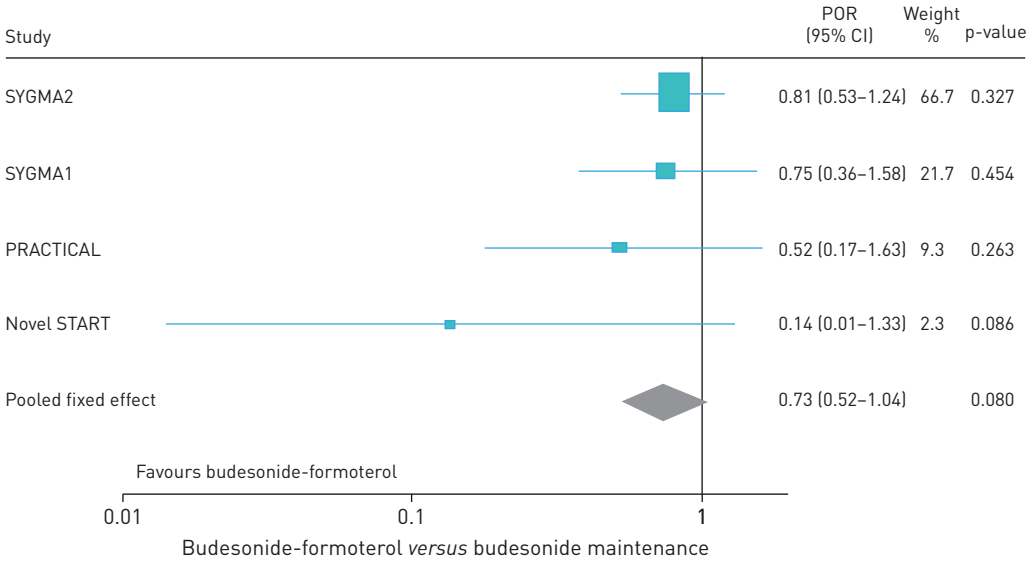

FIGURE 4 Pooled fixed effect of the combination of emergency department visits or hospitalisations. POR: Peto odds ratio.

treatment with maintenance budesonide, suggests that a substantial proportion would have met the GINA criteria for moderate asthma [1, 26]. Therefore, the findings may be generalisable to patients with both mild and moderate asthma.

There are several limitations to this review. First, multiple related outcomes were analysed in order to provide a comprehensive assessment of severe exacerbations. It was considered that this would be more informative than an individual measure of severe exacerbation; however, Type I error may be an issue, particularly for outcomes where event counts were sparse and confidence intervals wide. Second, a study by Lazarinis *et al.* [27] was excluded, as it did not report on severe exacerbations, risking selection bias for some of the secondary outcomes. Any potential bias would probably be minimal due to the short duration of the study (6 weeks) and the small number of participants included (n=44). Third, it is unclear if these results are applicable to other ICS/fast-onset β_2-agonist (both ICS/SABA and ICS/fast-onset LABA) combinations; further studies of alternative anti-inflammatory relievers are needed. Fourth, the findings in this meta-analysis are only relevant to adults and adolescents due to the absence of evidence in children aged ⩽11 years. Trials of ICS/SABA reliever combinations in children suggest possible efficacy of as-needed ICS-formoterol in this age group [28, 29], and there is a clear need for RCTs to confirm this [30–32]. Fifth, based on the current data from 1-year studies, it is not possible to determine the long-term effects of the as-needed ICS-formoterol regimen, including on lung function. Sixth, economic evaluation of the treatment regimens was beyond the scope of this review, but is necessary to guide practical implementation.

To conclude, this systematic review and meta-analysis provides evidence of moderate certainty that as-needed budesonide-formoterol prolonged the time to first severe exacerbation in adults and adolescents with mild and moderate asthma compared with maintenance low-dose ICS plus SABA reliever. These findings support the GINA 2020 recommendation that as-needed ICS-formoterol is a therapeutic alternative to maintenance ICS at step 2, particularly when prevention of severe exacerbation is the primary aim of treatment. This analysis also complements the evidence that as-needed ICS-formoterol reduces severe exacerbation risk when taken alone in mild asthma, or together with maintenance ICS-formoterol in more severe asthma, and is the preferred reliever across the spectrum of asthma severity.

Acknowledgements: We would like to thank Michael Fauchelle (Wellington Medical and Health Sciences Library, University of Otago, Wellington, New Zealand), for his help designing the literature search strategy. We would also like to thank the SYGMA, Novel START and PRACTICAL study teams for providing additional data relevant to this analysis. I. Braithwaite, M. Holliday, J. Fingleton, M. Weatherall and R. Beasley are all named authors on the Novel START and PRACTICAL studies.

Conflict of interest: L. Hatter has nothing to disclose. P. Bruce has nothing to disclose. I. Braithwaite reports personal fees from Equillium outside the submitted work. M. Holliday reports grants from AstraZeneca and the Health Research Council of New Zealand outside the submitted work. J. Fingleton reports grants, personal fees and nonfinancial support from AstraZeneca; grants from Genentech; grants, personal fees and nonfinancial support from GlaxoSmithKline; and

personal fees and nonfinancial support from Boehringer Ingleheim, all outside the submitted work. M. Weatherall has nothing to disclose. R. Beasley reports grants and personal fees from AstraZeneca, grants from Genentech and GlaxoSmithKline, and personal fees from Theravance and Avillion, outside the submitted work.

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