Self-titration of inhaled corticosteroid and β_2-agonist in response to symptoms in mild asthma: a pre-specified analysis from the PRACTICAL randomised controlled trial

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In mild asthma, the timing of the ICS dose, when self-titrated through the vehicle of β_2-agonist reliever use, is more important than total ICS dose in reducing severe exacerbation risk, when associated with greater overall as-needed β_2-agonist use https://bit.ly/2Zs5CJV

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ABSTRACT

Introduction: In mild asthma, as-needed budesonide–formoterol is superior or noninferior to maintenance budesonide plus as-needed short-acting β_2-agonist in reducing severe exacerbations. In this pre-specified analysis, we investigated patterns of inhaled corticosteroid (ICS) and β_2-agonist use in PRACTICAL, a randomised controlled trial.

Methods: Participants were randomised 1:1 to as-needed budesonide–formoterol (200/6 µg Turbuhaler, one actuation) or maintenance budesonide (200 µg Turbuhaler, one actuation twice a day) with as-needed terbutaline (250 µg, two actuations) for 52 weeks. 110 participants had electronic monitors attached to their study inhalers which captured the time and date of every actuation. Key outcome measures were patterns of ICS and β_2-agonist use. One actuation of budesonide–formoterol was considered to be an equivalent bronchodilator dose as two actuations of terbutaline.

Results: Participants randomised to as-needed budesonide–formoterol had more days with no ICS use compared with maintenance budesonide (median total days of no use 156 *versus* 22 days, respectively), lower median daily budesonide dose (164 *versus* 328 µg, respectively) and a greater median number of days of ⩾4 budesonide actuations (4 *versus* 1 days, respectively). Participants randomised to as-needed budesonide–formoterol took higher equivalent doses of β_2-agonist both overall (median number of actuations 0.8 *versus* 0.3 per day, respectively) and in response to worsening asthma (total number of "overuse days" of >8 or >16 actuations of budesonide–formoterol or terbutaline 33 *versus* 10 days, respectively).

Conclusions: The timing of ICS dose when self-titrated to β_2-agonist use is more important than total ICS dose in reducing severe exacerbation risk in mild asthma, when associated with greater overall use of as-needed β_2-agonist.

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Introduction

Poor adherence to inhaled corticosteroid (ICS) in asthma is common, and is associated with poor asthma control [1, 2], increased symptom burden and higher risk of asthma exacerbations [3, 4], oral corticosteroid use, hospitalisation due to asthma [5, 6], and death from asthma [7]. Observational studies [8–10], patient surveys [11], reviews of deaths from asthma [7] and *post hoc* analyses of randomised controlled trials (RCTs) [12–14] report that during asthma exacerbations patients preferentially increase their use of, and overuse, their short-acting β_2-agonist (SABA) inhalers, and are often poorly adherent to their ICS. These patterns of behaviour combined with delay in seeking medical review are associated with worse outcomes, hospitalisation and death from asthma [6, 10, 15].

One approach to address this entrenched behavioural problem in asthma management is the use of combination ICS–rapid-onset β_2-agonist as reliever therapy. This ensures patients receive ICS through the vehicle of bronchodilator reliever use, titrated to variations in symptom control, particularly in the setting of asthma exacerbations [16]. When used in this way by adults with moderate and severe asthma taking maintenance ICS–long-acting β_2-agonist (LABA) therapy, as-needed ICS–formoterol reduces the severe exacerbation risk by about one-third compared with as-needed SABA [17]. This approach is also effective in adults with mild asthma on no regular maintenance ICS-based therapy, in whom as-needed ICS–formoterol reduces the risk of severe exacerbations by >50% and is associated with improved asthma control compared with as-needed SABA [18, 19].

As-needed budesonide–formoterol has been shown to be either noninferior [18, 20] or superior [19, 21] to maintenance budesonide plus as-needed SABA for severe asthma exacerbation risk reduction, at a considerably lower cumulative exposure to ICS [18–21]. In the most recent of these clinical trials, the PRACTICAL study, a subset of 110 participants had electronic inhaler monitors incorporated onto all their study inhalers, thereby providing the opportunity to investigate patterns of inhaler use in detail [21]. The aim of this pre-specified analysis of the PRACTICAL study was to investigate the patterns of ICS and β_2-agonist use, in order to better understand the 31% reduction in severe exacerbation risk observed in this study with as-needed budesonide–formoterol compared with maintenance budesonide plus as-needed terbutaline.

Methods

Description of the PRACTICAL study

The methods and results for the PRACTICAL study are reported in detail elsewhere [21]. In summary, the PRACTICAL study was a 52-week open-label parallel group, multicentre, phase III RCT undertaken at sites across New Zealand. Adults aged 18–75 years with a self-reported doctor's diagnosis of asthma were recruited if they were either taking SABA alone and had partly or uncontrolled asthma symptoms, or were taking SABA reliever therapy together with maintenance low-dose ICS and had either good control or partly/uncontrolled controlled asthma with poor self-reported adherence or unsatisfactory inhaler technique. Therefore, all patients were eligible for step 2 treatment of the Global Initiative for Asthma 2014 strategy [22]. Participants were randomised 1:1, to either budesonide–formoterol Turbuhaler (Symbicort) 200/6 µg, one inhalation for relief of symptoms as needed, or budesonide Turbuhaler (Pulmicort) 200 µg, one inhalation twice a day, plus terbutaline (Bricanyl) 250 µg, two inhalations as needed for relief of symptoms. Participants were provided with an asthma action plan specific to their randomised treatment arm (supplementary figure S1). Neither participants nor investigators were blinded to treatment allocations and no placebo inhalers were used.

The PRACTICAL study had ethical approval from the New Zealand Northern B Health and Disability Ethics Committee (15/NTB/178) and was registered with the Australian New Zealand Clinical Trials Registry with identifier ACTRN12616000377437.

Participants and electronic inhaler monitors

Within the PRACTICAL study, a total of 890 patients were randomised at 15 sites. Among these, a subgroup of 110 participants at two sites had electronic inhaler monitors (Adherium, Auckland, New Zealand) incorporated onto all their study inhalers. Participants were recruited sequentially to the electronic monitoring substudy. The electronic inhaler monitors recorded the time and date of each inhaler actuation, and have been validated to have 99.9% accuracy at recording actuations during bench

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testing [23]. Prior to dispensing at baseline or being re-issued at follow-up study visits, each monitor was checked to ensure data were being accurately recorded and any faulty monitors were replaced. Data from the electronic monitors were downloaded at each study visit. Participants were aware the monitors recorded their inhaler use; however, the data from the monitors were not analysed or discussed during the study.

Definitions

A day was defined as the 24-h period from midnight to midnight; a week of no budesonide use was defined as 7 consecutive days of no budesonide use either alone or in combination with formoterol; a 2-week period of no budesonide use was defined as 14 consecutive days of no budesonide use either alone or in combination with formoterol.

Adherence with maintenance budesonide was calculated as the mean daily dose as a percentage of daily dose prescribed, without capping. The therapeutic ratio between formoterol and terbutaline for bronchodilator dose was defined as one actuation of formoterol 6 µg per actuation being equivalent to two actuations of terbutaline 250 µg per actuation. This definition was based on a study showing similar bronchodilation with repeated use of formoterol at an emitted dose of 6 µg and terbutaline at a dose of 500 µg [24], four RCTs in which randomised interventions included formoterol 6 µg and terbutaline 500 µg for as-needed medication [25–28], and from the data sheets for these drugs [29, 30].

"Overuse days" of the reliever medications was defined as >8 actuations of budesonide–formoterol or >16 actuations of terbutaline in a day, as previously specified [31]. These overuse cut-points were used in the participants' asthma action plan to indicate the level at which they should contact their general practitioner. "Marked overuse" of the reliever medications was defined as >12 or >24 actuations of budesonide–formoterol or terbutaline, respectively, in accordance with the approved maximum daily use of formoterol of 72 µg per day [29].

A severe exacerbation of asthma was defined as the use of systemic corticosteroids for at least 3 days because of asthma, or hospital admission or emergency department visit because of asthma, requiring systemic corticosteroids [32]. A moderate asthma exacerbation was defined as worsening asthma resulting in unplanned medical review (primary care, visit to emergency department or hospital admission) or worsening asthma resulting in use of systemic corticosteroids for any duration. The period before, and after, a moderate exacerbation or severe exacerbation was defined as the 5 and 14 days before, and after, the day the patient first met the criteria for a moderate exacerbation or severe exacerbation.

Outcomes

As this was a pre-specified exploratory analysis a primary outcome was not specified. Outcomes calculated per patient relating to budesonide use were the number of days, weeks, 2-week periods and the longest number of consecutive days of no budesonide use, the maximum number of actuations of budesonide-containing medication in a single day, and the number of days where $\geqslant$2, $\geqslant$4 or $\geqslant$6 actuations of budesonide-containing medication were taken. Outcomes in relation to β_2-agonist use were the maximum number of actuations of β_2-agonist in a single day, the number of days where $\geqslant$2 actuations of formoterol and $\geqslant$4 actuations of terbutaline or $\geqslant$4 actuations of formoterol and $\geqslant$8 actuations of terbutaline were taken, the number of days where "overuse" and "marked overuse" of β_2-agonist occurred, all calculated per patient, and the number of participants with at least 1 day of β_2-agonist overuse. Outcomes in relation to inhaler use in the 5 and 14 days before and after a moderate or severe exacerbation were counts of number of actuations of each medication in this time period.

Statistical analysis

Continuous variables are summarised by mean and standard deviation or median and interquartile range, and categorical variables by counts and proportions (expressed as percentages). No correction for multiplicity of analysis was undertaken. Statistical testing of differences between treatment groups was only conducted for pre-specified outcomes and not for *post hoc* outcomes. Comparisons of the number of days, weeks and 2-week periods of no ICS use were analysed by the Mann–Whitney test with the Hodges–Lehmann estimator of locations difference. Inhaler use around asthma exacerbations was summarised by individual plots of number of inhaler actuations per day for each medication and locally weighted scatterplot smoothing (LOESS) plots showing cumulative use for each medication; quantitative summaries of the number of actuations per day of each medication in the 14- and 5-day periods before and after an exacerbation. β_2-agonist overuse episodes were summarised by counts and proportions. Severe exacerbation rate was analysed by Poisson regression with an offset for length of time in study. Exhaled nitric oxide fraction (F_{ENO}) was analysed on a logarithmic scale as the data were highly skewed and the differences were analysed as the ratio of geometric means. The five-item Asthma Control Questionnaire (ACQ-5) was

analysed by ANCOVA. An interaction analysis tested if there was a difference in relative rate of severe exacerbations, ACQ-5 and F_{ENO} by randomised treatment and inclusion in the electronic monitoring substudy or not. All analyses were conducted using SAS version 9.4 (SAS, Cary, NC, USA).

Results

Overall, 110 participants were enrolled in the substudy, representing 12% of the total PRACTICAL population and 24% of participants at the two study sites. Seven substudy participants were withdrawn prior to completion. The baseline characteristics of participants in the electronic monitoring substudy (55 in each randomisation group) are presented in table 1. Baseline characteristics were similar between the two groups. The baseline characteristics of participants who were not part of the electronic monitoring substudy were similar to those who were (supplementary table S1). A moderate or severe asthma exacerbation occurred in 22 substudy participants who experienced a total of 27 moderate or severe exacerbations during the study: 12 exacerbations with budesonide–formoterol (nine participants) and 15 exacerbations with maintenance budesonide (13 participants).

ICS use during the whole study

Participants randomised to as-needed budesonide–formoterol had significantly more days of no ICS use (median 156 *versus* 22 days; Hodge–Lehman estimation of location difference 119, 95% CI 90–191; p<0.001) and more weeks, 2-week periods and longest number of consecutive days of no use (table 2). Overall, those randomised to as-needed budesonide–formoterol took a median of 0.8 *versus* 1.6 actuations

TABLE 1 Patient demographics

	Budesonide–formoterol as needed	Maintenance budesonide
Patients	55	55
Age years	48.1±14	51.4±14
Age at diagnosis years	23.1±20	23.3±19.2
Female	28 (51)	28 (51)
Ethnicity		
Asian	1 (2)	2 (4)
European	45 (82)	46 (84)
Māori	4 (7)	3 (6)
Other	1 (2)	2 (4)
Pacific	4 (7)	2 (4)
Smoking status		
Current smoker	1 (2)	2 (4)
Ex-smoker	13 (24)	20 (36)
Never-smoker	41 (75)	33 (60)
Pack-years (ever-smoker)	4.9±4.8	6.2±5.9
ICS use ever[#]	51 (93)	47 (86)
ICS use at randomisation[#]	36 (66)	37 (67)
Self-reported adherence to ICS % prescribed dose[¶]	50.4±34.8	60.1±33.8
Weekly SABA use occasions		
Mean	3.7±4.9	3.3±4.1
Median	2 (1–5)	2 (1– 5)
Severe exacerbation in year prior to randomisation	0.1±0.3	0.1±0.3
ACQ-5 score at randomisation[+]	1.1±0.9	0.9±0.7
Eosinophil count at randomisation $\times 10^9$ L^{-1}	0.3±0.2	0.2±0.2
FEV_1 % pred at randomisation[§]	87.4±15.3	88.4±14.4
F_{ENO} ppb	23 (14–63)	19 (12–31)

Data are presented as n, mean±SD, n (%) or median (interquartile range). ICS: inhaled corticosteroid; SABA: short-acting β_2-agonist; ACQ-5: five-item Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 s; F_{ENO}: exhaled nitric oxide fraction. [#]: participants self-reported ICS use ever and in the 12 weeks prior to randomisation; [¶]: participant-reported adherence to ICS in the 4 weeks prior to enrolment; [+]: the ACQ-5 consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment) and averaged, in which a 0.5-unit change represents the minimal clinically important difference; [§]: participants received no specific instruction to withhold use of their bronchodilator before measurement of FEV_1 [32].

TABLE 2 Patterns of inhaled corticosteroid (ICS) use

	Budesonide–formoterol as needed	Maintenance budesonide	Difference
Subjects n	55	55	
Daily ICS use[#]			
Dose µg			
Mean±SD	176.0±143.0	302.5±84.8	−126.5 (95% CI −171.0– −81.9)[¶]
Median (IQR)	164.3 (74.0–251.7)	328.3 (245.8–364.0)	
Range (minimum–maximum)	6.7–682.5	26.8–458.1	
Mean adherence %		76	
Actuations			
Mean±SD	0.9±0.7	1.5±0.4	
Median (IQR)	0.8 (0.4–1.3)	1.6 (1.2–1.8)	
Range (minimum–maximum)	0.0–3.4	0.1–2.3	
Days of no ICS use			119 (95% CI 90–191)[¶]
Mean±SD	182.0±109.4	45.9±64.6	
Median (IQR)	156 (95–284)	22 (6–70)	
Range (minimum–maximum)	0–352	0–327	
Weeks of no ICS use			3 (95% CI 1–8)[¶]
Mean±SD	12.6±15.4	1.8±6.6	
Median (IQR)	4 (0–24)	0 (0–1)	
Range (minimum–maximum)	0–48	0–38	
2-week periods of no ICS use			0 (95% CI 0–2)[¶]
Mean±SD	4.6±6.8	0.7±2.8	
Median (IQR)	0 (0–7)	0 (0–0)	
Range (minimum–maximum)	0–23	0–17	
Longest period of no ICS use days			
Mean±SD	40.3±59.9	8.7±19.4	
Median (IQR)	12 (5–48)	3 (1–8)	
Range (minimum–maximum)	0–260	0–129	
Maximum ICS actuations in a single day			
Mean±SD	6.0±2.9	4.3±2.0	
Median (IQR)	5 (4–8)	4 (3–5)	
Range (minimum–maximum)	1–13	2–14	
Days ⩾2 ICS actuations			
Total days across all participants in the whole study n	4175	10 672	
Mean±SD per participant	75.9±72.8	194.0±89.7	
Median (IQR) per participant	48 (15–114)	204 (122.5–273)	
Range (minimum–maximum)	0–329	14–333	
Days ⩾4 ICS actuations			
Total days across all participants in the whole study n	675	172	
Mean±SD per participant	12.3±26.0	3.1±7.7	
Median (IQR) per participant	4 (1–10)	1 (0–3)	
Range (minimum–maximum)	0–153	0–52	
Days ⩾6 ICS actuations			
Total days across all participants in the whole study n	176	23	
Mean±SD per participant	3.2±8.2	0.4±1.8	
Median (IQR) per participant	0 (0–2)	0 (0–0)	
Range (minimum–maximum)	0–39	0–12	

IQR: interquartile range. [#]: data previously reported in the main publication of the PRACTICAL study [21] but presented again here for illustrative purposes; [¶]: p<0.001.

per day in those randomised to maintenance budesonide. The mean adherence to the prescribed daily dose of 400 µg of budesonide was 76%. Two (4%) participants in the maintenance budesonide group took budesonide on every day of the study. Of the participants randomised to as-needed budesonide–formoterol, one participant self-administered budesonide every day; this patient withdrew from the study after 2 weeks. Over 70% of those randomised to as-needed budesonide–formoterol had a total of >100 days of no ICS use in the study compared with <10% of those randomised to maintenance

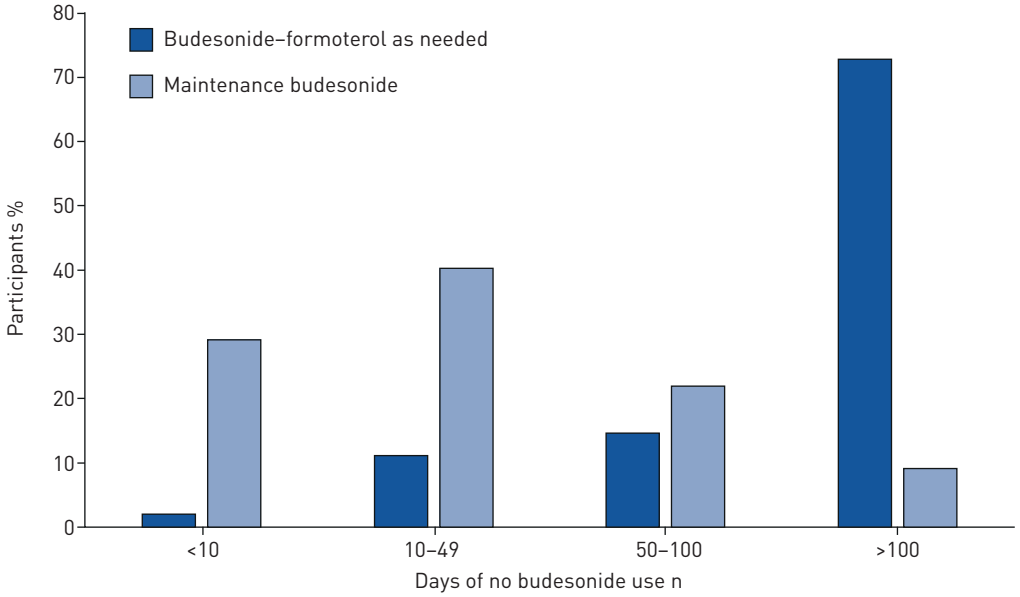

FIGURE 1 Total number of days of no budesonide use.

budesonide (figure 1). Participants randomised to as-needed budesonide–formoterol took ⩾4 actuations of budesonide on 675 study days compared with 172 study days in participants randomised to maintenance budesonide.

There were 19 severe exacerbations in 16 participants in the electronic monitoring substudy: six randomised to as-needed budesonide–formoterol and 10 randomised to maintenance budesonide. In these participants experiencing a severe exacerbation, there was no use of budesonide-containing medication on a median of 164 days over the course of the study in participants randomised to as-needed budesonide–formoterol *versus* a median of 24 days over the course of the study in those randomised to maintenance budesonide (table 3); the median longest period of no ICS use was 72 days and 3.5 days, respectively.

TABLE 3 Inhaled corticosteroid (ICS) use in participants who had a severe asthma exacerbation

	Budesonide–formoterol as needed	Maintenance budesonide
Patients n	6	10
Daily ICS actuations		
Mean±SD	1.0±0.6	1.6±0.4
Median (IQR)	1.1 (0.6–1.5)	1.6 (1.3–1.8)
Range (minimum–maximum)	0.1–1.6	0.9–2.0
Mean adherence % of prescribed dose		77±17
Days of no ICS use		
Mean±SD	176.5±139.5	39.6±35.8
Median (IQR)	164 (51.0–281.5)	24 (15.5–69.25)
Range (minimum–maximum)	47–350	2–103
Weeks of no ICS use		
Mean±SD	19.0±20.1	0.2±0.4
Median (IQR)	16 (1.25–33)	0 (0–0)
Range (minimum–maximum)	0–47	0–1
2-week periods of no ICS use		
Mean±SD	8.3±9.0	0±0
Median (IQR)	6.5 (0.5–14.75)	0 (0–0)
Range (minimum–maximum)	0–21	0–0
Longest period of no ICS use days		
Mean±SD	68.8±65.0	4.3±3.8
Median (IQR)	72 (9–119.25)	3.5 (1.25–5)
Range (minimum–maximum)	2–144	1–13

IQR: interquartile range.

Use of ICS before and after an exacerbation or severe exacerbation

The number of budesonide-containing actuations per day in the 5- and 14-day periods before a moderate or severe exacerbation in those randomised to budesonide–formoterol and to maintenance budesonide were a median 1.7 *versus* 2.0 and 1.5 *versus* 1.7 actuations, respectively (table 4). For each exacerbation, individual patterns of budesonide–formoterol use (figure 2a) and maintenance budesonide use (figure 2b) show marked individual variation. LOESS plots representing summated budesonide–formoterol and budesonide actuations for the 14 days before and after an exacerbation are shown in supplementary figure S3.

β_2-agonist use during the whole study

Overall, participants randomised to as-needed budesonide–formoterol took a median of 0.8 actuations of formoterol per day *versus* 0.3 actuations of terbutaline per day in those randomised to maintenance budesonide (table 5). Based on the therapeutic ratio of one actuation of formoterol 6 µg being equivalent

TABLE 4 Actuations per day before and after an asthma exacerbation

	Budesonide–formoterol as needed	Maintenance budesonide with terbutaline as needed
Patients	12	15
Budesonide use actuations		
Use in the 14 days before an exacerbation		
Mean±SD	2.1±1.7	1.7±0.3
Median (IQR)	1.5 (0.9–2.4)	1.7 (1.5–2.0)
Range (minimum–maximum)	0.4–6.0	1.1–2.2
Use in the 5 days before an exacerbation		
Mean±SD	2.4±1.6	2.0±0.4
Median (IQR)	1.7 (1.2–3.7)	2.0 (1.8–2.2)
Range (minimum–maximum)	0.8–5.2	1.2–2.4
Use in the 14 days after an exacerbation		
Mean±SD	1.2±0.8	1.7±0.9
Median (IQR)	1.0 (0.9–1.3)	1.9 (1.4–1.9)
Range (minimum–maximum)	0.0–3.4	0.4–4.1
Use in the 5 days after an exacerbation		
Mean±SD	1.5±0.7	1.9±1.2
Median (IQR)	1.5 (1.1–2.0)	1.8 (1.1–1.9)
Range (minimum–maximum)	0.0–2.4	0.4–5.4
β_2-agonist use actuations		
Use in the 14 days before an exacerbation		
Mean±SD	2.1±1.7	1.9±1.6
Median (IQR)	1.5 (0.9–2.4)	1.8 (0.7–2.9)
Range (minimum–maximum)	0.4–6.0	0.0–5.9
Use in the 5 days before an exacerbation		
Mean±SD	2.4±1.6	2.8±1.8
Median (IQR)	1.7 (1.2–3.7)	2.8 (1.6–3.8)
Range (minimum–maximum)	0.8–5.2	0.0–6.2
Use in the 14 days after an exacerbation		
Mean±SD	1.2±0.8	1.6±1.4
Median (IQR)	1.0 (0.9–1.3)	1.1 (0.4–2.8)
Range (minimum–maximum)	0.0–3.4	0.0–4.1
Use in the 5 days after an exacerbation		
Mean±SD	1.5±0.7	2.2±2.0
Median (IQR)	1.5 (1.1–2.0)	2.0 (0.5–3.3)
Range (minimum–maximum)	0.0–2.4	0.0–6.0

IQR: interquartile range.

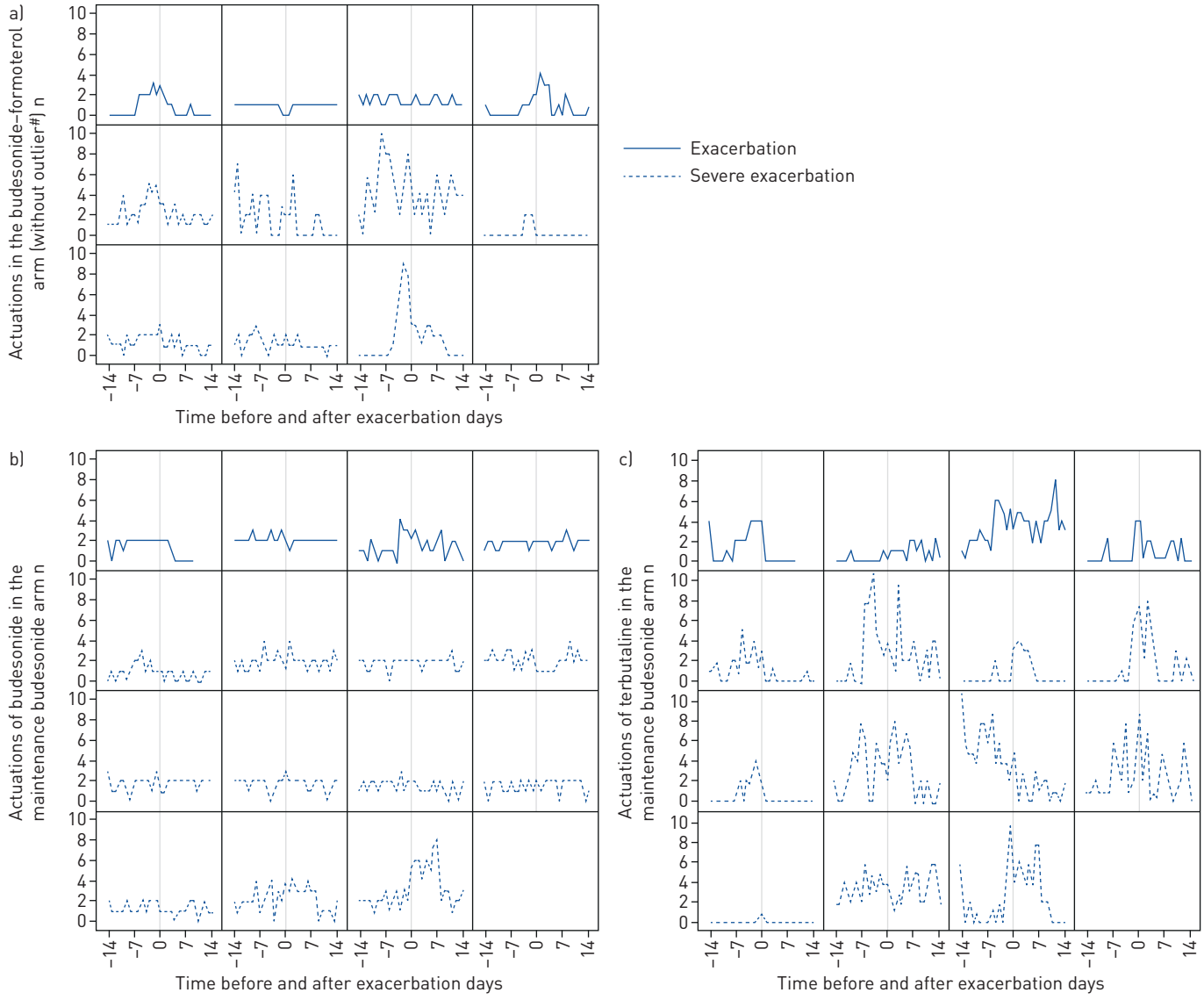

FIGURE 2 Individual participant inhaler use in the 14 days before and after the start of a moderate or severe exacerbation: a) budesonide–formoterol[#], b) budesonide and c) terbutaline. [#]: one participant was not included in this panel as they used 36 actuations of budesonide–formoterol on day −14 and inclusion of their data distorted the *y*-axis (their usage is presented separately in supplementary figure S2).

to two actuations of terbutaline 250 µg, use of ⩾2 actuations of formoterol or ⩾4 actuations of terbutaline occurred on a median of 48 *versus* 3 days per participant, respectively, and use of ⩾4 actuations of formoterol or ⩾8 actuations of terbutaline occurred on a median of 4 *versus* 0 days per participant, respectively.

Across the study, there were 33 days (11 participants) on which >8 inhalations of budesonide–formoterol were used and 10 days (four participants) on which >16 inhalations of terbutaline were used (supplementary table S2). The rate of "overuse days" per year for budesonide–formoterol and maintenance budesonide groups was 0.62 and 0.19, respectively (relative rate 3.3, 95% CI 1.6–6.6; p=0.001). After an overuse episode no participant sought medical review within 48 h.

Use of β_2-agonist before and after an exacerbation or severe exacerbation

The number of β_2-agonist-containing actuations per day in the 5- and 14-day periods before a moderate or severe exacerbation in those randomised to budesonide–formoterol and maintenance budesonide was a median of 1.7 *versus* 2.8 and 1.5 *versus* 1.8 actuations, respectively (table 4). For each exacerbation, individual patterns of budesonide–formoterol use (figure 2a) and terbutaline use (figure 2c) before and after an exacerbation showed marked individual variation. LOESS plots representing the

TABLE 5 Patterns of β_2-agonist use

	Budesonide–formoterol as needed	Maintenance budesonide
Patients	55	55
β_2-agonist	Formoterol 6 µg	Terbutaline 250 µg
Daily β_2-agonist actuations#		
Mean±SD	0.9±0.7	0.5±0.6
Median (IQR)	0.8 (0.4–1.3)	0.3 (0.1–0.6)
Range (minimum–maximum)	0.0–3.4	0.0–2.7
Maximum actuations in a single day		
Mean±SD	6.0±2.9	8.0±10.9
Median (IQR)	5 (4–8)	6 (3–9.5)
Range (minimum–maximum)	1–13	0–80
Days ⩾2 actuations of formoterol or ⩾4 actuations of terbutaline		
Total days across all participants in the whole study n	4175	694
Mean±SD	75.9±72.8	12.6±23.5
Median (IQR)	48 (15–114)	3 (0–14.5)
Range (minimum–maximum)	0–329	0–139
Days ⩾4 actuations of formoterol or ⩾8 actuations of terbutaline		
Total days across all participants in the whole study n	675	94
Mean±SD	12.3±26.0	1.7±3.9
Median (IQR)	4 (1–10)	0 (0–2)
Range (minimum–maximum)	0–153	0–21

IQR: interquartile range. #: data previously reported in the main publication of the PRACTICAL study [21] but presented again here for illustrative purposes.

summated budesonide–formoterol and terbutaline actuations before and after an exacerbation are shown in supplementary figure S3.

Clinical outcomes in the electronic monitoring substudy

The clinical outcomes were of a similar magnitude in the electronic monitoring subgroup as in the main study group (table 6). There was no evidence of an interaction between inclusion in the electronic monitoring substudy and randomised treatment for rate of severe exacerbations ($p_{interaction}$=0.92), F_{ENO} ($p_{interaction}$=0.89) or ACQ-5 ($p_{interaction}$=0.50).

TABLE 6 PRACTICAL study outcomes by inclusion in the electronic monitoring substudy or not

	Budesonide–formoterol as needed		Maintenance budesonide		$p_{interaction}$ between inclusion in electronic monitoring substudy and outcome
	Electronic monitoring subgroup	Not in electronic monitoring subgroup	Electronic monitoring subgroup	Not in electronic monitoring subgroup	
Patients	55	382	55	393	
Severe exacerbations	8	40	11	57	
Rate of severe exacerbations per participant per year	0.15	0.11	0.21	0.17	0.92
F_{ENO} ppb end of study	23 (15–48)	26 (16–45) (n=346)	18 (13–32)	27 (16–41) (n=351)	0.89
ACQ-5# end of study	0.87±0.69	0.86±0.76 (n=348)	0.64±0.72	0.82±0.88 (n=351)	0.50

Data are presented as n, median (interquartile range) or mean±SD. F_{ENO}: exhaled nitric oxide fraction; ACQ-5: five-item Asthma Control Questionnaire. #: the ACQ-5 consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), and averaged, in which a 0.5-unit change represents the minimal clinically important difference.

Discussion

In this pre-specified analysis we identified different patterns of ICS and β_2-agonist use between the as-needed budesonide–formoterol and maintenance budesonide groups in adults with mild–moderate asthma. Those using as-needed budesonide–formoterol had significantly more days of no ICS use and longer periods of no use overall. However, they repeatedly increased their use of ICS to higher levels than those taking maintenance budesonide throughout the 52 weeks of the study. Different patterns of β_2-agonist use were apparent, with those randomised to as-needed budesonide–formoterol having higher use, both overall and during worsening asthma. In the PRACTICAL study as a whole, adults with mild–moderate asthma randomised to as-needed budesonide–formoterol were 31% less likely to experience a severe exacerbation than those randomised to maintenance budesonide plus as-needed terbutaline. The present findings in a subset of the PRACTICAL population therefore suggest that the timing of ICS use may be more important than the total ICS dose taken in reducing severe exacerbation risk. With regular scheduled maintenance ICS therapy there are likely to be periods when the patient takes more ICS than is required and other periods when insufficient ICS is taken in the situation of worsening asthma, whereas with as-needed ICS–formoterol use it is likely that through the vehicle of bronchodilator reliever use the ICS dose is more closely titrated according to need. The greater bronchodilator dose of the β_2-agonist formoterol self-administered during worsening asthma with this regimen may contribute to this exacerbation risk reduction. The greater efficacy of formoterol compared with SABA reliever therapy in reducing severe exacerbation risk has been shown in adolescents and adults with moderate–severe asthma, with a magnitude of benefit similar to that observed with budesonide–formoterol compared with formoterol reliever therapy [26].

The participants who experienced a severe exacerbation taking as-needed budesonide–formoterol had more weeks of no ICS use than those who did not experience a severe exacerbation. This suggests they may represent a subgroup of adults in whom the as-needed budesonide–formoterol regimen is not appropriate. By contrast, the participants randomised to maintenance budesonide who had an exacerbation were all highly adherent with no full weeks of no ICS use, suggesting that poor adherence was not the cause of their exacerbations.

To interpret the data on β_2-agonist use it is necessary to consider both the instruction to patients to take one actuation of formoterol 6 µg and two actuations of terbutaline 250 µg for symptom relief and their therapeutic ratio. Thus, the observation that the median number of actuations per day in the as-needed budesonide–formoterol group was 0.8 compared with 0.3 in the maintenance budesonide group means that although the absolute amount of β_2-agonist use with both regimens was low, the relative amount was almost five times greater in the as-needed budesonide–formoterol group than in the maintenance budesonide group.

The observation that there was a lower risk of severe exacerbations in the as-needed budesonide–formoterol group suggests that the amount of β_2-agonist use has a different predictive value when given as budesonide–formoterol reliever compared with SABA reliever therapy. Evidence in support of this view comes from the SYGMA 1 study, in which the risk of a severe exacerbation in the 21 days after >4, >6 or >8 actuations of as-needed budesonide–formoterol 200/6 µg was markedly lower than in the 21 days following >4, >6 or >8 actuations with as-needed terbutaline use [33]. This analysis avoids the bias that occurs if one examines only the events that resulted in an exacerbation, as undertaken in our analysis of a small subset of participants, in which the protective effect cannot be calculated. This suggests that the strong association between increasing SABA use and increasing risk of severe exacerbations and mortality risk may not necessarily apply to ICS–formoterol reliever therapy [8, 34].

Weaknesses of this study are it is an exploratory analysis and although key outcomes were pre-specified, additional *post hoc* analyses were undertaken and so the findings should not be used to make definitive inferences. As only 110 participants in the PRACTICAL study had electronic inhaler monitors and only 22 participants experienced an exacerbation, there was limited power for some outcomes. The PRACTICAL study utilised an open-label, real-world design in an attempt to ensure the findings were representative of how the regimens would be used by patients with mild–moderate asthma in clinical practice. However, participation in this trial clearly influenced behaviour, as the adherence rate of 76% with the maintenance group was similar to that observed in the SYGMA 1 study in which patients had daily diaries and reminders [18], and considerably higher than that usually observed in clinical practice [35]. While the participants were aware that their data was not analysed or viewed during the study, we suspect the high adherence rate is because the patients in the electronic monitoring subgroup saw the same investigator for almost every study visit, which may have led to high levels of motivation.

In conclusion, the data provide insight into the manner in which the self-titration of ICS through the vehicle of a bronchodilator reliever use is more effective in reducing the risk of severe exacerbations than

regular ICS use. The greater efficacy of budesonide–formoterol reliever therapy in reducing severe exacerbation risk may also be due in part to the increased delivery of LABA therapy.

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De-identified individual participant data collected during the PRACTICAL trial (Australian New Zealand Clinical Trials Registry identifier ACTRN12616000377437) will be shared beginning 2 years after article publication with no end date. These data will be available to researchers who provide a methodologically sound proposal for the purposes of achieving specific aims outlined in that proposal. Proposals should be directed to Richard Beasley *via* e-mail (richard.beasley@mrinz.ac.nz) and will be reviewed by the PRACTICAL study management committee. Requests to access data to undertake hypothesis-driven research will not be unreasonably withheld. To gain access, data requesters will need to sign a data access agreement and to confirm that data will only be used for the agreed purpose for which access was granted.

Conflict of interest: C. Baggott reports grants from the Health Research Council of New Zealand, during the conduct of the study; support for meeting attendance from AstraZeneca and Novartis, outside the submitted work. J. Hardy reports grants from the Health Research Council of New Zealand, during the conduct of the study; travel costs from AstraZeneca, outside the submitted work. J. Sparks reports grants from the Health Research Council of New Zealand, during the conduct of the study. M. Holliday reports grants from the Health Research Council of New Zealand, during the conduct of the study. D. Hall reports grants from the Health Research Council of New Zealand, during the conduct of the study. A. Vohlidkova reports grants from the Health Research Council of New Zealand, during the conduct of the study. R. Hancox reports grants from the Health Research Council of New Zealand, during the conduct of the study; support for meeting attendance from AstraZeneca and Boehringer Ingelheim, fees for lectures from Menarini, outside the submitted work. M. Weatherall reports grants from the Health Research Council of New Zealand, during the conduct of the study. J. Fingleton reports grants from the Health Research Council of New Zealand, during the conduct of the study; grants, personal fees for lectures and support for meeting attendance from AstraZeneca, grants and personal fees for lectures from GlaxoSmithKline, grants from Genentech, personal fees for lectures and support for meeting attendance from Boehringer Ingelheim, outside the submitted work. R. Beasley reports grants from the Health Research Council of New Zealand, during the conduct of the study; grants and personal fees from AstraZeneca and GlaxoSmithKline, grants from Genentech, personal fees from Avillion and Theravance, outside the submitted work.

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