The management of mild asthma

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In the management of mild asthma, an ICS-containing reliever medication is superior to SABA as reliever alone, and is equivalent to maintenance ICS and SABA as reliever, particularly in reducing risks of severe asthma exacerbations https://bit.ly/3dovSKc

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ABSTRACT Inhaled corticosteroids (ICSs) have been recommended as a maintenance treatment, either alone or together with long-acting inhaled β_2-agonists, for all asthma patients. Short-acting β_2-agonists (SABAs) are rapid-onset bronchodilators, which provide symptom relief, but have no anti-inflammatory properties, yet are the most widely used as-needed reliever treatment for asthma and often the only treatment prescribed. Asthma patients can find adhering to daily preventative medication with ICS difficult and will often revert to using as-needed SABA as their only treatment, increasing their risk of exacerbations. The purpose of this review is to evaluate the efficacy of reliever medications that contain ICS compared with SABA as reliever, or with maintenance ICS and SABA as reliever, in mild asthma patients.

Nine studies were identified that have evaluated the use of ICS as a component of an as-needed reliever in patients with mild asthma. Four of the most recent studies compared the combination of ICS/formoterol to SABA as reliever.

ICS-containing reliever medication was superior to SABA as reliever alone, and was equivalent to maintenance ICS and SABA as reliever, particularly in reducing risks of severe asthma exacerbations, in studies which compared these reliever options.

SABAs should not be used as a reliever without ICS. The concern about patients with mild asthma not being adherent to maintenance ICS supports a recommendation that ICS/formoterol should be considered as a treatment option instead of maintenance ICS, to avoid the risk of patients reverting to SABA alone.

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Identifying mild asthma

Asthma is a common disease with a worldwide prevalence of more than 340 million. It is characterised by airway inflammation and variable airflow obstruction, associated with symptoms of wheeze, cough, shortness of breath and chest tightness.

As with many chronic diseases, asthma was traditionally classified by severity into mild, moderate or severe disease. This classification was based on symptom frequency, degree of airflow obstruction, and number and frequency of asthma exacerbations, and was used to provide treatment recommendations. The earliest iteration of the Global Initiative for Asthma (GINA) strategy document in 1995 stated that "descriptions of asthma severity are useful because asthma therapy has a stepwise approach in which the level of therapy is increased as the severity of the asthma increases" [1]. However, in a seminal paper, published in 1996, Cockcroft and Swystun [2] argued that asthma severity and asthma control were inextricably linked. Thus, asthma severity can only be established retrospectively after the minimal treatment requirement to achieve asthma control is known. This approach was adopted in subsequent iterations of the GINA strategy document [3] and other national asthma guidelines [4], and was recommended by an American Thoracic Society/European Respiratory Society Task Force on asthma control, severity and exacerbations [5, 6]. As a consequence of this approach, mild asthma is currently identified for clinical practice as a patient with well-controlled asthma, manifest by infrequent symptoms (twice or less per week), no nocturnal awakenings and normal activities of daily living, while treated with as-needed controller medication alone, low-dose maintenance inhaled corticosteroids (ICSs) or leukotriene receptor antagonists (LTRAs) [7]. In the case of clinical trials in mild asthma, most studies have included patients who would have been eligible for treatment with maintenance ICS or LTRA according to then-current guidelines.

Treatment options for mild asthma

Inhaled adrenergic agonists were initially used to treat asthma as early as the 1930s [8]. Short-acting β_2-agonists (SABAs) were the first inhaled therapy to be developed for common use in asthma [9]. These are rapid-onset bronchodilators, selective for the β_2-receptor, and which provide symptom relief, but have no anti-inflammatory properties. Subsequently, ICSs were introduced as maintenance treatment for asthma [10], being very effective in reducing eosinophilic airway inflammation [11], improving airway hyperresponsiveness [12], asthma control [13] and reducing asthma exacerbation risk [14]. However, it is reported that, at least initially, general practitioners were reluctant to prescribe ICSs because of fear of the severe side-effects that had been seen with systemic corticosteroids [15].

These two classes of drugs remain the most commonly prescribed treatments for asthma. Until recently, the way in which they were prescribed did not closely align with the evidence base for their efficacy and safety [16]. Although it was known that asthma is an airway inflammatory disorder, even in the mildest patients [17, 18], for many years the recommendation in asthma treatment guidelines for first-line treatment for mild disease was a SABA, which has no anti-inflammatory properties. This recommendation was based on the belief that if asthma is mild enough to only warrant "occasional" short-acting bronchodilator, the utility of recommending regular ICS seemed disproportionate and unnecessary. Another class of medication approved for the treatment of mild asthma was LTRAs [19]. However, studies comparing the efficacy of LTRAs to low-dose maintenance ICS have demonstrated the superiority of ICS in mild asthma patients previously taking SABA alone, particularly for reduction in severe exacerbations [20, 21]. From 2014, finding a lack of evidence to support SABA-only treatment, GINA recommended maintenance ICS for patients with symptoms more than twice a month or with any risk factors for asthma exacerbations [22], a position that was supported by findings from the START study [23]; however, most guidelines continue to limit ICSs to patients with symptoms more than twice a week.

From a patient's perspective, the most tangible measure of asthma control is day-to-day symptoms, which vary with time. Fast and effective symptom relief is a priority for patients. In mild asthma, when symptoms are not present, patients can find adhering to daily preventative medication with ICS difficult without any obvious immediate improvement that might provide a rationale for their use and reluctance due to potential side-effects. In contrast, because treatment with a SABA is so effective during acute attacks, it may appear logical to patients for this to also be beneficial for the control of chronic asthma.

For several decades, it has been recognised that SABA overuse is associated with increased risk of asthma mortality [24], a finding unfortunately confirmed by the National Review of Asthma Deaths in the UK which demonstrated increased SABA use and lack of ICS use associated with increased mortality [25]. These concerns have been supported by mechanistic studies showing regular SABA use, for a little as 1 week, is associated with increased exercise bronchoconstriction [26] and allergic airway inflammation [27], and by studies showing that dispensing of three or more SABA canisters a year (usage $\geqslant$3–4 times per week) is associated with increased asthma exacerbations [28] and all-cause mortality [29].

Low-dose maintenance ICS has been extensively evaluated as a treatment option for mild asthma. These studies have demonstrated that low-dose (even once-daily) ICS was superior to SABA as-needed as the only treatment in reducing asthma exacerbation risk [23, 30], and this benefit persisted even when patients with very infrequent symptoms (0–1 days per week) were evaluated [31].

A major challenge with recommending the use of maintenance ICS for patients with mild asthma is adherence to the treatment. There is a very consistent body of evidence which shows that adherence to maintenance treatment in asthma is problematic, with many studies indicating that patients take <50% of recommended doses of maintenance treatment, which can be improved with a strategy of providing electronic inhaler reminders [32]. Adherence to maintenance treatment also decreases with time and can be as low as 10–15% of patients refilling prescriptions for maintenance inhaled treatments, over a 1-year time frame [33].

ICS/LABA maintenance and reliever therapy

The long-acting β_2-agonists (LABAs) salmeterol and fast-acting formoterol were developed in the 1990s. Initial studies were conducted to determine both safety and efficacy, particularly in combination with inhaled steroids (ICS/LABA) [34, 35]. In patients receiving maintenance ICS therapy, clinical effectiveness was demonstrated by reducing severe exacerbations with ICS/LABA compared with ICS alone [36]. By contrast, in patients considered to have mild asthma not treated with maintenance ICS, adding formoterol to ICS as part of maintenance treatment did not provide any additional benefit compared with maintenance ICS alone [30]. However, formoterol for symptom relief reduced severe exacerbations, both with [36, 37] and without [38] maintenance ICS, compared with as-needed SABA.

In a real-world setting, where LABAs were being used as the only treatment or not in combination with ICS, asthma-related mortality was increased [39]. This led to the recommendation that LABAs be only used together with an ICS (ideally from the same device) in moderate and severe asthma [40]; however, despite these justifiable concerns about the use of LABA as monotherapy in asthma, SABA monotherapy remained as the first-line treatment option for patients with mild asthma.

For patients with moderate to severe asthma, maintenance treatment with ICS/LABA combinations has become the standard of care. In addition, the use of a combination ICS/rapid-onset LABA (formoterol) inhaler as both maintenance and reliever therapy has been demonstrated to be superior to fixed-dose ICS or combination ICS/LABA with SABA as reliever. This approach demonstrated a 25–40% relative risk reduction in severe exacerbation risk compared with fixed-dose regimens in patients with a history of severe exacerbations [41]. This set a precedent of a patient-centred approach in moderate to severe asthma, where patients have autonomy and control over escalating and de-escalating additional ICS/formoterol use based on current day-to-day symptoms. The rationale was that the fast-acting bronchodilator formoterol improves symptoms, but at the same time the underlying worsening inflammation is addressed with up-titration of treatment with ICS; however, both ICS and formoterol in the reliever inhaler contribute to the reduction in exacerbations [42].

ICS/SABA as reliever therapy in mild asthma

The hypothesis that using a reliever that contained both a rapid-onset β_2-agonist and an ICS would be superior to a β_2-agonist only as a reliever was initially evaluated in 2007 in patients considered, at that time, to have mild asthma (table 1) [43]. The BEST study consisted of four treatment arms, after a run-in period on moderate-dose ICS: as-needed combination ICS (beclometasone) and SABA (salbutamol) from a single inhaler, as-needed SABA only, maintenance ICS with SABA as-needed, and maintenance combination ICS/SABA with SABA as-needed. The study demonstrated that symptom-driven use of as-needed combination ICS/SABA improved peak expiratory flow rates and forced expiratory volume in 1 s (FEV_1) and reduced exacerbations compared with as-needed SABA alone, but was not different to the maintenance ICS and maintenance combination ICS/SABA groups. The cumulative dose of ICS was, however, substantially lower in the as-needed ICS/SABA group when compared with the other two ICS-containing treatment arms.

In the TREXA study, in children aged 5–18 years with mild asthma (table 1), using a similar design and intervention arms, but with the ICS and SABA delivered from separate inhalers, Martinez *et al.* [44] showed that treatment with maintenance low-dose ICS reduced asthma exacerbations risk by 50% compared with SABA as-needed alone. Treatment with ICS/SABA as-needed also reduced the risk of exacerbations by almost 40%, but this did not reach statistical significance. Importantly, the use of maintenance ICS was associated with a 1.1 cm decline in linear growth over 1 year, which was not seen with as-needed ICS/SABA, because of the lower cumulative dose of ICS in this group.

TABLE 1 Studies in mild asthma with inhaled corticosteroid (ICS) in combination with rapid-onset β_2-agonists as-needed

Study [ref.]	Patients n	Age years	Design	Duration weeks	Treatment groups	Primary outcome	Secondary outcomes
BEST [43]	455	18–65	Phase 3, double-blind, randomised, parallel group	26	1) Salbutamol as-needed; 2) BDP/salbutamol as-needed; 3) BDP twice-daily with salbutamol as-needed; 4) BDP/salbutamol twice-daily with salbutamol as-needed	Peak expiratory flow rates	Exacerbation rate, daytime and night-time symptoms, rescue medication use
TREXA [44]	843	5–18	Phase 3, double-blind, randomised, parallel group	44	1) Salbutamol as-needed; 2) BDP/salbutamol as-needed; 3) BDP twice-daily with BDP/salbutamol as-needed; 4) BDP twice-daily with salbutamol as-needed	Time to first severe exacerbation	Linear growth, FEV_1, F_{ENO}, symptoms, asthma control, medication use
BASALT [45]	342	>18	Phase 3, double-blind, randomised, parallel group	38	1) Physician assessment-based adjustment; 2) biomarker-based adjustment; 3) symptom-based adjustment, ICS taken with each salbutamol rescue	Time to treatment failure	Treatment failure rates, mean monthly ICS use, asthma exacerbations, lung function, symptoms, sputum eosinophils
ASIST [46]	206	6–17	Phase 4, open-label, randomised, parallel group	52#	1) Symptom-based adjustment, BDP taken with each salbutamol rescue use; 2) guideline-based adjustment by primary care providers	Change in symptom control (ACT or cACT) at 12 months	Average monthly BDP dose, proportion with ⩾1 exacerbations, change in QoL, change in pre-BD FEV_1 % pred, missed school days for asthma, change in ACT or cACT at 6 months
SYGMA 1 [49]	3836	⩾12	Phase 3, placebo controlled, double-blind, randomised, parallel group	52	1) Placebo twice-daily with budesonide/formoterol as-needed; 2) placebo twice-daily with terbutaline as-needed; 3) budesonide twice-daily with terbutaline as-needed	Number of well-controlled asthma weeks	Rates and time to first severe and moderate exacerbation, ACQ-5, FEV_1, AQLQ, medication use
SYGMA 2 [50]	4215	⩾12	Phase 3, double-blind, randomised, parallel group	52	1) Placebo twice-daily with budesonide/formoterol as-needed; 2) budesonide twice-daily with terbutaline as-needed	Annual rate of severe exacerbations	Time to first severe exacerbation, steroid use, FEV_1, ACQ-5, AQLQ, medication use
Novel START [51]	675	18–75	Phase 3, open-label, randomised, parallel group	52	1) Salbutamol as-needed; 2) budesonide twice-daily with salbutamol as-needed; 3) budesonide/formoterol as-needed	Annual rate of exacerbations	Number of severe exacerbations, time to first exacerbation, ACQ-5, F_{ENO}, medication use
PRACTICAL [54]	890	18–75	Phase 3, open-label, randomised, parallel group	52	1) Budesonide/formoterol as-needed; 2) budesonide twice-daily with terbutaline as-needed	Number of severe exacerbations	Time to first severe exacerbation, FEV_1, F_{ENO}, ACQ-5

Continued

TABLE 1 Continued

Study [ref.]	Patients n	Age years	Design	Duration weeks	Treatment groups	Primary outcome	Secondary outcomes
Lazarinis *et al.* [56]	66	>12	Phase 2, double-blind, randomised, placebo controlled, parallel group	6	1) Placebo once-daily and budesonide/formoterol as-needed; 2) placebo once-daily and terbutaline as-needed; 3) budesonide once-daily and terbutaline as-needed	Change in maximal post-exercise decrease in FEV_1 after 6 weeks	Change in maximal post-exercise FEV_1 fall after 3 weeks, ACQ-5, symptoms, use of as-needed medications before exercise and for symptom relief

See main text for further details [43–56]. BDP: beclomethasone dipropionate; FEV_1: forced expiratory volume in 1 s; F_{ENO}: exhaled nitric oxide fraction; ACT: Asthma Control Test; cACT: childhood Asthma Control Test; QoL: quality of life; BD: bronchodilator; ACQ-5: five-item Asthma Control Questionnaire-5; AQLQ: Asthma Quality of Life Questionnaire. #: 12 months.

The Best Adjustment Strategy for Asthma in the Long Term (BASALT) study in adults with well-controlled or partly controlled asthma on ICS therapy used a similar model of patients adjusting ICS use according to their requirement for SABA, again with separate inhalers [45]. The symptom-driven approach of instructing patients to take two actuations of their low-dose beclomethasone (ICS) inhaler every time they took a SABA was at least as effective in terms of the time to treatment failure compared with a "gold standard" physician-based strategy of 6-weekly adjustment of maintenance ICS dose or a novel biomarker ICS-adjusted strategy.

A recent pragmatic study in African-American children and adolescents with well-controlled asthma on low-dose ICS, LTRA or ICS/LABA randomised patients to symptom-based treatment with ICS taken whenever SABA was taken or to guidelines-based adjustment of treatment by primary care providers. Asthma outcomes were similar between groups, with average ICS dose in the symptom-based treatment arm 26% of that with physician-adjusted treatment (table 1) [46].

ICS/LABA as reliever therapy in mild asthma

Evidence that budesonide/formoterol as a reliever treatment reduces severe exacerbation risk compared with SABA in patients with moderate to severe asthma on maintenance ICS/LABA (later summarised in a meta-analysis [47]) led to investigation of the use of budesonide/formoterol (Symbicort) as-needed in mild asthma (table 1). The SYmbicort Given as-needed in Mild Asthma (SYGMA) 1 Study was a randomised, double-blind, 52-week, three-way parallel group study of 3849 patients. The study evaluated the efficacy and safety of budesonide/formoterol used as-needed compared with the SABA terbutaline as-needed and with budesonide (200 µg) twice-daily plus terbutaline as-needed. Patients were eligible if they needed maintenance low-dose ICS treatment (GINA 2012 step 2, including use of SABA on ⩾3 days in the week before randomisation) [48].

The primary efficacy results showed that budesonide/formoterol as-needed was superior to terbutaline as-needed at reducing the number of well-controlled asthma weeks (based on an old definition of asthma control), but was inferior to maintenance budesonide [49]. Secondary outcomes demonstrated that budesonide/formoterol as-needed resulted in a 64% lower rate of severe exacerbations and a 60% lower rate of moderate to severe exacerbations compared with terbutaline as-needed, and prolonged the time to first severe exacerbation and the time to first use of additional corticosteroids for asthma. The budesonide/formoterol as-needed group also had a small, but significant, improvement in the five-item Asthma Control Questionnaire (ACQ-5) score and a higher FEV_1 than the terbutaline as-needed group. Compared with maintenance budesonide, there was no difference in the exacerbation outcomes, but these were achieved with an 83% lower ICS dose with budesonide/formoterol as-needed. However, maintenance budesonide also had a small, but significant, improvement in ACQ-5 score and a higher FEV_1 than the budesonide/formoterol as-needed group. These differences did not achieve levels considered to be clinically important. Importantly, with twice-daily inhaler reminders, adherence to the maintenance treatments in all three study arms was almost 80%. The median use of a reliever in this study was about one inhalation every 3 days, and while this had a wide distribution, on <0.5% of days in the study were more than four inhalations of as-needed budesonide/formoterol used.

The SYGMA 2 study (table 1) randomly assigned 4215 patients who met the same entry criteria as SYGMA 1, but the study did not include electronic diaries or adherence reminders and had less oversight

from clinical research teams at the recruiting centres, to mimic a more real-world clinical setting [50]. Subjects were randomised to receive either 52 weeks of budesonide/formoterol as-needed or twice-daily maintenance budesonide with terbutaline as-needed. The primary outcome in this study was the annual rate of severe exacerbations. For this outcome, budesonide/formoterol as-needed was noninferior to maintenance budesonide, but with a 75% lower median daily ICS dose in the budesonide/formoterol group. There was no difference between groups in the number of severe exacerbations that led to hospitalisation or emergency room visits, or in the time to first severe asthma exacerbations. Similar to the SYGMA 1 study, maintenance budesonide had a small, but significant, improvement in ACQ-5 score and a higher FEV_1 than the budesonide/formoterol as-needed group. The adherence to maintenance treatment in the two study arms was 64%.

A third, more pragmatic study (Novel START) (table 1) was a randomised, open-label, parallel three-way group trial in 675 patients treated with the SABA salbutamol as-needed, maintenance budesonide plus salbutamol as-needed or budesonide/formoterol as-needed [51]. Patients were eligible if they used SABA as their only asthma therapy in the 3 months prior to their inclusion and by including patients with baseline SABA use as infrequent as twice a month, extended the evidence of efficacy to patients with infrequent symptoms; overall, 54% of patients had used SABA twice a week or less in the previous 4 weeks. The primary efficacy outcome was the annualised asthma exacerbation rate, which was 51% lower in the budesonide/formoterol as-needed group compared with the salbutamol as-needed group, but was not different to the maintenance budesonide group. Interestingly, in contrast to the SYGMA studies, the number of severe exacerbations, although small, was significantly lower in the budesonide/formoterol as-needed group compared with both the salbutamol as-needed and the maintenance budesonide groups. However, maintenance budesonide demonstrated the greatest improvements in ACQ-5 scores, albeit the differences were small and again did not meet the minimally clinical important difference. There was no significant difference in FEV_1 across all time-points between the three groups. Both of the ICS-containing arms of the study significantly reduced the exhaled nitric oxide fraction (F_{ENO}) compared with the SABA treatment arm. The geometric mean F_{ENO} in the budesonide/formoterol treatment arm was slightly higher than in the maintenance budesonide group, but the difference was small and of no clinical importance. These results demonstrate that budesonide/formoterol combination has anti-inflammatory activity when administered by an as-needed reliever regimen in mild asthma and do not support any concern that its use in this way will allow eosinophilic airway inflammation to progressively worsen; however, further long-term studies need to be done to confirm this. Of interest, in this study, patients with mild asthma with elevated baseline blood eosinophils (>0.3 *versus* $<0.15\times10^9$ L^{-1}) had a higher risk of experiencing a severe asthma exacerbation [52] and the benefits of maintenance inhaled budesonide compared with salbutamol were greater in patients with high blood eosinophil counts. However, importantly, effects of budesonide/formoterol as-needed on exacerbations and symptom control were independent of blood eosinophil or F_{ENO} biomarker profiles. This indicates that the efficacy of budesonide/formoterol is generalisable to all patients with mild asthma, without the need for inflammatory phenotyping. This differs from more severe asthma, where biomarker assessment may be helpful in titrating maintenance ICS dose [53].

The Novel START study was followed by another open-label study (PRACTICAL) [54], enrolling 890 patients requiring or eligible for GINA step 2 treatments (table 1). The study had two treatment arms: budesonide/formoterol as-needed or maintenance budesonide with terbutaline as-needed. The results were very similar to Novel START, with a 31% reduction in the rate of severe asthma exacerbations with budesonide/formoterol as-needed and an increase in the time to first exacerbation compared with maintenance budesonide. Also, as in Novel START, the benefit with this regimen for risk reduction and asthma control in PRACTICAL was independent of baseline characteristics, including inflammatory markers such as blood eosinophils and F_{ENO}. Another important clinical finding from the PRACTICAL study was that 90% of patients who were randomised to budesonide/formoterol reported a preference for this regimen rather than maintenance ICS and SABA at the end of the trial [55].

Finally, a study by Lazarinis *et al.* [56] provided evidence that as-needed budesonide/formoterol taken for symptom relief and before exercise reduced the risk of exercise-induced bronchoconstriction to the same extent as 6 weeks of maintenance ICS, indicating that patients do not need to be given a SABA inhaler for pre-exercise use.

Conclusions

The studies comparing reliever medications that contain an ICS with using SABA alone, in patients with mild asthma, have put to rest the question of the optimal reliever treatment for these patients. In studies spanning childhood, adolescence and adults, an ICS-containing reliever medication was superior to SABA reliever alone in almost every domain (figure 1). For this reason, the GINA treatment algorithm now

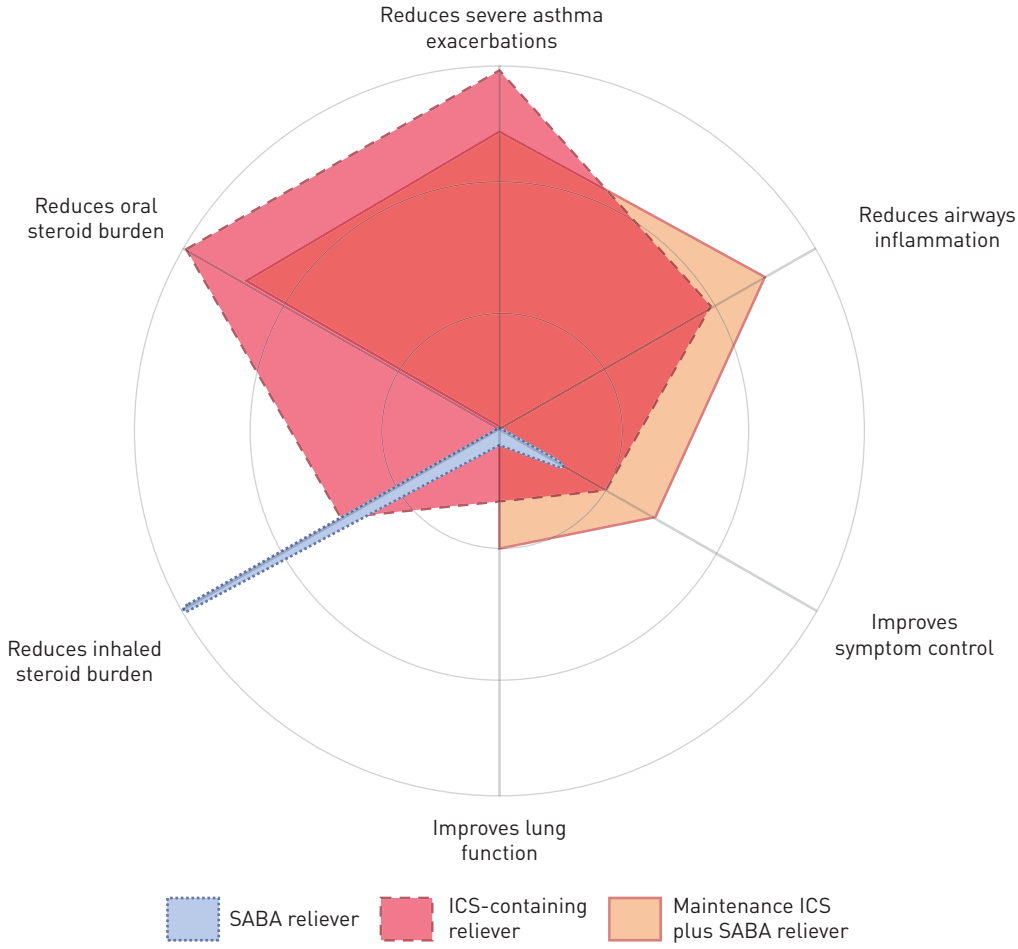

FIGURE 1 Conceptual comparison of the relative benefits of the three treatment regimens for asthma: short-acting β_2-agonist (SABA) reliever, combination inhaled corticosteroid (ICS)/fast-onset β_2-agonist reliever and maintenance ICS plus SABA reliever. The relative performance of each regimen is presented across six domains: reduction in severe exacerbations, reduction in airways inflammation, improvement in symptom control, improvement in lung function, reduction in ICS burden and reduction in oral corticosteroid burden. The relative performance of each regimen for each domain is based on the literature referenced in this review. The greater the distance of each point from the axes centre, the better the performance in that domain.

recommends that SABAs should not be used alone as sole therapy without ICS, and that combination ICS/formoterol is preferred to SABA as reliever therapy in adults and adolescents [7]; however, there is no evidence for the safety of using ICS/formoterol as reliever for patients taking other ICS/LABA combinations. In addition, while maintenance ICS treatment for mild asthma is superior for some clinical outcomes, the concerns about many patients with mild asthma not being adherent to maintenance ICS resulted in the GINA treatment algorithm recommending ICS/formoterol as an alternative to maintenance ICS, to avoid the risk of patients reverting to SABA alone.

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References

1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. NIH Publication 95-3659A. Bethesda, National Heart, Lung, and Blood Institute, 1995.
2 Cockcroft DW, Swystun VA. Asthma control versus asthma severity. *J Allergy Clin Immunol* 1996; 98: 1016–1018.
3 Bateman ED, Hurd SS, Barnes PJ, *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31: 143–178.
4 National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma – Summary Report 2007. *J Allergy Clin Immunol* 2007; 120: S94–S138.
5 Taylor DR, Bateman ED, Boulet LP, *et al.* A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008; 32: 545–554.
6 Reddel HK, Taylor DR, Bateman ED, *et al.* An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180: 59–99.
7 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2020. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf Date last accessed: October 31, 2020.
8 Graeser JBR, Rowe AH. Inhalation of adrenaline for the relief of asthma. *Cal West Med* 1935; 43: 110.
9 Tattersfield AE. Current issues with β_2-adrenoceptor agonists. *Clin Rev Allergy Immunol* 2006; 31: 107–117.
10 Brown HM, Storey G, George WH. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1972; 1: 585–590.
11 Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β_2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992; 90: 32–42.
12 Juniper EF, Kline PA, Vanzieleghem MA, *et al.* Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990; 142: 832–836.
13 O'Byrne PM, Naya IP, Kallen A, *et al.* Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled β_2-agonists in achieving asthma control. *Chest* 2008; 134: 1192–1199.
14 Haahtela T, Jarvinen M, Kava T, *et al.* Comparison of a β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991; 325: 388–392.
15 Crompton G. A brief history of inhaled asthma therapy over the last fifty years. *Prim Care Respir J* 2006; 15: 326–331.
16 O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J* 2017; 50: 1701103.
17 Kirby JG, Hargreave FE, Gleich GJ, *et al.* Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. *Am Rev Respir Dis* 1987; 136: 379–383.
18 Beasley R, Roche WR, Roberts JA, *et al.* Cellular events in the bronchi in mild asthma and after bronchial provocation. *Am Rev Respir Dis* 1989; 139: 806–817.
19 Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999; 340: 197–206.
20 Bleecker ER, Welch MJ, Weinstein SF, *et al.* Low-dose inhaled fluticasone propionate versus oral zafirlukast in the treatment of persistent asthma. *J Allergy Clin Immunol* 2000; 105: 1123–1129.
21 Busse W, Raphael GD, Galant S, *et al.* Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol* 2001; 107: 461–468.
22 Reddel HK, Bateman ED, Becker A, *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46: 622–639.
23 Pauwels RA, Pedersen S, Busse WW, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071–1076.
24 Spitzer WO, Suissa S, Ernst P, *et al.* The use of β-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326: 501–506.
25 Levy M, Andrews R, Buckingham R, *et al.* Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD). London, Royal College of Physicians, 2014.
26 Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; 153: 65–69.
27 Gauvreau GM, Jordana M, Watson RM, *et al.* Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997; 156: 1738–1745.
28 Stanford RH, Shah MB, D'Souza AO, *et al.* Short-acting β-agonist use and its ability to predict future asthma-related outcomes. *Ann Allergy Asthma Immunol* 2012; 109: 403–407.
29 Nwaru BI, Ekstrom M, Hasvold P, *et al.* Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020; 55: 1901872.
30 O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, *et al.* Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; 164: 1392–1397.
31 Reddel HK, Busse WW, Pedersen S, *et al.* Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017; 389: 157–166.
32 Foster JM, Usherwood T, Smith L, *et al.* Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014; 134: 1260–1268.
33 Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006; 118: 899–904.
34 Greening AP, Ind PW, Northfield M, *et al.* Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994; 344: 219–224.
35 Pearlman DS, Chervinsky P, LaForce C, *et al.* A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med* 1992; 327: 1420–1425.

36 Pauwels RA, Lofdahl CG, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997; 337: 1405–1411.
37 Tattersfield AE, Lofdahl CG, Postma DS, *et al.* Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001; 357: 257–261.
38 Pauwels RA, Sears MR, Campbell M, *et al.* Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003; 22: 787–794.
39 Nelson HS, Weiss ST, Bleecker ER, *et al.* The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129: 15–26.
40 Busse WW, Bateman ED, Caplan AL, *et al.* Combined analysis of asthma safety trials of long-acting β_2-agonists. *N Engl J Med* 2018; 378: 2497–2505.
41 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.
42 Rabe KF, Atienza T, Magyar P, *et al.* Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006; 368: 744–753.
43 Papi A, Canonica GW, Maestrelli P, *et al.* Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; 356: 2040–2052.
44 Martinez FD, Chinchilli VM, Morgan WJ, *et al.* Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 650–657.
45 Calhoun WJ, Ameredes BT, King TS, *et al.* Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012; 308: 987–997.
46 Sumino K, Bacharier LB, Taylor J, *et al.* A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. *J Allergy Clin Immunol Pract* 2020; 8: 176–185.
47 Edwards SJ, von Maltzahn R, Naya IP, *et al.* Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. *Int J Clin Pract* 2010; 64: 619–627.
48 O'Byrne PM, FitzGerald JM, Zhong N, *et al.* The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials. *Trials* 2017; 18: 12.
49 O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.
50 Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide–formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.
51 Beasley R, Holliday M, Reddel HK, *et al.* Controlled trial of budesonide–formoterol as needed for mild asthma. *N Engl J Med* 2019; 380: 2020–2030.
52 Pavord ID, Holliday M, Reddel HK, *et al.* Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med* 2020; 8: 671–680.
53 Green RH, Brightling CE, McKenna S, *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002; 360: 1715–1721.
54 Hardy J, Baggott C, Fingleton J, *et al.* Budesonide–formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019; 394: 919–928.
55 Baggott C, Reddel HK, Hardy J, *et al.* Patient preferences for symptom-driven or regular preventer treatment in mild to moderate asthma: findings from the PRACTICAL study, a randomised clinical trial. *Eur Respir J* 2020; 55: 1902073.
56 Lazarinis N, Jorgensen L, Ekstrom T, *et al.* Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014; 69: 130–136.