



European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma

Alberto Papi ^{1,19,21}, Diogenes S. Ferreira ^{2,19,21}, Ioana Agache³, Eugenio Baraldi ⁴, Richard Beasley ⁵, Guy Brusselle ⁶, Courtney Coleman ⁷, Mina Gaga ⁸, Carolina Maria Gotera Rivera⁹, Erik Melén ¹⁰, Ian D. Pavord ¹¹, Deborah Peñate Gómez¹², Daniel Schuermans ¹³, Antonio Spanevello^{14,15}, Thomy Tonia^{16,20} and Florence Schleich ^{17,18,20,21}

¹Respiratory Medicine, University of Ferrara, Ferrara, Italy. ²Private Practice, Allergy and Immunology, Belo Horizonte, Brazil. ³Faculty of Medicine, Transylvania University, Brasov, Romania. ⁴Department of Women's and Children's Health, University of Padova, Institute of Pediatric Research "Città della Speranza", Padova, Italy. ⁵Medical Research Institute of New Zealand, Wellington, New Zealand. ⁶Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. ⁷European Lung Foundation, Sheffield, UK. ⁸Athens Chest Hospital, Athens, Greece. ⁹Pulmonology Department, IIS-Fundación Jiménez Díaz, ISCIII, CIBERES, Madrid, Spain. ¹⁰Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Sachsska Children's Hospital, Stockholm, Sweden. ¹¹Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK. ¹²Asthma Patient Representative, London, UK. ¹³Respiratory Division, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium. ¹⁴Department of Medicine and Surgery, University of Insubria, Varese, Italy. ¹⁵Istituti Clinici Scientifici Maugeri IRCCS, Department of Medicine and Cardiopulmonary Rehabilitation, Tradate Institute, Tradate, Italy. ¹⁶Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. ¹⁷Respiratory Medicine, CHU Liege, Liege, Belgium. ¹⁸GIGA-I3, University of Liege, Liege, Belgium. ¹⁹A. Papi and D.S. Ferreira contributed equally to this work. ²⁰T. Tonia and F. Schleich contributed equally to this work. ²¹A. Papi, D.S. Ferreira and F. Schleich are Task Force co-chairs.

Corresponding author: Alberto Papi (papa@unife.it)



Shareable abstract (@ERSpublications)

ERS Task Force recommends mild asthma patients use as-needed ICS/formoterol instead of as-needed SABA, and suggests adults use as-needed ICS/formoterol instead of regular ICS maintenance treatment plus as-needed SABA and adolescents use either strategy <https://bit.ly/482XWPa>

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Abstract

Recent clinical trials of as-needed fixed-dose combination of inhaled corticosteroid (ICS)/formoterol have provided new evidence that may warrant a reconsideration of current practice. A Task Force was set up by the European Respiratory Society to provide evidence-based recommendations on the use of as-needed ICS/formoterol as treatment for mild asthma. The Task Force defined two questions that were assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. The Task Force utilised the outcomes to develop recommendations for a pragmatic guideline for everyday clinical practice. The Task Force suggests that adults with mild asthma use as-needed ICS/formoterol instead of regular ICS maintenance treatment plus as-needed short-acting β_2 -antagonist (SABA) and that adolescents with mild asthma use either as-needed ICS/formoterol or ICS maintenance treatment plus as-needed SABA (conditional recommendation; low certainty of evidence). The recommendation for adults places a relatively higher value on the reduction of systemic corticosteroid use and the outcomes related to exacerbations, and a relatively lower value on the small differences in asthma control. Either treatment option is suggested for adolescent patients as the balance is very close and data more limited. The Task Force recommends that adult and adolescent patients with mild asthma use as-needed ICS/formoterol instead of as-needed SABA (strong recommendation; low certainty of evidence). This recommendation is based on the benefit of as-needed ICS/formoterol in mild asthma on several outcomes and the risks related to as-needed SABA in the absence of anti-inflammatory treatment. The implementation of this recommendation is hampered in countries (including European Union countries) where as-needed ICS/formoterol is not approved for mild asthma.

Introduction

Asthma is primarily an inflammatory disorder of the airways and anti-inflammatory treatment is the cornerstone of asthma management. Until 2018 the Global Initiative for Asthma (GINA) document [1] recommended a pharmacological strategy based on regular scheduled maintenance treatment with an anti-inflammatory controller, with a short-acting β_2 -agonist (SABA) as rescue intervention. Patients with milder asthma were recommended only as-needed SABA treatment. SABAs effectively induce rapid symptom relief but are ineffective on the underlying inflammatory process.

Despite being labelled as mild asthma, this large group of patients [2, 3] can have active airway inflammation [4] and may experience severe, potentially fatal, asthma attacks (termed asthma exacerbations) [5–7], and the absence of an anti-inflammatory treatment is a potential problem.

Poor adherence to inhaled therapy is a major limitation of maintenance controller treatments [8], particularly in adolescents. Low rates of adherence are associated with higher risk of severe asthma exacerbations [9]. Indeed, several surveys have highlighted a common pattern in the use of inhaled medication [10]: patients self-manage their condition using the medications when they feel the need and adjust their treatment by increasing the intake of SABA, aiming for immediate relief from symptoms [11]. This may result in SABA overuse, which has been associated with an increased risk of severe exacerbations and asthma death in adults [7, 12–14] as well as in children and adolescents [15]. The concomitant use of an inhaled corticosteroid (ICS) in addition to a rapid bronchodilator as reliever medication (*i.e.* an anti-inflammatory reliever) [8] would provide rapid relief while administering anti-inflammatory therapy, titrated according to severity through the vehicle of reliever medication use. This approach was first developed in patients regularly treated with ICS/formoterol where the same combination was used also as reliever therapy, given the rapid onset of action of the long-acting β_2 -agonist (LABA) formoterol. The combination of an ICS and a rapid-acting LABA in one inhaler for both maintenance and reliever therapy (MART) has been tested and found to be effective across the range of asthma severity [16–19].

The same principle was applied in mild asthma in a pilot study showing the equivalence of a rescue ICS/SABA (beclomethasone/salbutamol) combination, in the absence of maintenance treatment, compared with regular low-dose ICS plus rescue salbutamol, and the superiority compared with as-needed salbutamol alone [20]. The findings of this initial proof-of-concept trial have been reinforced by the results of several recent clinical trials of as-needed fixed-dose combination of ICS/formoterol in mild asthma. Collectively, this evidence supported the current indication of ICS/rapid-acting bronchodilators in the absence of maintenance treatment as first-line therapy for mild asthma in international documents [8] and is recommended in guidelines in multiple countries.

The purpose of the present European Respiratory Society (ERS) clinical practice guideline is to provide physicians, healthcare professionals, patients and other stakeholders with recommendations on the use of rescue ICS/formoterol for the treatment of adult and adolescent patients with mild asthma, based on a systematic review of the literature and application of the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [21].

Methods

Rationale for a short guideline

This document was developed as a “short ERS guideline” [22] following the requirements for guidelines of the ERS [23]. Short guidelines aim to respond quickly to new evidence that could lead to changes in clinical practice. Since the efficacy in mild asthma of as-needed ICS/formoterol combination without its use as maintenance therapy cannot be extrapolated from MART studies, the evidence discussed here will focus on the use of as-needed ICS/formoterol in mild asthma in the absence of maintenance treatment. The topic of the document is of primarily clinical importance, with the potential to produce a change in clinical outcomes and impacting also on patients’ attitudes/preferences to asthma management.

Methodology

For full methodology details, please refer to the supplementary material.

Group composition and management of conflicts of interest

The guideline Task Force included three co-chairs, 12 clinicians and researchers with experience in the field of asthma, one ERS Early Career Member representative, and a patient representative. The methodological work was overviewed by one of the ERS in-house methodologists. The standard ERS policy for the management of conflicts of interest was followed. See supplementary material for further details.

Formulation of questions and rating of importance of outcomes

Guideline Task Force members agreed on the formulation of two PICO (Patient, Intervention, Comparator, Outcome) questions [24]. The Task Force decided that they would review the evidence separately for adults and adolescents (aged ≥ 12 to < 18 years), when possible. Following GRADE guidance [24], the Task Force rated the importance of the outcomes for clinical decision making before seeing the evidence (see supplementary material for full list of outcomes).

Literature searches and selection of studies

An externally commissioned methodologist designed and conducted the literature searches in October 2021 in various databases (see supplementary material for full search strategies and databases used).

The identified studies were screened by two authors (F. Schleich and I. Agache) based on predefined inclusion and exclusion criteria (supplementary material). Disagreements (one single case during full-text screening) were resolved by a third author (G. Brusselle). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowcharts for each question are presented in the supplementary material.

Evidence synthesis

Data extraction, meta-analyses when appropriate, assessment of certainty of the evidence using GRADE [25] and creation of GRADE evidence profiles were performed by the external methodologist and one co-chair (D.S. Ferreira). Thresholds for clinically important changes were agreed upon prior to seeing the evidence (see supplementary material).

The Task Force unanimously agreed on thresholds for the clinically important changes.

Formulating and grading recommendations

We used the evidence-to-decision framework to structure and document the discussions around the evidence and reach recommendations [26, 27]. Strong or conditional recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (harms) of the intervention, the certainty of evidence, patient values and preferences, feasibility, acceptability, health equity, and costs (see supplementary material for detailed grading process). Consensus was reached mainly by discussion. Formal voting also took place for the recommendation statement of each PICO question. A threshold of 70% was considered for voting in favour of a recommendation.

Manuscript preparation

The initial drafts of the manuscript and the supplementary material were prepared by A. Papi and edited by D.S. Ferreira. Both the manuscript and the supplementary material were reviewed and approved by all Task Force members prior to submission.

Results

PICO 1

Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared with regular low-dose ICS maintenance treatment plus as-needed SABA in adult/adolescent patients with mild asthma (i.e. GINA [1] treatment steps 1 or 2)?

Summary of the evidence

We identified a total of 548 publications, of which six were finally included [28–33].

All six studies used budesonide as the ICS component of the ICS/formoterol combination; terbutaline and salbutamol were the SABAs tested in three [28, 29, 31] and one [30] randomised controlled trials, respectively. The study by TANAKA *et al.* [33], available only in the form of an abstract, does not specify the SABA used.

Detailed definitions and data are presented in the supplementary material.

Summary of benefits and harms

The effects in favour of as-needed ICS/formoterol in severe exacerbation prevention (relative risk 0.82 (95% CI 0.64–1.04)) [28–31], annualised rate of severe exacerbation (rate ratio 0.86 (95% CI 0.71–1.04)) [28, 29, 31] and emergency department (ED) visits for asthma worsening (relative risk 0.70 (95% CI 0.44–1.09)) [28, 29] were statistically non-significant. Further, no statistically significant difference was found in hospitalisation for severe asthma exacerbations (relative risk 0.92 (95% CI 0.52–1.62)) [28, 29]

and number of patients experiencing at least one exacerbation (not limited to severe) (rate ratio 0.88 (95% CI 0.69–1.13)) [18, 28, 31].

There was no clinically important difference in quality of life (Asthma Quality of Life Questionnaire (AQLQ) change from baseline mean difference (MD) -0.10 (95% CI -0.14 – -0.05)) [29] and asthma control (Asthma Control Questionnaire (ACQ)-5 change from baseline MD 0.13 (95% CI 0.09 – 0.17) [28, 29] and ACQ-5 across all time-points MD 0.09 (95% CI 0.02 – 0.17) [30, 31]).

Total systemic corticosteroid exposure over 1 year was lower for the as-needed ICS/formoterol arm (prednisone MD -7.00 (95% CI -13.97 – -0.03) mg; mean percentage reduction 31.2% (95% CI 0.13–62.2%)) [30, 31] and there was a reduction in mean daily ICS dose (budesonide MD -154 (95% CI -206.87 – -101.14) μg ; mean percentage reduction 56.5% (95% CI 37.1–76%)) [28–31].

Change in pre- and post-bronchodilator forced expiratory volume in 1 s (FEV_1) from baseline favoured maintenance ICS (MD -42.50 (95% CI -63.68 – -21.31) mL and -23.1 (95% CI -41.9 – -4.2) mL, respectively) [28, 29]. On-treatment FEV_1 across all time-points did not differ between treatment strategies (MD 0.01 (95% CI -0.02 – 0.03) L) [30, 31]. Fractional exhaled nitric oxide (F_{ENO}) values at week 52 were higher with as-needed ICS/formoterol (ratio of geometric means 1.13 (95% CI 1.06–1.20)) [30, 31].

There was no difference between as-needed ICS/formoterol and maintenance ICS in the number of patients experiencing adverse events (AEs) (relative risk 0.98 (95% CI 0.92–1.05)) or serious AEs (SAEs) (relative risk 1.13 (95% CI 0.83–1.54)) [28–31]. The data on mortality in the pooled analysis was too limited, leading to very serious imprecision (six events in total: two ICS/formoterol and four maintenance ICS) (Peto OR 0.52 (95% CI 0.10–2.57)) [28–31].

Detailed data are presented in the supplementary material.

Summary of benefits and harms: adolescent subgroup

There was no difference between as-needed ICS/formoterol and maintenance ICS plus as-needed SABA on the annualised rate of severe exacerbations (rate ratio 0.97 (95% CI 0.39–2.40)) or asthma control (ACQ-5 MD 0.06 (95% CI -0.08 – 0.21)). There was a reduction in mean ICS dose with as-needed ICS/formoterol at 52 weeks in the Symbicort Given as-needed in Mild Asthma (SYGMA) 1 study (median (interquartile range) daily ICS dose 35.1 (9.3–91.6) μg versus 292.2 (193.6–341.9) μg) and in the SYGMA 2 study (42.3 (10.4–104.7) μg versus 198.9 (127–285.8) μg) [32].

Mean change from baseline in pre-bronchodilator FEV_1 was lower with as-needed ICS/formoterol (MD -2.6% (95% CI -4.95 – -0.25%)).

The proportion of adolescents experiencing an AE (33.9% and 33.2%; no statistical result reported) or a SAE (1.9% and 1.1%; $p=0.316$) was similar between the two treatment strategies [32].

Recommendations

- We suggest that *adult patients* with asthma on GINA [1] treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler without maintenance treatment instead of regular ICS maintenance treatment plus as-needed SABA. (Conditional recommendation for the intervention; low certainty of evidence.)
- We suggest that *adolescent patients* with asthma on GINA [1] treatment steps 1 or 2 use either as-needed ICS/formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed SABA. (Conditional recommendation for the intervention; low certainty of evidence.)

The Task Force unanimously approved these recommendations.

Justification of the recommendations

- The recommendation for adults places a relatively higher value on the reduction of systemic corticosteroid use and the potential clinical benefit in favour of ICS/formoterol for the outcomes related to severe exacerbations, and a relatively lower value on the small and not clinically relevant differences in asthma control and quality of life.
- Due to the low certainty of evidence we made a conditional recommendation.
- Limited data is available in adolescents compared with adults, therefore the Task Force suggested either treatment option for adolescent patients as the balance between the two options is very close.

Research needs

Alternative strategies such as the use of ICS as a rescue medication in addition to rapid short-acting bronchodilators in two separate inhalers should be tested further, in those countries where as-needed ICS/formoterol has no regulatory approval for use in mild asthma [34–37], since the current recommendation is off-label in those countries. However, such an approach might be rendered obsolete by the availability of alternative combination ICS/salbutamol inhalers [38] recently approved by the US Food and Drug Administration in adults, as a reliever medication across the range of asthma severity [39].

Studies in children are another research priority as this is a population in high need of effective and feasible treatment strategies. Considering the low adherence of adolescents to regular ICS maintenance treatment, studies on adolescents would be of value especially to clarify uncertainty in the effect of as-needed ICS/formoterol on outcomes such as exacerbations and asthma control.

The effects of as-needed budesonide/formoterol on exacerbations are independent of biomarker profile, whereas the benefits of maintenance inhaled budesonide are greater in patients with high blood eosinophil counts than in patients with low counts [40]. Studies undertaken to date found no evidence of an effect modification with severe exacerbation risk based on a wide range of characteristics such as age, sex, ethnicity, smoking status, exacerbation history, baseline SABA use, level of asthma control, lung function, blood eosinophil level or F_{ENO} [41]. Future studies might further explore additional predictors of responsiveness such as poor perceivers of symptoms.

Values, patients' perspective and preferences

Some clinicians will value differently the importance of the outcomes based on patients' different clinical needs and preferences. The guideline Task Force is aware that some clinicians and some patients interpret small changes in exacerbations or quality of life as important while others may not regard them as clinically significant.

Patient education is important to help patients understand the rationale of treatment recommendations and alleviate any concerns.

As-needed ICS/formoterol combination would be preferable for patients with limited financial resources in healthcare systems where patients pay a prescription charge or co-payment per item prescribed (e.g. England) [42–44] and where the costs of rescue ICS/formoterol combination is lower than that of regular ICS plus as-needed SABA.

Only few cost-effectiveness data based on probabilistic models are available [45–47]. Future cost-effectiveness analyses in different populations would also be of value [43].

PICO 2

Is as-needed ICS/formoterol (single inhaler) without maintenance treatment the preferred treatment compared with as-needed SABA without maintenance treatment in adult/adolescent patients with mild asthma (i.e. GINA [1] treatment steps 1 or 2)?

Summary of the evidence

We identified a total of 547 publications, of which three were finally included [28, 30, 32].

All three studies used budesonide as the ICS component of the ICS/formoterol combination; terbutaline [28] and salbutamol [30] were used in one study each.

Detailed definitions and data are presented in the supplementary material.

Summary of benefits and harms

There were statistically significant differences in favour of as-needed ICS/formoterol in the number of patients experiencing at least one severe exacerbation (relative risk 0.46 (95% CI 0.36–0.59)) [28, 30], annualised severe exacerbation rate (rate ratio 0.36 (95% CI 0.27–0.48)) [28], number of patients experiencing at least one ED visit (relative risk 0.24 (95% CI 0.11–0.55)) [28] and annualised exacerbation (not limited to severe) rate (rate ratio 0.42 (0.35–0.50)) [28, 30]. The reduction of number of patients requiring hospitalisation in favour of ICS/formoterol (relative risk 0.40 (95% CI 0.16–1.03)) was non-significant [28].

There was a difference in favour of as-needed ICS/formoterol in asthma control (ACQ-5 change from baseline MD -0.15 (95% CI -0.20 – -0.10) [28, 30] and ACQ-5 across all time-points MD -0.15 (95% CI -0.24 – -0.06) [30]) and in AQLQ score difference after 52 weeks of about 0.10 (reported only in a graph, with apparently overlapping 95% confidence intervals) [28].

Total systemic corticosteroid exposure over 1 year was lower for the as-needed ICS/formoterol arm (prednisone MD -9.90 (95% CI -19.38 – -0.42) mg; mean percentage reduction 56.9% (95% CI 2.4–111.4%)) [30] as well as rescue medication use (mean change from baseline of daily as-needed inhalations MD -0.16 (95% CI -0.20 – -0.12) inhalations per day [28] and mean daily as-needed actuations throughout follow-up MD 0.48 (95% CI -0.7 – -0.26) actuations per day [30]).

Change in pre-bronchodilator FEV₁ from baseline favoured as-needed ICS/formoterol (MD 53.80 (95% CI 29.07–78.53) mL) [28], but on-treatment FEV₁ across all time-points was similar between the two treatment groups (MD 0.03 (95% CI -0.01 – 0.07) L) [30]. F_{ENO} values at week 52 were lower in as-needed ICS/formoterol (ratio of geometric means 0.83 (95% CI 0.75–0.92)) [30].

There was no difference between as-needed ICS/formoterol and as-needed SABA in the number of patients experiencing AEs (relative risk 0.92 (95% CI 0.85–1.00)) or SAEs (relative risk 1.06 (95% CI 0.45–2.49)) [28, 30]. The data on mortality was too limited, leading to very serious imprecision (one single event in the ICS/formoterol arm, not asthma or treatment related; Peto OR 7.52 (0.15–379.21)) [28, 30].

Detailed data are presented in the supplementary material.

Summary of benefits and harms: adolescent subgroup

There were differences favouring as-needed ICS/formoterol in the annualised rate of severe exacerbations (rate ratio 0.23 (95% CI 0.09–0.65)), asthma control (ACQ-5 change from baseline to treatment average MD -0.17 (-0.30 – -0.03)) and mean daily ICS inhalations (-0.10 (95% CI -0.22 – 0.02) inhalations) [32].

There were no differences between treatment arms in the changes in pre-bronchodilator FEV₁ from baseline to treatment average (MD 0.9% (95% CI -1.1 – 2.8)) [32].

The proportion of adolescents experiencing an AE (33.9% and 41.9%) or a SAE (1.9% and 4.2%) was lower for as-needed ICS/formoterol than with as-needed SABA, respectively (no statistical results reported) [32].

Recommendation

- We recommend that *adult and adolescent* patients with asthma on GINA [1] treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of as-needed SABA. (Strong recommendation for the intervention; low certainty of evidence.)

The Task Force concluded that efficacy and safety of as-needed ICS/formoterol in adolescents is consistent with adult data and that the evidence is sufficient to include adolescents in the overall recommendation.

The Task Force unanimously approved this recommendation.

Justification of the recommendation

- This strong recommendation places a relatively higher value on the benefit of as-needed ICS/formoterol in mild asthma on several outcomes tested, in particular those related to exacerbations and reduction of systemic corticosteroids use, and a relatively lower value on medication costs. In addition, the Task Force weighted as important the risks related to as-needed SABA use and overuse in the absence of anti-inflammatory treatment, as consistently reported in population-based studies [7, 13, 14, 48–50]. The overall “low” certainty of evidence was imputed to the very serious imprecision in the assessment of mortality. Since the randomised controlled trials assessed are not adequately powered to investigate such a rare event as asthma mortality, the overall balance was considered strongly in favour of as-needed ICS/formoterol *versus* as-needed SABA. In addition, GRADE has identified a paradigmatic situation in which a strong recommendation may be warranted despite low certainty evidence, when high certainty evidence suggests modest benefit and low certainty evidence suggests possibility of catastrophic harm [51]. Our assessment showed a similar scenario with high or moderate certainty evidence of great benefit with as-needed ICS/formoterol in reducing exacerbation-related outcomes, but with a low certainty non-significant increased risk of mortality in this treatment arm (due to only one non-asthma or treatment-related death).

Research needs

Studies in children are a research priority as this is a population in high need of effective and feasible treatment strategies. Studies on adolescents would be of value especially for the assessment of additional outcomes.

Alternative strategies to use ICS as rescue medication in addition to rapid short-acting bronchodilators such as salbutamol should be tested, to avoid SABA-only use in those countries where as-needed ICS/formoterol has no regulatory approval for use in mild asthma or where ICS/formoterol is not available.

Only few cost-effectiveness data based on probabilistic models are available [45–47]. Cost-effectiveness analyses in different populations are required, and will need to include assessment of the cost of severe exacerbations in terms of both direct medical costs and non-medical costs such as time off work.

Values, patients' perspective and preferences

There is likely to be variability in the interpretation of the clinical importance of the size of the effects. Health professionals should provide information to help patients understand that the combined regime may reduce total oral corticosteroid (OCS) exposure, as well as explaining differences in side-effect profiles of ICSs and OCSs [52, 53].

Since patients consider that speed of onset is important [54], it will be necessary to explain that the speed of onset might not be similar for SABA and ICS/formoterol and that there may be variability between patients [55], with some patients reporting slower onset of efficacy and lower symptom relief from as-needed ICS/formoterol *versus* as-needed SABA therapy [56, 57].

The cost of ICS/formoterol may be [43] higher than that of SABA and cost can be seen as a disincentive [42, 58–60]. Likely, this is offset by the reduction in exacerbations, ED visits and hospitalisations with better productivity and social integration due to improved outcomes.

General considerations for PICO 1 and PICO 2

Although approved in many countries (more than 40, including Argentina, Australia, Brazil, Canada, China, Indonesia, Malaysia, New Zealand, Philippines, South Korea, Russia and the UK), the use of as-needed ICS/formoterol in the absence of maintenance treatment is off-label in countries where the combination has no regulatory approval for use in mild asthma (including the countries of the European Union (EU)). This is a major barrier to the implementation of these ERS recommendations in EU countries (and in other countries in the same position) where patients have no access to the treatments recommended. Alternative strategies of adding the ICS to the rescue bronchodilator medication such as salbutamol should be considered and further tested (see earlier) [20, 38].

Discussion

The purpose of this ERS clinical practice guideline is to provide recommendations for the use of as-needed ICS/formoterol in the absence of maintenance treatment in mild asthma based on a systematic review of the literature followed by the application of the GRADE approach.

The Task Force suggests that adult patients with asthma on GINA treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of regular ICS maintenance treatment plus as-needed SABA (conditional recommendation; low certainty of evidence). Due to the more limited evidence available in the adolescent population the Task Force adopted a more conservative conclusion in this population by suggesting that adolescent patients with asthma on GINA treatment steps 1 or 2 use either as-needed ICS/formoterol in a single inhaler or regular ICS maintenance treatment plus as-needed SABA (conditional recommendation; low certainty of evidence). Low adherence is particularly relevant in adolescents and the as-needed ICS/formoterol strategy should be specifically considered for non-adherent patients.

The results of the PICO 1 assessment are in line with recent meta-analyses [16, 61, 62], and the related recommendation is aligned with international and with some national asthma management guidelines [8, 63].

The recommendations recognise the reduction of corticosteroid use and the clinical benefit in favour of ICS/formoterol for the exacerbation outcomes and the minimal differences in asthma control which were substantially below the recognised minimal clinically important difference. Recent data from a *post hoc* analysis of the Novel START and PRACTICAL studies confirmed that there were no clinically important differences in the proportions of patients with “controlled” or “partly controlled” asthma symptoms, or proportions who improved or maintained their level of control, with as-needed budesonide/formoterol *versus* maintenance budesonide plus as-needed SABA [62].

Similar considerations have been taken into account for lung function and only one study provided post-bronchodilator data [29] that were prespecified for the assessment. Previous studies have shown that 1) the differences seen in pre-bronchodilator FEV₁ substantially reduce after bronchodilation [20], and that 2) the differences in post-bronchodilator FEV₁ occur mainly in the first year of treatment and then they progressively disappear [64]. Notably, the difference between treatments refers to group-level assessment, *i.e.* the value will be more or less pronounced in subgroups of patients. Thus, in clinical practice, lung function should be monitored over time in patients with mild asthma receiving as-needed ICS/formoterol to detect the fast decliners, as well as in patients who are poorly adherent with maintenance ICS [65]. Also for adolescents with low lung function, and in particular if lung function is worsening [66], regular ICS use treatment should be considered. The reduction in mean daily ICS dose with as-needed ICS/formoterol compared with maintenance ICS treatment plus as-needed SABA should be considered, in the light of recent evidence of the systemic effect of chronic use of low-dose ICS [67]. The impact of this therapeutic option on structural remodelling should also be further assessed as well as in patients with raised type 2 biomarkers and those who are poor perceivers of asthma symptoms. Future studies should also further investigate the cost-effectiveness for different healthcare systems.

From the patients' perspective, they value having one inhaler over two separate inhalers with the requirement to use the preventive inhaler on a daily or twice-daily basis regardless of symptoms. Indeed, the as-needed budesonide/formoterol regimen was preferred to maintenance ICS treatment in a group of patients with mild asthma enrolled in the Novel START study by semistructured interviews analysed thematically [56]. However, it is important for patients to have a choice and some patients may prefer the regular use of maintenance ICS. In addition, the type of inhaler device may be important for some patient groups: the use of dry powder inhalers is more difficult for patients with impaired inspiratory flow (*e.g.* older patients and children).

The Task Force recommends that both adult and adolescent patients with asthma on GINA treatment steps 1 or 2 use as-needed ICS/formoterol in a single inhaler instead of as-needed SABA (strong recommendation; low certainty of evidence). Although available data in adolescents is limited with respect to adults, the Task Force concluded that efficacy and safety of as-needed ICS/formoterol in adolescents is consistent with adult data and considered the evidence appropriate to include adolescents in the overall recommendation.

The Task Force valued the benefit of as-needed ICS/formoterol over as-needed SABA on several outcomes, in particular those related to exacerbations and reduction of systemic corticosteroid use. The Task Force considered the increased risk of severe exacerbations and mortality with SABA overuse in the absence of anti-inflammatory treatment to be important, as consistently reported in population-based studies [7, 13, 14, 48–50]. The evidence for adolescents, although more limited, was considered adequately supportive for a strong recommendation in favour of ICS/formoterol as-needed *versus* SABA as-needed, with substantial reduction in the risk of severe exacerbations and the need of systemic corticosteroid use.

The results of the assessment are in line with recent meta-analyses [16, 61], and the recommendation is supportive of international and some national guidelines [8, 63, 68].

From the patients' perspective, education is important to help patients understand the rationale of treatment recommendations and alleviate any concerns, such as corticosteroid exposure. Indeed, many patients will have been on SABA-only treatment for many years. It will be important to support them to transition to a new regime, with clear, accessible information, training in inhaler technique [56] and implementation of action plans.

Our recommendation cannot be currently implemented in the EU, given that as-needed ICS/formoterol has no regulatory approval for mild asthma. This means that patients with mild asthma within the EU might be missing the benefits of this treatment approach.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual

responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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References

- 1 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2018. Available from: <http://ginasthma.org/>
- 2 Rabe KF, Adachi M, Lai CK, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004; 114: 40–47.
- 3 Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010; 17: 74–80.
- 4 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.
- 5 Bloom CI, Nissen F, Douglas IJ, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018; 73: 313–320.
- 6 Bergstrom SE, Boman G, Eriksson L, et al. Asthma mortality among Swedish children and young adults, a 10-year study. *Respir Med* 2008; 102: 1335–1341.
- 7 Levy ML. The national review of asthma deaths: what did we learn and what needs to change? *Breathe* 2015; 11: 14–24.
- 8 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023. Available from: <http://ginasthma.org/>
- 9 Engelkes M, Janssens HM, de Jongste JC, et al. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J* 2015; 45: 396–407.
- 10 Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and Link to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med* 2014; 24: 14009.
- 11 Partridge MR, van der Molen T, Myrseth SE, et al. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006; 6: 13.
- 12 Suissa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. *Eur Respir J* 1994; 7: 1602–1609.

- 13 Janson C, Menzies-Gow A, Nan C, *et al.* SABINA: an overview of short-acting β_2 -agonist use in asthma in European countries. *Adv Ther* 2020; 37: 1124–1135.
- 14 Nwaru BI, Ekstrom M, Hasvold P, *et al.* Overuse of short-acting β -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.
- 15 Melén E, Nwaru BI, Wiklund F, *et al.* Short-acting β_2 -agonist use and asthma exacerbations in Swedish children: a SABINA Junior study. *Pediatr Allergy Immunol* 2022; 33: e13885.
- 16 Rogliani P, Ritondo BL, Ora J, *et al.* SMART and as-needed therapies in mild-to-severe asthma: a network meta-analysis. *Eur Respir J* 2020; 56: 2000625.
- 17 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting beta-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.
- 18 Beasley R, Harrison T, Peterson S, *et al.* Evaluation of budesonide-formoterol for maintenance and reliever therapy among patients with poorly controlled asthma: a systematic review and meta-analysis. *JAMA Netw Open* 2022; 5: e220615.
- 19 Reddel HK, Bacharier LB, Bateman ED, *et al.* Global Initiative for Asthma strategy 2021: executive summary and rationale for key changes. *Am J Respir Crit Care Med* 2022; 205: 17–35.
- 20 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.
- 21 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383–394.
- 22 European Respiratory Society. ERS short guidelines and statements. 2022. www.ersnet.org/science-and-research/development-programme/ers-short-guidelines-and-statements Date last accessed: 28 May 2023.
- 23 Nagavci B, Tonia T, Roche N, *et al.* European Respiratory Society clinical practice guidelines: methodological guidance. *ERJ Open Res* 2022; 8: 00655-2021.
- 24 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011; 64: 395–400.
- 25 Balshem H, Helfand M, Schunemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64: 401–406.
- 26 Alonso-Coello P, Oxman AD, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ* 2016; 353: i2089.
- 27 Alonso-Coello P, Schunemann HJ, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: introduction. *BMJ* 2016; 353: i2016.
- 28 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.
- 29 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.
- 30 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.
- 31 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.
- 32 Reddel HK, O’Byrne PM, FitzGerald JM, *et al.* Efficacy and safety of as-needed budesonide-formoterol in adolescents with mild asthma. *J Allergy Clin Immunol Pract* 2021; 9: 3069–3077.
- 33 Tanaka AOS, Yamamoto M, Jinno M, *et al.* Tolerability of as-needed treatment with budesonide and formoterol combination in adult patients with mild asthma. *Am J Respir Crit Care Med* 2017; 195: A3199.
- 34 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.
- 35 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.
- 36 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.
- 37 Israel E, Cardet JC, Carroll JK, *et al.* Reliever-triggered inhaled glucocorticoid in Black and Latinx adults with asthma. *N Engl J Med* 2022; 386: 1505–1518.
- 38 Papi A, Chipps BE, Beasley R, *et al.* Albuterol–budesonide fixed-dose combination rescue inhaler for asthma. *N Engl J Med* 2022; 386: 2071–2083.

- 39 Food and Drug Administration. FDA approves drug combination treatment for adults with asthma. 2023. www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-combination-treatment-adults-asthma Date last accessed: 28 May 2023.
- 40 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.
- 41 Beasley R, Bruce P, Houghton C, *et al*. The ICS/formoterol reliever therapy regimen in asthma: a review. *J Allergy Clin Immunol Pract* 2023; 11: 762–772.
- 42 Cole S, Seale C, Griffiths C. ‘The blue one takes a battering’ why do young adults with asthma overuse bronchodilator inhalers? A qualitative study. *BMJ Open* 2013; 3: e002247.
- 43 World Health Organization. WHO guideline on country pharmaceutical pricing policies, second edition. 2018. <https://iris.who.int/bitstream/handle/10665/335692/9789240011878-eng.pdf> Date last accessed: 20 September 2023.
- 44 National Health Service Business Services Authority. Help with NHS prescription costs. www.nhs.uk/help-nhs-prescription-costs Date last accessed: 22 March 2023.
- 45 FitzGerald JM, Arnetorp S, Smare C, *et al*. The cost-effectiveness of as-needed budesonide/formoterol versus low-dose inhaled corticosteroid maintenance therapy in patients with mild asthma in the UK. *Respir Med* 2020; 171: 106079.
- 46 Sadatsafavi M, FitzGerald JM, O’Byrne PM, *et al*. The cost-effectiveness of as-needed budesonide-formoterol versus low-dose inhaled corticosteroid maintenance therapy in patients with mild asthma in Canada. *Allergy Asthma Clin Immunol* 2021; 17: 108.
- 47 Buendia JA, Guerrero Patino D, Talamoni HL. Cost-utility of as-needed combination low-dose budesonide-formoterol in adolescents mild asthma. *Pediatr Pulmonol* 2021; 56: 3699–3705.
- 48 Beasley R, Pearce N, Crane J, *et al*. Asthma mortality and inhaled beta agonist therapy. *Aust NZ J Med* 1991; 21: 753–763.
- 49 Suissa S, Ernst P, Benayoun S, *et al*. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343: 332–336.
- 50 Pollack M, Gandhi H, Tkacz J, *et al*. The use of short-acting bronchodilators and cost burden of asthma across Global Initiative for Asthma-based severity levels: insights from a large US commercial and managed Medicaid population. *J Manag Care Spec Pharm* 2022; 28: 881–891.
- 51 Andrews JC, Schunemann HJ, Oxman AD, *et al*. GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation’s direction and strength. *J Clin Epidemiol* 2013; 66: 726–735.
- 52 Price D, Castro M, Bourdin A, *et al*. Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety. *Eur Respir Rev* 2020; 29: 190151.
- 53 Price DB, Trudo F, Voorham J, *et al*. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018; 11: 193–204.
- 54 Baggott C, Chan A, Hurford S, *et al*. Patient preferences for asthma management: a qualitative study. *BMJ Open* 2020; 10: e037491.
- 55 Kearns N, Williams M, Bruce P, *et al*. Single dose of budesonide/formoterol turbuhaler compared to salbutamol pMDI for speed of bronchodilator onset in asthma: a randomised cross-over trial. *Thorax* 2022; 78: 745–751.
- 56 Foster J, Beasley R, Braithwaite I, *et al*. Perspectives of mild asthma patients on maintenance versus as-needed preventer treatment regimens: a qualitative study. *BMJ Open* 2022; 12: e048537.
- 57 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.
- 58 Laba TL, Jan S, Zwar NA, *et al*. Cost-related underuse of medicines for asthma – opportunities for improving adherence. *J Allergy Clin Immunol Pract* 2019; 7: 2298–2306.
- 59 Asthma UK. Paying to breathe: why unfair asthma prescription charges must be stopped. 2019. www.asthmaandlung.org.uk/sites/default/files/2023-03/auk-prescription-charges-report-final.pdf Date last accessed: 23 March 2023.
- 60 De Simoni A, Horne R, Fleming L, *et al*. What do adolescents with asthma really think about adherence to inhalers? Insights from a qualitative analysis of a UK online forum. *BMJ Open* 2017; 7: e015245.
- 61 Crossingham I, Turner S, Ramakrishnan S, *et al*. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma. *Cochrane Database Syst Rev* 2021; 5: CD013518.
- 62 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.
- 63 Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC). 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and

- Prevention Program coordinating committee expert panel working group. *J Allergy Clin Immunol* 2020; 146: 1217–1270.
- 64 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.
- 65 Khaleva E, Rattu A, Brightling C, *et al.* Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA). *Eur Respir J* 2023; 61: 2200606.
- 66 Wang G, Hallberg J, Faner R, *et al.* Plasticity of individual lung function states from childhood to adulthood. *Am J Respir Crit Care Med* 2023; 207: 406–415.
- 67 Kachroo P, Stewart ID, Kelly RS, *et al.* Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma. *Nat Med* 2022; 28: 814–822.
- 68 Beasley R, Beckert L, Fingleton J, *et al.* Asthma and Respiratory Foundation NZ Adolescent and Adult Asthma Guidelines 2020: a quick reference guide. *NZ Med J* 2020; 133: 73–99.