Response from the authors: As-needed ICS/formoterol or as-needed SABA in mild asthma?

Received: 25 Feb 2024
Accepted: 29 Feb 2024

Reply to J.A. Krishnan and R. Buhl:

We thank J.A. Krishnan and R. Buhl for their commentary on our document "European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma", which was published in this journal in October 2023 [1]. We appreciate their willingness in building trust in the guideline development process.

In relation to PICO question 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 treatment steps 1 or 2)?*", the authors of the commentary support the strength of the task force's recommendation (strong), although they criticise the inclusion of mortality as a critical outcome in the context of mild asthma.

The content and final version of the guideline was unanimously approved by the entire panel and the document was extensively peer reviewed not only by clinical experts but also by methodologists specialised in Grading of Recommendations, Assessment, Development and Evaluation (GRADE). Finally, the guideline was endorsed by the European Respiratory Society (ERS) with no concerns regarding the suitability of the outcome of mortality being labelled as critical.

As highlighted by J.A. Krishnan and R. Buhl, following GRADE guidance [2], we rated the importance of outcomes *a priori*. Each task force member (including a patient representative) rated the importance of all suggested outcomes on a scale from 1 (not important for clinical decision-making) to 9 (critical for clinical decision-making). For PICO question 2, mortality was rated as having critical importance by the majority of panellists. Notably, for PICO question 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 treatment steps 1 or 2)*?") mortality was rated as important but not critical for decision-making by the task force panellists. The different ratings of the importance of mortality (PICO 1 – important but not critical; PICO 2 – critical) reflect the task force panel's concern with the increased risk of deaths due to asthma associated with the (over)use of as-needed short-acting β2-antagonist (SABA) without maintenance inhaled corticosteroid (ICS) [3, 4], even in patients with mild asthma.

J.A. Krishnan and R. Buhl argue that asthma deaths can occur in people but are rare, and they "recommend re-scoring the certainty of evidence after removing mortality from the list of "critically important" outcomes and […] including it as an "important" outcome."

While we acknowledge that GRADE guidance allows for reconsideration of the importance of outcomes under specific circumstances, this should occur after the systematic review of the relevant literature but before judging the balance between desirable and undesirable effects of an intervention [2] and during the guideline development process. GRADE also specifies that justifiable changes of the importance of outcomes is probably rare [5], and that hard rules as to when to do so cannot be provided [2]. Given the complexity of the issue, this is not routinely done in ERS guidelines. The ERS applies the main GRADE principles as strictly as possible, hence we took the lowest certainty of the critical outcomes as overall certainty of evidence.

Shareable abstract (@ERSpublications)
The ERS guidelines do not ignore the increased risk of deaths associated with (over)use of as-needed SABA in mild asthma. The recommendation for as-needed ICS/formoterol *versus* as-needed SABA is strong, even if mortality was considered a critical outcome. https://bit.ly/437bhnk

Cite this article as: Papi A, Ferreira DS, Tonia T, *et al*. Response from the authors: As-needed ICS/formoterol or as-needed SABA in mild asthma? *Eur Respir J* 2024; 63: 2400395 [DOI: 10.1183/13993003.00395-2024].

The task force has indeed considered the limited statistical power of randomised controlled trials to assess a rare event such as asthma mortality. This limitation has been included in the explanation for making a strong recommendation for the intervention (PICO 2) despite the low certainty of the evidence assessed for mortality (see section "Justification of the recommendation") [1]. In our view, this limited statistical power to evaluate mortality as an outcome is one additional reason why the change of the degree of importance of the mortality outcome based on this data would not be appropriate. In addition, the fact that mortality is a harmful outcome makes us even more reluctant to change it *a posteriori*.

Overall, the task force judged the balance between desirable and undesirable effects to be strongly in favour of as-needed ICS/formoterol *versus* as-needed SABA.

Importantly, the overall recommendation for PICO question 2 remains strong, even if mortality was considered a critical (and not an important) outcome.

One should not miss the forest while looking at a single tree.

Additional note from the authors on relative risk reported in the guideline:

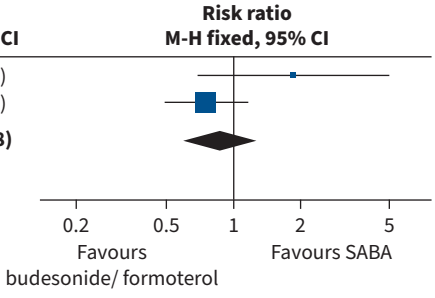
At the bottom of the table included in their commentary, J.A. Krishnan and R. Buhl add a note stating that "the relative risk of >1.0 (higher in the as-needed ICS/formoterol group than in the as-needed SABA group) appears to be inconsistent with the lower absolute proportion of serious adverse effects reported in the as-needed ICS/formoterol group (3.3% *versus* 3.7%) in the PICO question 2 evidence profile."

This alleged "inconsistency" is a result of an inappropriate approach of summing up the proportions of severe adverse events from different studies in order to draw conclusions. It should be noted that the proportions of severe adverse events presented in the evidence profile have been generated by the GRADEpro GDT online software (GRADEpro Guideline Development Tool; McMaster University and Evidence Prime, 2022; available from gradepro.org). Comparing rates is risky and can result in the Simpson paradox [6, 7] when the studies vary in size and events, as in this case. The proportions should not be solely summed up for the studies but rather be reported separately for each study and in addition to the results from meta-analysis (*e.g.* in a forest plot).

Fixed effects model

Study or subgroup	Budesonide/formoterol Events	Total	SABA Events	Total	Weight (%)	Risk ratio M-H fixed, 95% CI
Beasley (2019)	11	222	6	226	10.6	1.87 (0.70–4.96)
O'Byrne (2018)	38	1277	50	1277	89.4	0.76 (0.50–1.15)
Total (95% CI)		**1499**		**1503**	**100**	**0.88 (0.60–1.28)**
Total events	49		56			

Heterogeneity: Chi^2=2.75, df=1 (p=0.10), I^2=64%
Test for overall effect: z=0.68 (p=0.50)



Random effects model

Study or subgroup	Budesonide/formoterol Events	Total	SABA Events	Total	Weight (%)	Risk ratio M-H random, 95% CI
Beasley (2019)	11	222	6	226	37.4	1.87 (0.70–4.96)
O'Byrne (2018)	38	1277	50	1277	62.6	0.76 (0.50–1.15)
Total (95% CI)		**1499**		**1503**	**100**	**1.06 (0.45–2.49)**
Total events	49		56			

Heterogeneity: Tau^2=0.26, Chi^2=2.75, df=1 (p=0.10), I^2=64%
Test for overall effect: z=0.14 (p=0.89)

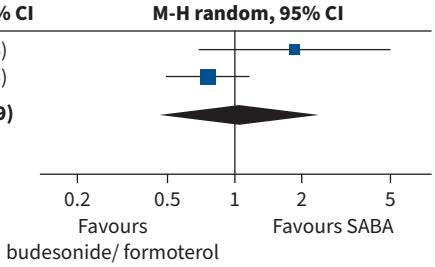


FIGURE 1 The different forest plots obtained when applying fixed or random effects models, causing differences of the pooled point estimate (risk ratio) due to different weights for the two studies. Performed with Review Manager software, Version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Applying the fixed or random effects model can cause differences of the pooled point estimate (risk ratio or relative risk in our analysis) by using different weights for the two studies. We provide the forest plots for both models in figure 1: we can see that the confidence intervals are quite wide in both models and include relevant effects in both directions. The pooled point estimate changes due to the different weights applied by each model.

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Conflicts of interest: A. Papi has received grants for research from Chiesi, AstraZeneca, GSK and Sanofi, consulting fees or advisory board fees from Chiesi, AstraZeneca, GSK, Mundipharma, Novartis, Edmond, Sanofi, Avillion, IQVIA, Elpen Pharmaceuticals, Roche, Dompè, Galvanize and MSD, and lecture fees from Chiesi, AstraZeneca, GSK, Menarini, Mundipharma, Sanofi, MSD, Novartis and Zambon. F. Schleich has received grants from GSK, AstraZeneca and Chiesi, fees from GSK, AstraZeneca, Chiesi and TEVA, and participates on data safety monitoring boards/advisory boards for GSK and AstraZeneca. T. Tonia acts as ERS methodologist. D.S. Ferreira has no potential conflicts of interest to disclose.

References

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