

Food and Drug Administration–mandated Trials of Long-Acting β -Agonist Safety in Asthma Bang for the Buck?

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The uncertainty regarding the safety of long-acting β -agonists (LABAs) in the treatment of asthma has been lingering for the last 25 years, an ongoing concern for patients, clinicians, and regulators (1). Questions regarding the safety of these drugs arose initially from two large randomized controlled trials in which researchers reported an increased incidence of asthma-related deaths in patients assigned to salmeterol (2, 3). Although there is solid evidence that the risk is increased when LABAs are used without concurrent inhaled corticosteroids (ICS), the dilemma has been whether this risk is also increased when LABAs are given together with regular ICS therapy (ICS–LABA).

To address this uncertainty, the Food and Drug Administration (FDA) required from the four manufacturers of LABAs the conduct of four large randomized trials with adult patients with asthma and one trial in children, all aimed at comparing the effect of ICS–LABA combinations with ICS alone on the incidence of major adverse asthma outcomes (4). To date, four of these trials have been completed, including three for which the results have been published (5–7). The fifth trial was discontinued by the manufacturer when the recruitment was deemed insufficient to attain the goal of 11,700 adult patients with asthma.

As members of the data monitoring committee for one of these trials, we were

involved in some discussion on the usefulness of these trials in view of the available knowledge to date regarding these major adverse asthma outcomes (8, 9). In this paper, we review the data published to date and evaluate the extent of new knowledge that these mega-trials could have produced on the safety of LABAs when used concurrently with ICS in treating asthma.

Meta-analyses of Prior Trials

Before mandating these trials, scientists at the FDA performed a pooled analysis of data derived from 43 randomized trials involving over 15,000 patients with asthma, all of whom were assigned to receive ICS, comparing the effect of the addition of LABA with no added LABA on the risk of a composite adverse asthma-related endpoint, including death, intubation, or hospitalization (10, 11). The incidence rate of the asthma composite outcome was not shown to be significantly increased with LABA use (our calculation was rate ratio [RR], 1.11; 95% confidence interval [CI], 0.66–1.87), whereas there was only one asthma-related death that occurred in the group in which LABA was added. In parallel, authors of a meta-analysis of 57 trials, likely including many of the same trials used in the FDA pooled analysis, involving close to 35,000 patients with asthma, also reported a null difference

in the risk of a life-threatening asthma event with the LABA (RR, 0.98; 95% CI, 0.57–1.68) (12). The authors of this meta-analysis also reported that patients in the ICS–LABA group had a lower incidence of an asthma exacerbation requiring treatment (RR, 0.73; 95% CI, 0.67–0.79).

New FDA-mandated Trials

The first of the FDA-mandated trials to be published were the ones by Stempel and colleagues, one involving 11,679 adult and adolescent patients with asthma, the other involving 6,208 children, randomly allocated to fluticasone-salmeterol or fluticasone only and followed for 6 months (5, 7). The third trial, by Peters and colleagues, involved 11,693 patients with asthma randomly allocated to budesonide-formoterol or budesonide only and followed for 6 months (6). In all trials, the risk of a serious asthma-related event, including asthma-related death, intubation, or hospitalization, was not significantly increased with the addition of 1) salmeterol in adults (hazard ratio, 1.03; 95% CI, 0.64–1.66) and in children (hazard ratio, 1.28; 95% CI, 0.73–2.27) or 2) formoterol (hazard ratio, 1.07; 95% CI, 0.70–1.65), respectively. Figure 1A depicts these findings together with the corresponding values derived from the meta-analysis of previous trials involving several different products (12).

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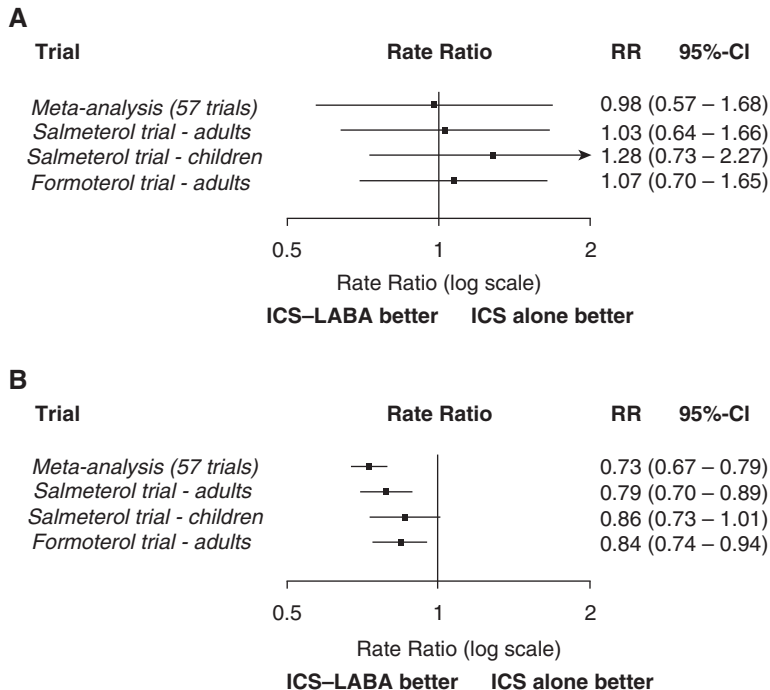


Figure 1. Rate ratios (RRs) and 95% confidence intervals (CIs) for (A) the composite adverse asthma-related endpoint including death, intubation, or hospitalization and (B) the incidence of an asthma exacerbation requiring treatment, comparing inhaled corticosteroid and long-acting β -agonists combined (ICS-LABA) with inhaled corticosteroid only in the meta-analysis of prior trials and in the three recent Food and Drug Administration-mandated trials.

In terms of efficacy, these trials showed that the risk of an asthma exacerbation requiring treatment was decreased with the addition of 1) salmeterol in adults (hazard ratio, 0.79; 95% CI, 0.70–0.89) and in children (hazard ratio, 0.86; 95% CI, 0.73–1.01) or 2) formoterol (hazard ratio, 0.84; 95% CI, 0.74–0.94). These findings regarding efficacy are depicted in Figure 1B together with the values from the meta-analysis of previous trials (12).

The Lingering Asthma-related Death Question

The uncertainty regarding the safety of LABAs in asthma has always revolved around asthma-related death, a signal reported in two trials involving salmeterol, namely the SNS (Serevent Nationwide Surveillance) and SMART (Salmeterol Multicenter Asthma Research Trial) trials (2, 3). The authors of a meta-analysis of 57 trials involving close to 35,000 patients with asthma, all using ICS, either used in practice or assigned by randomization, found three asthma-related deaths with a LABA and none in patients not randomized

to a LABA (RR, 2.96; 95% CI, 0.50–17.57) (12). Moreover, authors of a pooled analysis of randomized trials of formoterol involving close to 60,000 patients with asthma, all taking ICS, reported seven asthma-related deaths among 46,000 patients assigned to formoterol and one among 14,000 patients not allocated to formoterol (RR, 2.12; 95% CI, 0.26–17.20) (13). In these two meta-analyses, however, the extent of the concurrent ICS being assigned by randomization or not is unknown, and there may be differences in ICS doses between LABA users and nonusers.

In the three recent FDA-mandated trials, there were zero deaths in the salmeterol trials of adults and children and two deaths in the formoterol trial. Pooling the data on asthma-related death from the three trials results in an RR of 3.00 (95% CI, 0.24–37.70). Table 1 displays these findings together with the corresponding values derived from the two meta-analyses of previous trials. The table also presents the results on all-cause mortality derived from the trials and one meta-analysis that provided this information, showing that no such signal is present with this endpoint.

Conclusions

The three published FDA-mandated trials conducted to compare ICS-LABA combinations with ICS alone in the treatment of asthma have produced the anticipated results expected from prior trials. Indeed, the trials all showed that the incidence of life-threatening adverse asthma events is not different between ICS-LABA and ICS alone, but they demonstrated that the incidence of asthma exacerbations is lower with the ICS-LABA combination. These results replicate quite accurately the data derived from meta-analyses of previous trials performed among patients all using ICS. These meta-analyses, conducted before the trials began, included more patients and had several trials with longer follow-up than the 6 months used in the FDA-mandated trials.

However, the link between ICS-LABA and asthma-related death remains unsettled. Indeed, since the SNS and SMART publications, authors of meta-analyses of randomized trials have systematically reported a numerically higher incidence of asthma-related death with the ICS-LABA combination than with ICS only. The three published FDA-mandated trials together also had two asthma-related deaths under ICS-LABA versus none with ICS only, with these two deaths being exclusively in one trial. Although these numbers are much too small to make any statistical inference, the fact remains that the signal is in the same direction as that of the meta-analyses. Although not statistically significant, these two asthma-related deaths represent an excess incidence rate of 2.7 per 10,000 per year, which translates to a number needed to treat of 7,692 for 6 months with ICS-LABA to cause one asthma-related death, compared with treatment with ICS only. Whether such a risk of asthma-related death is real will remain unresolved through randomized trials simply because of the rarity of asthma-related death, particularly with the significant effectiveness of ICS in preventing this outcome when used regularly (14). Indeed, with such low asthma-related death rates, one would need an unattainable randomized trial of around 9 million patients with asthma per arm followed over 1 year to detect a twofold increase in the risk of asthma-related death with 80% power.

Table 1. Rate Ratios of Asthma-related and All-Cause Deaths Derived from Meta-analyses and from FDA-mandated Trials

	ICS-LABA		ICS Only		Rate Ratio (95% CI)
	Number of Patients	Number of Deaths	Number of Patients	Number of Deaths	
Asthma-related deaths					
Meta-analyses					
Any LABA (21)	17,212	3	14,202	0	2.96 (0.50–17.57)
Formoterol (13)	46,003	7	13,905	1	2.12 (0.26–17.20)
Three FDA-mandated trials					
Pooled data	14,787	2	14,793	0	3.00 (0.24–37.70)
Salmeterol (adults)	5,834	0	5,845	0	
Salmeterol (children)	3,107	0	3,101	0	
Formoterol (adults)	5,846	2	5,847	0	
All-cause deaths					
Meta-analysis					
Any LABA (10)	7,862	4	7,330	4	0.93 (0.23–3.73)
Three FDA-mandated trials					
Pooled data	14,787	9	14,793	14	0.64 (0.28–1.49)
Salmeterol (adults)	5,834	3	5,845	6	
Salmeterol (children)	3,107	0	3,101	0	
Formoterol (adults)	5,846	6	5,847	8	

Definition of abbreviations: CI = confidence interval; FDA = Food and Drug Administration; ICS = inhaled corticosteroids; LABA = long-acting β -agonist. Rate ratios were derived from meta-analyses of 57 and 43 randomized trials of multiple LABAs, the meta-analysis of formoterol trials, and the three recent FDA-mandated trials, all comparing ICS-LABA therapy with ICS only.

In light of the impossibility of such randomized trials, an alternative could be observational studies. Indeed, ICS and ICS-LABA have been used for a long time to treat asthma, so retrospective studies are feasible. Nevertheless, the rarity of the asthma-related death outcome will likely require multiple databases to conduct such studies. Thus, a joint effort between the FDA's Sentinel network in the United States and the similar Canadian Network for Observational Drug Effect Studies in Canada could provide the data and know-how to address this question (15, 16). Using data on millions of patients, these networks have evaluated the safety of

several medications (17–20). Moreover, such a study could also investigate all-cause mortality, an outcome that was numerically reduced with LABA treatment. However, even such a study would be limited in that a signal suggesting increased deaths resulting from LABA treatments could not rule out confounding by indication.

In all, although randomized trials are crucial to gain better understanding of the effects of drug treatment in patients with asthma, a more in-depth cost-benefit evaluation of a trial could be considered before it is undertaken. The example of the FDA-mandated trials to assess the safety of

ICS-LABA may have resulted in a high cost with no tangible added benefit, although it has resulted in removal of the so-called black box warning regarding excess deaths in relation to use of LABAs in asthma when used concurrently with ICS. However, no advancement has been made with respect to the core issue of the link between LABA use and asthma-related death, which remains uncertain. A large-scale multinational observational study may provide some additional information on the effect of LABAs on death caused by asthma. ■

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References

- Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *N Engl J Med* 2010;362:1169–1171.
- Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034–1037.
- Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15–26.
- Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med* 2011;364:2473–2475.
- Stempel DA, Rappiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, et al.; AUSTRI Investigators. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016;374:1822–1830.
- Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. *N Engl J Med* 2016;375:850–860.
- Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al.; VESTRI Investigators. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med* 2016;375:840–849.
- Sears MR. The FDA-mandated trial of safety of long-acting beta-agonists in asthma: finality or futility? *Thorax* 2013;68:195–198.
- Suissa S, Ariel A. US Food and Drug Administration-mandated trials of long-acting β -agonists safety in asthma: will we know the answer? *Chest* 2013;143:1208–1213.
- Levenson M. Long-acting beta-agonists and adverse asthma events meta-analysis. Statistical briefing package for joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee on December 10–11, 2008 [accessed 2018 Mar 12]. Available from: <https://www.fda.gov/ohrtms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>.

11. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics* 2011;128:e1147–e1154.
12. Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma: a systematic review. *Pulm Pharmacol Ther* 2009;22:9–19.
13. Sears MR, Ottosson A, Radner F, Suissa S. Long-acting beta-agonists: a review of formoterol safety data from asthma clinical trials. *Eur Respir J* 2009;33:21–32.
14. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332–336.
15. Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System—a national resource for evidence development. *N Engl J Med* 2011;364:498–499.
16. Suissa S, Henry D, Caetano P, Dormuth CR, Ernst P, Hemmelgarn B, et al.; Canadian Network for Observational Drug Effect Studies (CNODES). CNODES: the Canadian Network for Observational Drug Effect Studies. *Open Med* 2012;6:e134–e140.
17. Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, Raymond CB, et al.; Canadian Network for Observational Drug Effect Studies (CNODES). Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 2013;346:f880.
18. Yih WK, Lieu TA, Kulldorff M, Martin D, McMahon-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med* 2014;370:503–512.
19. Fillion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, et al.; CNODES Investigators. A multicenter observational study of incretin-based drugs and heart failure. *N Engl J Med* 2016;374:1145–1154.
20. Toh S, Reichman ME, Graham DJ, Hampp C, Zhang R, Butler MG, et al.; Mini-Sentinel Saxagliptin-AMI Surveillance Writing Group. Prospective postmarketing surveillance of acute myocardial infarction in new users of saxagliptin: a population-based study. *Diabetes Care* 2018;41:39–48.
21. Rodrigo GJ, Castro-Rodríguez JA. Safety of long-acting β agonists for the treatment of asthma: clearing the air. *Thorax* 2012;67:342–349.