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Ann W. McMahon, Mark S. Levenson, Bradley W. McEvoy, Andrew D. Mosholder
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Age and Risks of FDA–Approved Long-Acting β_2 -Adrenergic Receptor Agonists

AUTHORS: Ann W. McMahon, MD, MS,^a Mark S. Levenson, PhD,^b Bradley W. McEvoy, DrPH,^b Andrew D. Mosholder, MD, MPH,^c and Dianne Murphy, MD^a

^aOffice of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, Silver Spring, Maryland, ^bOffice of Translational Sciences, Office of Biostatistics, Division of Biometrics VII, and ^cOffice of Surveillance and Epidemiology, Division of Epidemiology, Center for Drug Evaluation and Research

KEY WORDS

asthma, meta-analysis, hospitalization, death

ABBREVIATIONS

LABA—long-acting β -adrenergic receptor agonist
FDA—Food and Drug Administration
CI—confidence interval
ICS—inhaled corticosteroid

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Address correspondence to Ann W. McMahon, MD, MS, Food and Drug Administration, Office of Pediatric Therapeutics, 10903 New Hampshire Ave., W032/Room 5158, Silver Spring, MD 20993. E-mail: ann.mcmahon@fda.hhs.gov

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WHAT'S KNOWN ON THIS SUBJECT: Two randomized controlled safety trials found that long-acting β -adrenergic receptor agonists (LABAs) were associated with three- to fourfold risks for asthma-related death. A meta-analysis later revealed that the greatest risks for severe asthma outcomes associated with LABAs were among children.



WHAT THIS STUDY ADDS: Results of this study substantiate the risks of LABAs for children and indicate that simultaneous use of inhaled corticosteroids might mitigate those risks. However, additional study of this question is needed.

abstract

OBJECTIVE: To determine the risk, by age group, of serious asthma-related events with long-acting β_2 -adrenergic receptor agonists marketed in the United States for asthma.

METHODS: The US Food and Drug Administration performed a meta-analysis of controlled clinical trials comparing the risk of LABA use with no LABA use for patients 4 to 11, 12 to 17, 18 to 64, and older than 64 years old. The effects of age on a composite of asthma-related deaths, intubations, and hospitalizations (asthma composite index) and the effects of concomitant inhaled corticosteroid (ICS) use were analyzed.

RESULTS: One hundred ten trials with 60 954 patients were included in the meta-analysis. The composite event incidence difference for all ages was 6.3 events per 1000 patient-years (95% confidence interval [CI]: 2.2–10.3) for using LABAs compared with not using LABAs. The largest incidence difference was observed for the 4- to 11-year age group (30.4 events per 1000 patient-years [95% CI: 5.7–55.1]). Differences according to age were statistically significant ($P = .020$). Results for the subgroup of patients with concomitant ICS use ($n = 36\,210$) were similar to the overall results; with assigned ICSs ($n = 15\,192$), the incidence difference was 0.4 events per 1000 patient-years (95% CI: –3.8 to 4.6), and there was no statistically significant difference according to age group.

CONCLUSIONS: The excess of serious asthma-related events attributable to LABAs was greatest among children. Additional data are needed to assess risks of LABA use for children with simultaneous ICS use. *Pediatrics* 2011;128:e1147–e1154

Concerns regarding the safety of inhaled β -adrenergic receptor agonists for the treatment of asthma emerged when deaths attributable to asthma occurred with the marketing of high-dose isoproterenol inhalers and fenoterol inhalers.^{1–3} The safety of salmeterol, the first inhaled long-acting β -adrenergic receptor agonist (LABA) marketed in the United States, was the subject of 2 large trials. The first trial involved 25 180 persons older than 12 years (6.4% adolescents) and found a threefold increase in the asthma mortality rate with salmeterol ($P = .1$), compared with scheduled albuterol.⁴ The second trial involved 26 355 patients with asthma, 3267 of whom were 12 to 18 years of age,⁵ and it found the relative risk of asthma-related death in the salmeterol group to be 4.4 (95% confidence interval [CI]: 1.3–15.3), compared with placebo.

In 2007, the US Food and Drug Administration (FDA) Pediatric Advisory Committee reviewed safety information for salmeterol for children. The committee asked that LABA safety for children and adults be reviewed at a separate advisory committee meeting, which was convened in 2008. A FDA meta-analysis was performed for that meeting, by using patient-level data to estimate age-specific outcomes.⁶ The meta-analysis found a statistically significant trend across all ages, that is, the younger the patient receiving LABA therapy, the greater the risk difference for a composite asthma outcome index ($P = .018$). The advisory committee voted to restrict the use of LABAs to combination inhaled corticosteroid (ICS)/LABA products for children and adults and recommended that there be another advisory committee meeting. The follow-up meeting in 2010 discussed details of the study design for a postmarketing requirement for the sponsors of LABAs for a large trial to address the question of the safety of

TABLE 1 Summary of LABAs Approved in United States for Treatment of Asthma in 2009

Product Name	Year of Approval	LABA	Inhaled Corticosteroid (ICS)	Current Ages Approved, y
Serevent MDI	1994	Salmeterol xinafoate	None	≥ 12
Serevent Diskus	1997	Salmeterol xinafoate	None	≥ 12
Advair Diskus	2000	Salmeterol xinafoate	Fluticasone	≥ 4
Advair HFA	2006	Salmeterol xinafoate	Fluticasone	≥ 12
Foradil Aerolizer	2001	Formoterol fumarate	None	≥ 5
Foradil Certihaler	2006	Formoterol fumarate	None	≥ 5
Symbicort	2006	Formoterol fumarate	Budesonide	≥ 12

LABAs in the setting of assigned ICS use. Currently, preparations for such trials are ongoing. Also in 2010, important labeling changes were made for LABAs, including a recommendation that, for children, LABAs be used as combination ICS/LABA products.⁷

The identification of a safety signal in the pediatric population is more difficult because of the smaller size of drug development trials, relative to those for adults. Investigators must use all of the data available and must assess any pediatric signal in the larger context of other information. The purpose of this study was to explore further the information from the 2008 FDA meta-analysis regarding safety of the US-approved LABA products among children and adolescents, compared with the overall population.

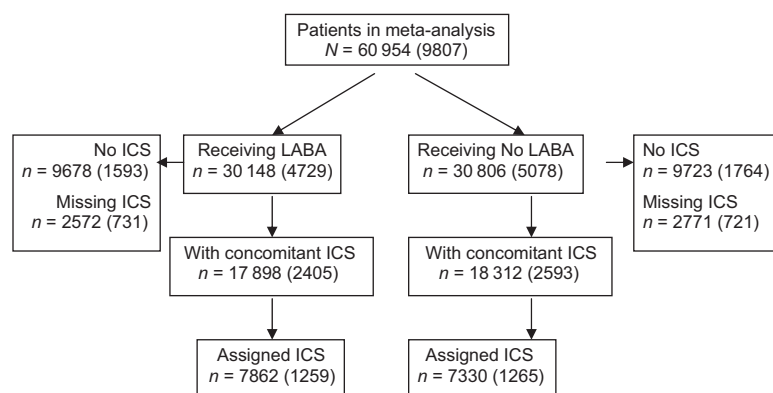
METHODS

The FDA meta-analysis was conducted to examine the relationship between LABA-containing drugs and adverse asthma-related events.⁶ The meta-analysis was based on a special request from the FDA to sponsors of LABA-containing drugs for patient-level and trial-level data from clinical trials of those drugs and was conducted in the context of an overall risk/benefit assessment of LABAs. To ensure that this risk/benefit assessment would be relevant to patients with asthma in the United States, we considered only FDA-approved LABA products and doses. At the time of the meta-analysis in 2009, 4 LABA-containing products had been

approved in the United States for the treatment of asthma, some of which had multiple approved delivery devices. Table 1 lists the products and a summary of their indications.

All data that met prespecified criteria from randomized trials of all approved drugs and were available to the sponsors were obtained and provided the basis for a broad analysis of the safety of LABAs. Submitted data were prespecified regarding trial inclusion criteria, comparison groups, end points, subgroups, and statistical methods. Additional analyses for this article that focused on pediatric populations were conducted for a better understanding of this population. By design, the meta-analysis included only studies available to the manufacturers, because we required detailed patient-level data and retrospective reviews of the events. Only the manufacturers could satisfy all of these requirements. In addition, this approach minimized publication bias.^{8,9} The request was for data that were available by January 1, 2008.

The meta-analysis was based on blinded, parallel-arm, randomized, placebo- or active comparator-controlled trials conducted with a LABA-containing drug for the treatment of asthma. The FDA requested that the sponsors review all serious adverse events reported in the trials with blinding to treatment, to determine whether the event involved death, hospitalization, or intubation and occurred “in the setting of an acute

**FIGURE 1**

Total adult and pediatric patients in the meta-analysis, according to comparison group and ICS-use subgroup. Numbers in parentheses indicate the numbers of children and adolescents aged 4 to 17 years. Age data were missing for 55 patients. Concomitant ICS means that patients used ICSs at any time during the study period. Assigned ICS means that patients were assigned randomly to receive ICSs during the study period.

asthma exacerbation” or was “otherwise asthma-related.” Although it was not feasible for FDA staff members to validate the manufacturers’ event adjudications, an earlier review of pediatric asthma events from the Salmeterol Multicenter Asthma Research Trial by one of the authors (Dr Mosholder) showed good agreement with the manufacturer’s classifications of asthma events. Only trials that matched ICS or other non-LABA therapy, and the respective doses, between the LABA treatment arm and the non-LABA control arm were included.

The primary analysis compared the risk of LABA use with no LABA use for patients aged 4 to 11, 12 to 17, 18 to 64, and more than 64 years. Secondary analyses examined the effects among the subgroups, that is, (1) patients with any amount of concomitant ICS use and (2) patients assigned to regular use of ICS. For this purpose, “concomitant ICS use” meant that the patient was recorded to have taken an ICS at baseline. Information on the frequency of usage, if any, during the trial was not available. “Assigned ICS use” meant that the patient was prescribed ICS in a regular scheduled regimen as part of the trial design; these patients received the ICS in a combination de-

vice with either LABA or placebo or in a separate device. All patients with assigned ICS use were included in the subgroup of patients with concomitant ICS use. Figure 1 presents the number of patients in each of these groups.

The primary end point was an asthma composite outcome consisting of asthma-related death, asthma-related intubation, and asthma-related hospitalization. Mantel-Haenszel incidence differences and associated CIs were used to estimate the effects of the LABAs.¹⁰ The incidence difference approach accounts for trials that have no events and is particularly relevant for weighing possible adverse effects of drugs against their benefits. The estimates were stratified according to trial, which maintained the randomized structure of the data. A small proportion of patients (2%) did not have an end date for therapy. For those patients, the duration of therapy was imputed as the mean therapy duration for the associated trial and treatment group. The homogeneity of the trials within each analysis was examined by using a χ^2 goodness of fit statistic.¹¹ The effect of age on risk was examined by using a logistic regression analysis of the end point with adjustment for trial and overall treat-

ment effects. *P* values based on the regression analysis were presented for evaluation of the relationship between age and risk. We examined the hazard pattern of the asthma composite outcome with Kaplan-Meier curves.

RESULTS

Study Group

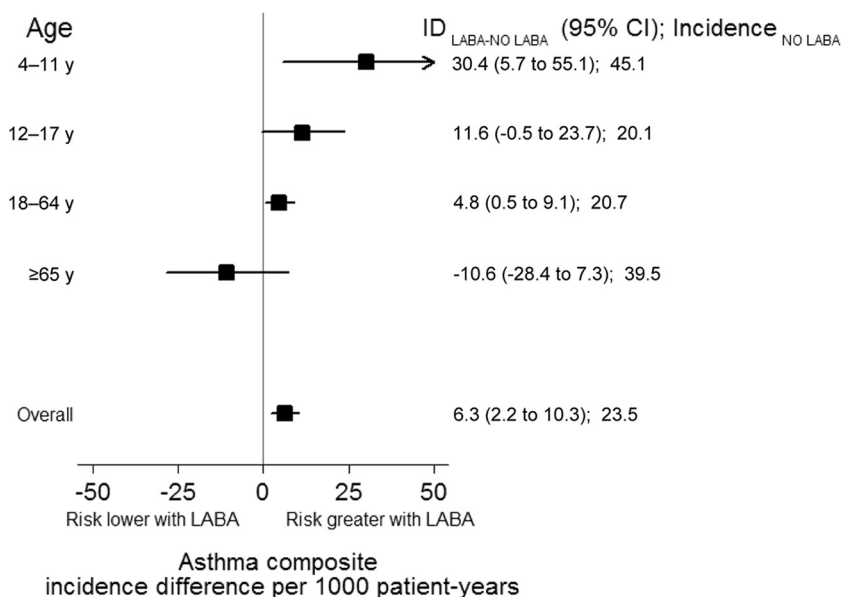
Overall, 110 trials with 60 954 patients met the inclusion criteria for the meta-analysis. There were 9807 children younger than 18 years, including 3415 in the 4- to 11-year age group and 6392 in the 12- to 17-year age group; approximately one-half of the children in each group were assigned to receive a LABA, and the other half was assigned to receive no LABA (Fig 1). Table 2 shows the numbers of patients, patient-years of exposure, and events according to age group and comparison group. There were notably more patients with hospitalization events than with any of the other event types in all age groups. However, across all age groups, there were 44 asthma deaths/intubations among patients treated with a LABA, compared with 27 among patients who did not receive a LABA (incidence difference: 1.30 deaths/intubations per 1000 patient-years [95% CI: -0.01 to 2.61]).

Overall Effect

The primary analysis considered all patients and compared LABA use and no LABA use. This analysis included 60 954 patients. The overall incidence difference of the asthma composite outcome (asthma-related death, asthma-related intubation, or asthma-related hospitalization) for all ages combined was 6.3 events per 1000 patient-years (95% CI: 2.2–10.3) for patients using LABAs, compared with those not using LABAs (Fig 2). Therefore, LABAs were associated with an overall increase in the risk of the asthma composite outcome.

TABLE 2 Asthma Composite Components According to Age Group and Comparison Group

	No LABA	LABA	Total
Age 4–11 y, <i>N</i> (person-years)	1789 (865)	1626 (807)	3415 (1672)
Asthma-related death, No. of cases	1	0	1
Asthma-related death/intubation, No. of cases	2	0	2
Asthma-related hospitalization, No. of cases	38	61	99
Asthma composite, No. of cases	39	61	100
All-cause death, No. of cases	1	0	1
Age 12–17 y, <i>N</i> (person-years)	3289 (1492)	3103 (1429)	6392 (2921)
Asthma-related death, No. of cases	0	1	1
Asthma-related death/intubation, No. of cases	2	2	4
Asthma-related hospitalization, No. of cases	30	47	77
Asthma composite, No. of cases	30	48	78
All-cause death, No. of cases	0	1	1
Age 18–64 y, <i>N</i> (person-years)	23 604 (9743)	23 274 (9679)	46 878 (19 422)
Asthma-related death, No. of cases	2	14	16
Asthma-related death/intubation, No. of cases	18	38	56
Asthma-related hospitalization, No. of cases	199	237	436
Asthma composite, No. of cases	202	246	448
All-cause death, No. of cases	18	33	51
Age ≥ 65 y, <i>N</i> (person-years)	2097 (811)	2117 (865)	4214 (1676)
Asthma-related death, No. of cases	1	1	2
Asthma-related death/intubation, No. of cases	5	4	9
Asthma-related hospitalization, No. of cases	31	23	54
Asthma-related composite, No. of cases	32	25	57
All-cause death, No. of cases	21	17	38

**FIGURE 2**

Incidence difference for asthma composite index according to age for LABA versus no-LABA therapy. The asthma composite index includes asthma-related hospitalizations, deaths, and intubations. ID indicates incidence difference per 1000 patient-years; Incidence_{NO LABA} indicates incidence in No LABA group per 1000 patient-years.

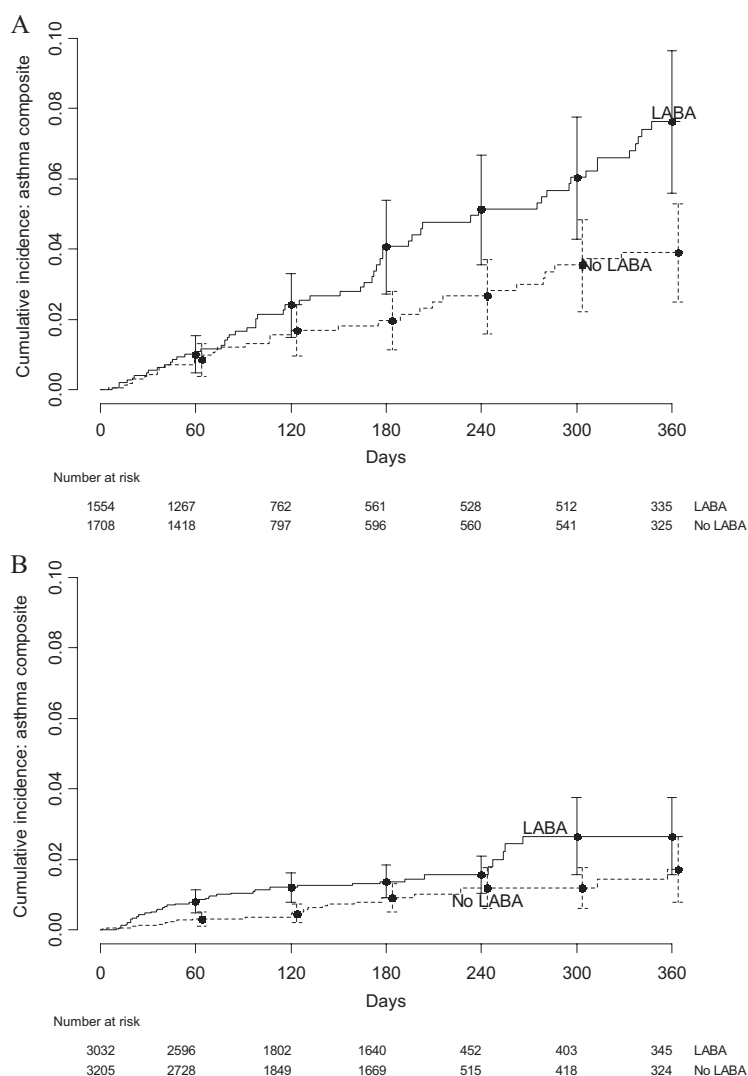
Age Effect

There was a general trend among the age groups toward higher estimates of incidence differences for the asthma

composite outcome among the younger age groups (Fig 2). The 4- to 11-year age group had the highest incidence difference at 30.4 events per

1000 patient-years (95% CI: 5.7–55.1). The incidence difference estimates and corresponding CIs for all age groups except for the 65-years-and-older age group were positive. The difference in the LABA effects among the age groups was statistically significant ($P = .020$). Therefore, the younger age groups had a greater increase in the risk associated with LABAs, compared with the older age groups. Overall and for each age subgroup, there was no evidence for heterogeneity among the trials.

The background incidence of events, as measured by the incidence in the non-LABA group, also was seen to be related to age (Fig 2). The 4- to 11-year age group had the highest non-LABA comparator risk (45.1 events per 1000 patient-years). To examine the effect of the differences in background rates among the age groups, a relative risk effect measure was used. The relative risk measure was calculated as the ratio of the LABA incidence to the non-LABA incidence. The relative risks for the 4- to 11-year, 12- to 17-year, 18- to

**FIGURE 3**

Kaplan-Meier plots of cumulative incidences of asthma composite index events for 4- to 11-year-old (A) and 12- to 17-year-old (B) patients.

64-year, and 65-years-and older age groups were 1.67, 1.58, 1.23, and 0.73, respectively, and the overall relative risk was 1.27. Therefore, the younger age groups had greater observed relative risks, as well as greater incidence differences, among the age groups. An examination of Kaplan-Meier plots of the asthma composite outcome for the 4- to 11-year and 12- to 17-year age groups showed that patients with LABA use seemed to have an increase in the risk of events, compared with patients without LABA use, throughout 1 year of exposure (Fig 3).

Effect of Concomitant ICS Use

A total of 36 210 patients were assigned ICS therapy or used an ICS as concomitant therapy. For the group of patients using ICSs either as assigned therapy or as concomitant therapy, the overall incidence difference for the asthma composite was 6.1 events per 1000 patient-years (95% CI: 0.9–11.4) for all ages combined; there was a marked age trend in the risk associated with LABA therapy ($P = .006$) (Fig 4). The highest incidence difference was for the 4- to 11-year age group

(48.5 events per 1000 patient-years [95% CI: 7.2–89.7]). Therefore, for the subgroup of patients who were assigned ICS therapy or used an ICS as concomitant therapy, the overall results and age trends were similar to those for the full analytic group of patients.

Effect of Assigned ICS Use

A total of 15 192 patients were assigned ICS therapy. Those patients were prescribed ICS in a regular scheduled regimen as part of the trial design, either in a combination device with a LABA or placebo or in a separate device. The overall incidence difference for all ages was 0.4 events per 1000 patient-years (95% CI: –3.8 to 4.6). For both the 4- to 11-year and 12- to 17-year age groups, there were few patients (886 and 1638 patients, respectively). There was no significant trend in the LABA risk according to age for this subset comparison ($P = .685$) (Fig 5). The incidence difference, in fact, was both positive and statistically significant only for the oldest age group (≥ 65 years), in contrast to the results for the overall analysis and the analysis of the concomitant ICS therapy subgroup.

DISCUSSION

There was a greater excess risk for the composite asthma outcome among younger children, compared with patients of all ages. This result was true for patients classified without respect to ICS use and for patients who reported receiving concomitant ICS therapy. The youngest group also had the highest relative risk. In the smaller subgroup of patients who were assigned to use ICSs, for which there were very few events overall, there did not seem to be an overall risk and the aforementioned age-related pattern was lacking. Although the majority of events in the asthma composite index were hospitalizations, we also consid-

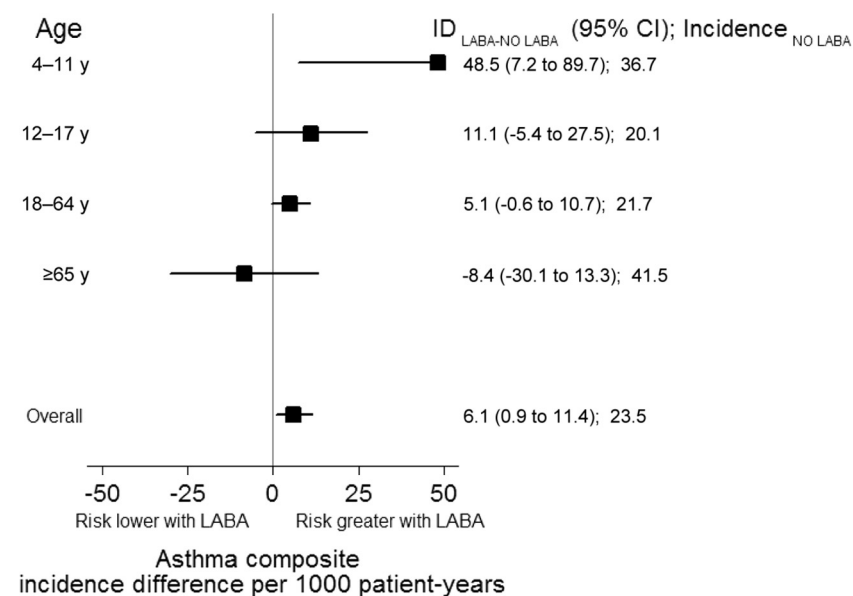


FIGURE 4

Incidence difference for asthma composite index according to age for LABA plus concomitant ICS therapy versus concomitant ICS therapy. The asthma composite index includes asthma-related hospitalizations, deaths, and intubations. ID indicates incidence difference per 1000 patient-years; Incidence_{NO LABA} indicates incidence in No LABA group per 1000 patient-years.

related deaths/intubations among patients treated with LABAs than among those who did not receive LABAs.

This meta-analysis showed that the risk of serious asthma-related events associated with LABA use seemed to be greater among children than in the overall population. Other clinical trial meta-analyses suggested a trend toward lower ages exhibiting a greater LABA safety signal.^{12,13} A meta-analysis performed by Salpeter et al¹² found odds ratios for asthma hospitalization of 2.0 for adults but 3.9 for children alone. Cates et al¹³ found odds ratios for all nonfatal serious adverse events of 1.57 for all ages and 2.92 for children, comparing formoterol with placebo.

Authors of 2 LABA meta-analyses concluded that ICSs, especially when administered together with a LABA, ameliorated the risks of LABAs.^{14,15} However, some results pointed to ICSs having limited ability to ameliorate LABA-related risks, a position that could be supported by the concomitant subgroup results in our meta-analysis. Weatherall et al¹⁴ showed an increased risk of asthma-related hospitalizations for patients (mostly adults) receiving salmeterol plus an ICS, compared with an ICS alone (odds ratio: 1.3 [95% CI: 1.1–1.5]). Salpeter et al¹⁶ pooled data on use of a LABA plus an ICS or an ICS alone (mostly among adults), looking for the comparative risk of the most-severe asthma-related events (defined as asthma-related deaths and intubations) in the 2 groups. They found an odds ratio of 3.65 for concomitant LABA and ICS treatment, compared with ICS treatment alone.¹⁶

Our result of an essentially neutral overall incidence difference for the asthma composite outcome with assigned ICSs for all ages combined is consistent with the results of a meta-analysis of salmeterol clinical trials by

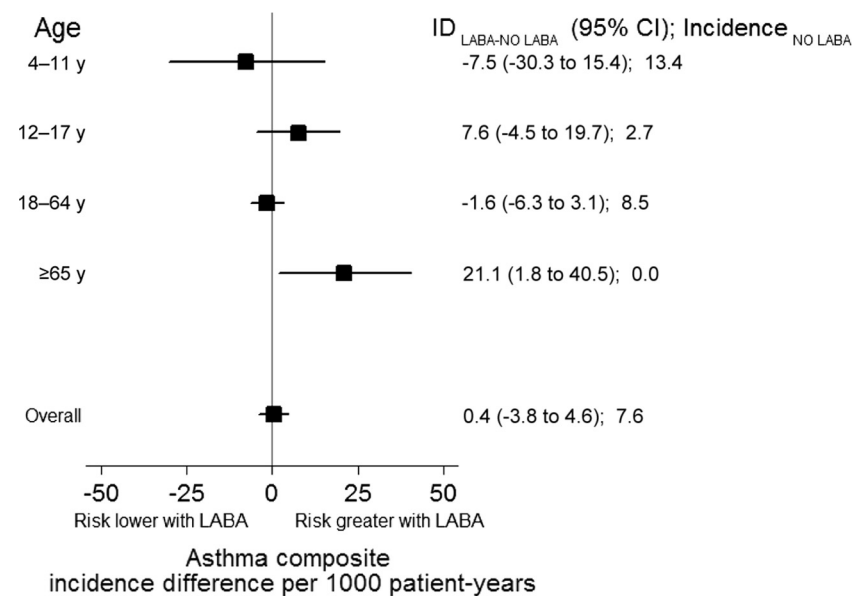


FIGURE 5

Incidence difference for asthma composite index according to age for LABA plus assigned ICS therapy versus assigned ICS therapy. The asthma composite index includes asthma-related hospitalizations, deaths, and intubations. ID indicates incidence difference per 1000 patient-years; Incidence_{NO LABA} indicates incidence in No LABA group per 1000 patient-years.

ered the more-severe outcomes of asthma-related intubations and asthma-related deaths. The sparseness of data on asthma-related deaths or intubations

among children and adolescents made it difficult to detect imbalances between treatment arms. Across all age groups, however, there were more asthma-

Bateman et al.¹⁵ With the use of trials that compared assigned ICS therapy with LABA plus ICS therapy, mainly among adults, the odds ratio for asthma-related hospitalizations was 1.07 (95% CI: 0.7–1.7). Our overall result was not consistent, however, with the results of a meta-analysis of formoterol clinical trials by Nelson et al,¹⁷ who reported an overall reduction in asthma-related hospitalizations with formoterol versus non-LABA treatment (relative risk: 0.73 [95% CI: 0.54–1.01]), although the point estimate for the relative risk increased with younger ages, as in our analysis. There are a number of possible reasons why the results reported by Nelson et al¹⁷ differed from ours, including the criteria for inclusion in the data set; the meta-analysis by those authors included trials of formoterol products not marketed in the United States and trials in which there were differences between randomized treatment regimens other than simply the presence or absence of a LABA.

There are several possible explanations in the present meta-analysis for the disparate findings regarding assigned (Fig 4) and concomitant (Fig 3) ICS use. There were relatively few patients with assigned ICS therapy in the pediatric population (Fig 1). The small number of patients might have resulted in the risk estimates for this population being less reliable, as reflected in the wider CIs. In addition, the finding of the higher risk in the population with concomitant ICS use is based on a broad definition of concomitant use. It is conceivable, although not known, that the population with “concomitant ICS use” is made up primarily of occasional ICS users. If that were true, then the contrast between

the assigned ICS users (Fig 4) and the concomitant ICS users (Fig 3) could represent effectively the difference between consistent ICS use with LABAs (Fig 4) and occasional ICS use with LABAs (Fig 3). Perhaps consistent with this, the incidences among the no-LABA users for the assigned ICS subgroups (Fig 4) were lower than those for the concomitant ICS subgroups (Fig 3). Details of the extent of ICS use in our concomitant ICS sample, unfortunately, were not available.

There are limitations of meta-analyses in general and of the one presented here in particular. (1) The trials were not designed prospectively to adjudicate hospitalizations, intubations, and deaths, to determine whether these events were asthma-related. (2) The information on concomitant ICS use was not detailed, and concomitant use might represent a range of usage from a single use to regular scheduled usage. (3) The meta-analysis was designed with knowledge of the findings of the Salmeterol Multicenter Asthma Research Trial, which was included in the meta-analysis. A sensitivity analysis excluding the Salmeterol Multicenter Asthma Research Trial did not result in notable changes in the overall findings.

The meta-analysis has several positive features. (1) Although data on the end points were not collected prospectively, common event search, end point definition, and treatment-blinded adjudication procedures were applied to all trials. These procedures made use of detailed patient data. (2) The meta-analysis was based on patient-level data, which allowed for subgroups analysis, time-to-event analysis, and checks of internal consistency. (3) Finally, the study objectives and analysis

plan were specified before the review of the data. These features would not be possible in a meta-analysis that used primarily previously published data.

Although to date there have been no large safety studies with the goal of determining the safety of the addition of LABAs to ICSs for any age group, it can be stated from the meta-analysis presented here that the risks of LABAs for children are obvious, both with at least some level of ICS use and without concomitant ICS use. The number of pediatric users of assigned ICS treatment was small; therefore, limited conclusions can be drawn from the results for this population.

CONCLUSIONS

Overall, there was an increased risk of serious asthma events with LABA use. The risk was greatest among the youngest patients. The same findings were seen for the subset of patients who reported some concomitant ICS use. Pediatric asthma composite outcomes mainly represented hospitalizations, and data on the more-severe outcomes of intubations and deaths were too sparse to analyze. The increased LABA composite outcome risk was not seen among children and adolescents who received an ICS as an assigned study treatment. Perhaps administering an ICS and a LABA in a single inhaler, as currently recommended,¹⁸ to ensure ICS adherence, might decrease the risk. Because of the small number of patients in the assigned ICS trials, however, limited conclusions can be drawn. Additional study is needed to understand the risks associated with LABAs when used regularly in conjunction with ICSs for the pediatric population.

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Ann W. McMahon, Mark S. Levenson, Bradley W. McEvoy, Andrew D. Mosholder
and Dianne Murphy

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