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Meta-Analysis: Effect of Long-Acting β-Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths

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Background: Long-acting β-agonists may increase the risk for fatal and nonfatal asthma exacerbations.

Purpose: To assess the risk for severe, life-threatening, or fatal asthma exacerbations associated with long-acting β-agonists.

Data Sources: English- and non–English-language searches of MEDLINE, EMBASE, and Cochrane databases; the U.S. Food and Drug Administration Web site; and references of selected reviews through December 2005.

Study Selection: Randomized, placebo-controlled trials that lasted at least 3 months and evaluated long-acting β-agonist use in patients with asthma. All trials allowed the use of as-needed short-acting β-agonists.

Data Extraction: Outcomes measured were Peto odds ratio (OR) and risk difference of severe exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma-related deaths. The OR for asthma-related deaths was obtained from the Salmeterol Multi-center Asthma Research Trial (SMART).

Data Synthesis: Pooled results from 19 trials with 33 826 participants found that long-acting β-agonists increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). The absolute increase in hospitalization was 0.7% (CI, 0.1% to 1.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%).

Limitations: The small number of deaths limited the reliability in assessing this risk, and 28 studies did not report information on the outcomes of interest.

Conclusions: Long-acting β-agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths.

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Long-acting β-agonists produce bronchodilation and improve asthma symptoms, effects that are maintained with regular use over time (1). However, monotherapy with β-agonists has consistently been shown to be inferior to the use of inhaled corticosteroids, which can reduce the underlying inflammation associated with the disease (2–5). For this reason, inhaled corticosteroids are recommended as first-line maintenance treatment for asthma (6). For patients whose condition is inadequately controlled with inhaled corticosteroids alone, the addition of a long-acting β-agonist is recommended (7). Studies have shown that adding a long-acting β-agonist can improve symptoms and reduce the risk for an asthma exacerbation, defined as clinical worsening of disease or an asymptomatic decrease in peak flows (8, 9). The conclusion from these studies was that long-acting β-agonists improve asthma control (1, 7). Another possible explanation is that they improve peak flows and symptoms while worsening disease control.

Much controversy has surrounded the use of β-agonists in patients with asthma ever since their introduction over 50 years ago (10–14). Regular β-agonist use is associated with tolerance to the drug's effects and a worsening of disease control (15–20). This effect results from a tight negative feedback mechanism that is an adaptive response to continued adrenergic stimulation (21). After the U.S. Food and Drug Administration (FDA) received postmarketing reports of several asthma-related deaths associated with the long-acting β-agonist salmeterol, the Salmeterol Multi-center Asthma Research Trial (SMART) was performed. This study followed more than 26 000 participants for 6 months and found a 4-fold increased risk for asthma-related deaths (22, 23). In July 2005, an advisory panel to the FDA met to examine whether long-acting β-agonists should be taken off the market (24). The panel concluded that strong warnings of increased risk should be placed on the labeling of all long-acting β-agonists, with recommendations that they be used only after other asthma drugs have failed (25, 26).

Life-threatening and fatal asthma attacks are relatively rare outcomes, even in large trials. For example, SMART found approximately 2 asthma-related deaths in 1000 patient-years of salmeterol use (23). The effect of long-acting β-agonists on these events can be more precisely estimated by pooling the results of many trials. The objective of our study was to assess the effect of long-acting β-agonists on severe asthma exacerbations requiring hospitalization, life-

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threatening asthma attacks, and asthma-related deaths. We used subgroup analyses to compare results for salmeterol and formoterol and for children and adults.

Context

Long-acting β-agonists may help improve asthma symptoms, but they also may increase risks for adverse outcomes.

Contribution

This meta-analysis summarizes data from 19 randomized, placebo-controlled trials involving 33 826 participants with asthma. Compared with placebo, long-acting β-agonists increased severe exacerbations requiring hospitalization (odds ratio, 2.6 [95% CI, 1.6 to 4.3]), life-threatening exacerbations (odds ratio, 1.8 [CI, 1.1 to 2.9]), and asthma-related deaths (odds ratio, 3.5 [CI, 1.3 to 9.3]; risk difference, 0.07%). Risks were similar for salmeterol and formoterol and in children and adults.

Cautions

Several trials did not report information about potential harms, and the number of reported deaths was small.

—*The Editors*

Methods

Search Strategy

We searched the MEDLINE, EMBASE, CINAHL, and Cochrane databases to identify randomized, controlled trials on long-acting β-agonist use in patients with asthma that were published between 1966 and December 2005. The search used the terms *bronchodilator, sympathomimetic, adrenergic beta-agonist, formoterol, eformoterol or salmeterol and asthma, bronchial hyperreactivity, wheeze, respiratory hypersensitivity, obstructive lung disease,* and *obstructive airway disease or obstructive pulmonary disease*. Trials were not excluded on the basis of language. The search was augmented by scanning references of identified reviews, as well as relevant files from the FDA Web site (www.fda.gov).

Study Selection and Assessment of Validity

We included studies if they were randomized, controlled trials of long-acting β-agonists compared with placebo and lasted at least 3 months. Two reviewers assessed the methodologic quality of each trial according to the following factors: 1) Was the randomization procedure adequate and was allocation concealment described? 2) Were patients and providers blinded to the interventions? 3) Were dropouts and withdrawals reported and was analysis performed by the intention-to-treat principle? Each of these quality domains was scored on a 3-point scale. Trials received an A score when all quality criteria for the domain were met, a B score when the criteria were partially met, and a C score when the criteria were not met. The quality assessment was used for a sensitivity analysis (27, 28).

Data Extraction and Synthesis

Two reviewers independently extracted data from the selected articles, reconciling differences by consensus. Outcomes assessed were severe asthma exacerbations requiring hospitalization, life-threatening asthma exacerbations requiring intubation and ventilation, and asthma-related deaths. Asthma deaths were those thought to be related to asthma as the underlying cause. Asthma deaths were also included as life-threatening exacerbations. We attempted to contact investigators to obtain additional information on asthma exacerbations and deaths.

The proportions of patients with severe exacerbations or asthma-related deaths to patients without those events from each trial were pooled by using the fixed-effects method expressed as a Peto odds ratio (OR) with corresponding 95% CIs (29, 30). We considered this method appropriate because we noted low event rates and minimal heterogeneity in the analyses. Evidence of interstudy heterogeneity was evaluated, with statistical significance set at an α value of 0.1. The analysis was performed by using Cochrane Review Manager 4.2 (Cochrane Library Software, Oxford, United Kingdom). Only trials that reported at least 1 event, such as hospitalization or death, could be used in the estimation of ORs. If more than 1 event occurred in the same patient, only the first event was counted.

Risk differences and exact 95% CIs were calculated for the difference between 2 independent binomial proportions (StatXact 7, Cytel Software, Cambridge, Massachusetts). The results for each trial were pooled by using the fixed-effects method (29). Trials that reported no events were included in the analysis of risk difference.

Subgroup analyses, chosen a priori, were performed to evaluate the difference in ORs between trials of salmeterol versus formoterol and trials in children (<12 years of age) versus adults. The results of the subgroups were compared with each other by using the test of interaction (31).

Role of the Funding Source

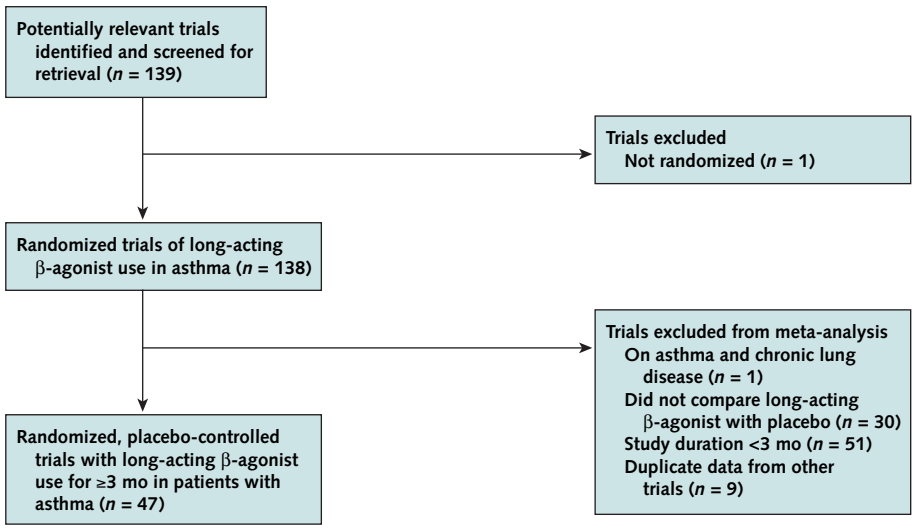
This analysis was funded by salary support from Santa Clara Valley Medical Center for Drs. Salpeter and Ormiston. The institution had no role in the design, conduct, or reporting of the study. All investigators had complete access to the data, and no sponsorship from the institution or the pharmaceutical industry was provided to conduct this analysis.

Data Synthesis

Search Results

Figure 1 shows the results of the search for articles. Through the MEDLINE search, we identified approximately 5000 articles, of which 133 were potentially relevant trials of long-acting β-agonist use in patients with asthma. After scanning references from selected articles and the FDA Web site, we identified an additional 6 trials. The

Figure 1. **Study flow diagram.**



EMBASE and Cochrane databases provided no additional trials. Of these 139 trials, 47 met the inclusion criteria (4, 23, 32–76). Thirty of these trials did not report outcomes of interest. After we attempted to contact investigators, 2 responded with unpublished information on deaths (36, 39). The 28 trials that did not provide adequate information on exacerbations or asthma-related deaths (4, 50–76) were not included in the primary pooled analysis but were used in a sensitivity analysis to estimate the lower limit of risk difference by assuming that no deaths occurred in them.

Trials were excluded for the following reasons: One trial was not randomized, 1 trial was on asthma and chronic obstructive pulmonary disease (COPD), 30 trials did not compare a long-acting β-agonist with placebo, 51 trials lasted less than 3 months, and 9 trials provided duplicate data on participants from other trials.

Trial Characteristics

The primary analysis included 19 trials, with a total of 33 826 participants followed for 16 848 patient-years (**Table**). The mean trial duration was 6.0 months (range, 3 to 12 months), with a mean sample size of 1780 participants (range, 110 to 26 353 participants). The mean age of participants at baseline was 37.2 years (SD, 5.7) in the β-agonist group and 37.7 years (SD, 4.7) in the placebo group. The percentage of men in the 2 groups was 51.2% and 50.2%, respectively. Approximately 15% of the participants were African American. The dropout rate was 20.3% in the β-agonist group and 22.6% in the placebo group.

The long-acting β-agonists used in the studies were salmeterol, formoterol, and eformoterol. During the trials, concomitant inhaled corticosteroids were used in 53.9% of participants in the β-agonist group and 53.2% of those in the placebo group. Of note, all trials except 2 (36, 48) were sponsored by a pharmaceutical company that manufactures a long-acting β-agonist, and all allowed the use of as-needed short-acting β-agonists.

All trials were randomized, double-blind, placebo-controlled trials that performed analysis according to the intention-to-treat principle and described withdrawals. Nine trials described the method of randomization or allocation concealment, and 10 did not. No trial received the lowest quality score on any domain; therefore, no sensitivity analysis was performed.

Quantitative Data Synthesis

Hospitalizations for Asthma Exacerbations

The OR for hospitalization was 2.6 (CI, 1.6 to 4.3) (**Figure 2**) for long-acting β-agonists compared with placebo. The risk difference for hospitalization attributed to long-acting β-agonists was 0.7% (CI, 0.1% to 1.3%) over 6 months. We did not include SMART in this analysis because the investigators did not provide information on hospitalizations due to asthma, just life-threatening exacerbations. When we included the SMART data on life-threatening exacerbations, the OR was 2.1 (CI, 1.5 to 3.0).

Subgroup analyses evaluated results for children (33, 37, 46, 49) and adults (23, 34, 38, 40–45), and for salmeterol (23, 38, 40, 42, 46, 49) and formoterol (33, 34, 37, 41, 43–45). The risk for hospitalization was increased in children (OR, 3.9 [CI, 1.7 to 8.8]) and in adults (OR, 2.0 [CI, 1.0 to 3.9]). Results did not statistically significantly differ between the 2 groups ($P = 0.22$). The risk for hospitalization was also increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and with formoterol (OR, 3.2 [CI, 1.7 to 6.0]), without a statistically significant difference in results for the 2 agents ($P = 0.109$).

Life-Threatening Asthma Exacerbations

The OR for life-threatening asthma attacks attributed to long-acting β-agonists was 1.8 (CI, 1.1 to 2.9) (**Figure 3**), with a risk difference of 0.12% (CI, 0.01% to 0.3%) over 6 months. Results did not significantly differ between trials of children and adults or between salmeterol and formoterol.

Asthma-Related Deaths

Fourteen trials provided data on asthma-related deaths. Two trials reported 1 asthma death in the treatment group and 0 deaths in the placebo group. The SMART investigators reported 13 asthma-related deaths among 13 174 participants in the β-agonist group and 3 deaths among 13 179 participants in the placebo group. The OR for asthma-related deaths in SMART was 3.5 (CI, 1.3 to 9.3; $P = 0.013$). The life-table estimate for relative risk for asthma-related deaths provided by SMART was 4.4 (CI, 1.3 to 15.3). When all trials with and without deaths were included in the analysis, the pooled risk difference was 0.07% (CI, 0.01% to 0.1%) over 6 months.

We did not include 28 trials in the primary analysis because they did not provide information on asthma-related deaths (2949 participants in the β-agonist group and 2795 in the placebo group). If we assume that no asthma-related deaths occurred in any of these trials and include them in the analysis, thus adding to the denominator, the absolute increase in risk is 0.06% over 6 months.

DISCUSSION

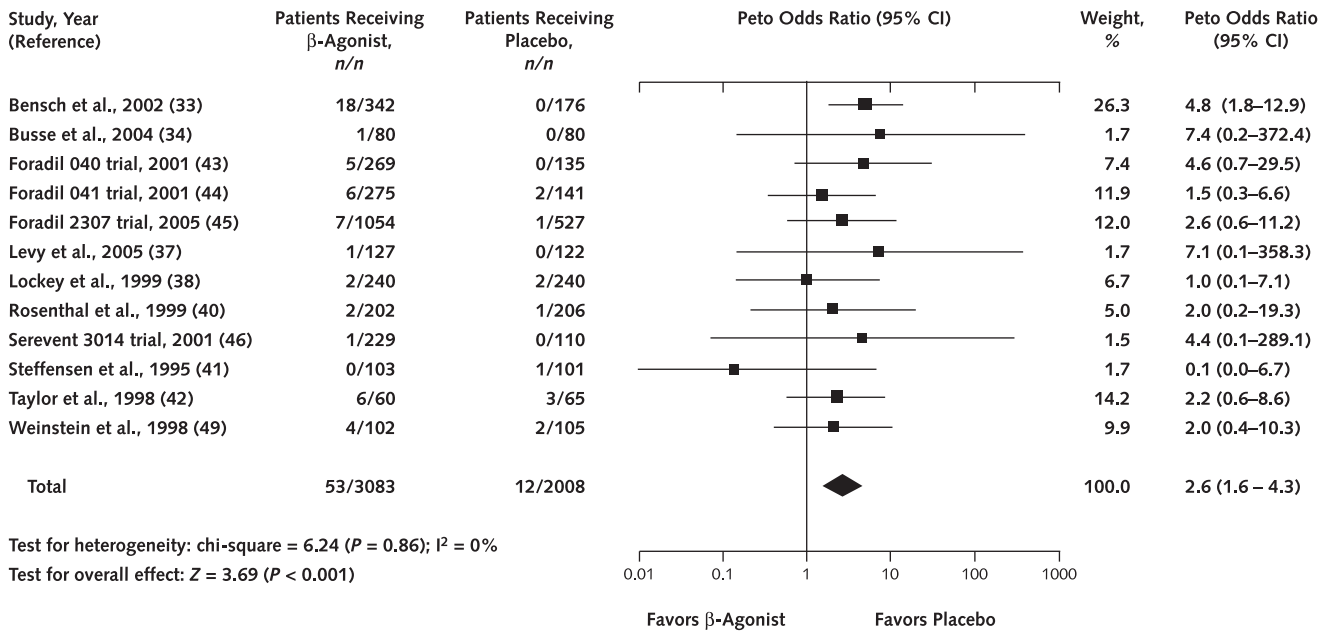
Pooled results from 19 trials with 33 826 participants followed for 16 848 patient-years showed that long-acting β-agonists increased the risk for hospitalization for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo. Hospitalizations increased among adults and children and with salme-

Table. **Studies Included in Primary Analysis***

Study, Year (Reference), Duration	Study Group	Patients, *n*	Mean Age, *y*	Men, %	Dropouts, %	Patients Receiving Inhaled Corticosteroids, %	Smokers, %	African-American Ethnicity, %	Quality Score†	Intervention	Comments
Bensch et al., 2001 (32), 12 wk	LABA Placebo	271 136	35.4 36.2	58.5 54	15.3 15.3	NS	NS	6 6	8	Formoterol, 12 μg and 24 μg BID	Albuterol also studied; sponsored by Novartis
Bensch et al., 2002 (33), 52 wk	LABA Placebo	342 176	9 9	60 68	20 23	>75 >75	0 0	7 6	8	Formoterol, 12 μg and 24 μg BID	All patients received anti-inflammatory agents; trial 049; sponsored by Novartis
Busse et al., 2004 (34), 12 wk	LABA Placebo	80 80	39.1 36.8	38.5 38.5	12.5 16.3	81.3 78.8	0 0	NS	9	Formoterol, 10 μg BID	Albuterol also studied; sponsored by Novartis
D'Urzo et al., 2001 (35), 26 wk	LABA Placebo	455 456	46.5 45.9	47 45	19 24	93 93	NS	NS	8	Salmeterol, 50 μg BID	Sponsored by Glaxo Wellcome
Foradil 040 trial, 2001 (43), 12 wk	LABA Placebo	269 135	35.5 35.5	53 47	5.9 6.7	NS	NS	NS	9	Formoterol, 12 μg and 24 μg BID	Phase III study; sponsored by Novartis
Foradil 041 trial, 2001 (44), 12 wk	LABA Placebo	275 141	32.6 33.5	53 47	6.2 6.4	45 49	NS	NS	9	Formoterol, 12 μg and 24 μg BID	Phase III study; sponsored by Novartis
Foradil 2307 trial, 2005 (45), 12 wk	LABA Placebo	1054 527	38.8 37.8	46 41.1	13.8 15.2	65 66.7	NS	12.7 11.9	9	Formoterol, 12 μg and 24 μg BID	Phase IV study; sponsored by Novartis
Lazarus et al., 2001 (36), 16 wk	LABA Placebo	54 56	31.6 31.2	38.9 32.1	24 12.5	53 52	0 0	12.9 16.1	9	Salmeterol, 42 μg BID	Triamcinolone also studied; unpublished information received‡
Levy et al., 2005 (37), 12 wk	LABA Placebo	127 122	9.4 9.5	74.8 59.0	8.7 9.0	74.8 68.9	0 0	NS	8	Formoterol, 10 μg BID	Sponsored by Novartis
Lockey et al., 1999 (38), 12 wk	LABA Placebo	240 234	40 38	41 50	15.0 23.1	67 62	0 0	4 10	8	Salmeterol, 42 μg BID	Sponsored by GSK
Price et al., 2002 (39), 26 wk	LABA Placebo	250 255	37.2 38.3	38.8 42.4	19.6 21.9	100 100	NS	NS	8	Eformoterol, 9 μg BID	Sponsored by AstraZeneca; unpublished information received
Rosenthal et al., 1999 (40), 24 wk	LABA Placebo	202 206	29.3 28.7	56.4 61.6	16.8 25.7	NS	NS	NS	8	Salmeterol, 42 μg BID	Sponsored by GSK
Salmeterol SLD-390 trial, 2001 (47), 12 wk	LABA Placebo	102 105	8.5 8.3	69 69	2.9 2.9	57 57	0 0	11 11	9	Salmeterol, 50 μg BID	Sponsored by GSK
SMART, 2006 (23), 28 wk	LABA Placebo	13 174 13 179	39.2 39.1	NS	22.5 23.8	49 49	NS	18 18	9	Salmeterol, 50 μg BID	Phase IV safety study; sponsored by GSK
Serevent 3014 trial, 2001 (46), 12 wk	LABA Placebo	229 110	8 8	NS	14.8 13.6	47 47	0 0	12 12	9	Salmeterol, 25 μg and 50 μg BID	Phase III study; sponsored by GSK
Steffensen et al., 1995 (41), 12 wk	LABA Placebo	103 101	49 48	43.7 52.5	11.6 20.8	88 92	35.0 26.7	NS	8	Formoterol, 12 μg BID	Salbutamol also studied; sponsored by Ciba-Geigy
Taylor et al., 1998 (42), 24 wk	LABA Placebo	60 65	38 38	44.2 38	11.7 18.5	92 92	0 0	NS	9	Salmeterol, 50 μg BID	Salbutamol also studied; sponsored by GSK
Von Berg et al., 2003 (48), 12 wk	LABA Placebo	164 84	11.4 11.3	66 63	6.1 3.6	82.1 82.2	0 0	NS	8	Formoterol, 4.5 μg and 9 μg BID	–‡
Weinstein et al., 1998 (49), 12 wk	LABA Placebo	102 105	8.5 8.3	68 70	9.8 9.5	57 57	0 0	14 9	8	Salmeterol, 50 μg BID	Sponsored by GSK

* BID = 2 times per day; GSK = GlaxoSmithKline; LABA = long-acting β-agonist; NS = not stated; SMART = Salmeterol Multi-center Asthma Research Trial.
† Quality score was tabulated for each quality domain, with 3 points for an A score, 2 points for a B score, and 1 point for a C score, for a maximum total of 9 points.
‡ Not sponsored by a pharmaceutical company.

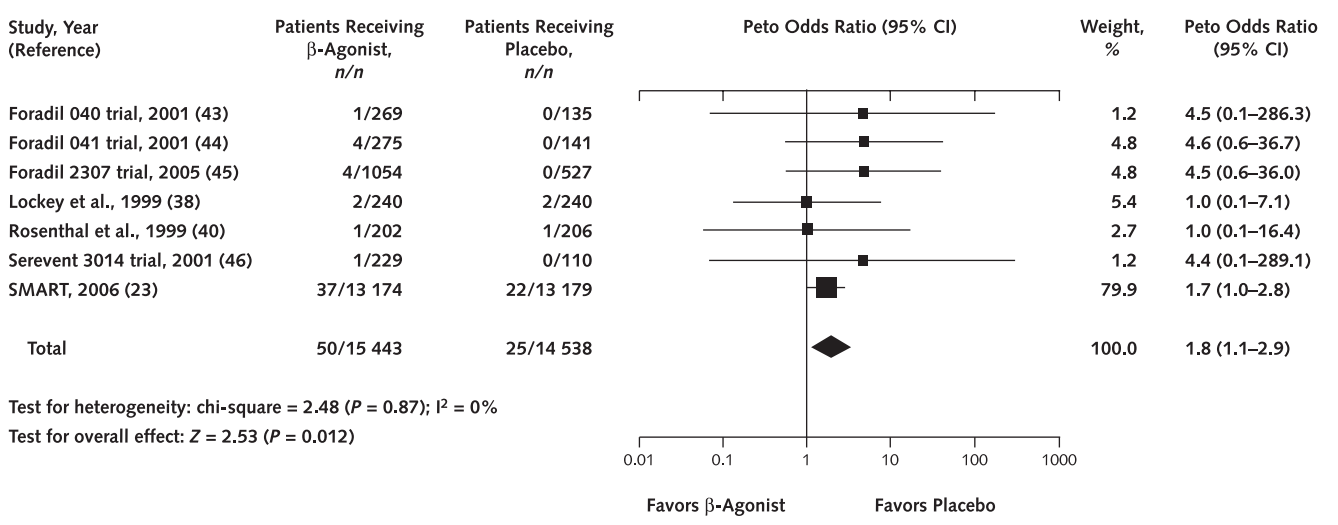
Figure 2. **Effect of long-acting β-agonists compared with placebo on odds ratio of hospitalizations for asthma exacerbation.**



terol and formoterol. The results of SMART were similar to the pooled results from smaller studies.

In SMART, which followed 26 000 participants for 6 months, salmeterol compared with placebo was associated with a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma-related deaths (23). The trial did not provide data on asthma-related hospitalizations but reported an increase in all-cause hospitalization in the salmeterol group (4%) compared with the placebo group (3%) that approached statistical significance. One limitation of SMART is that patients with COPD were not excluded from the trial, and deaths from COPD were included as asthma-related deaths (23). Of note, 2 of the 3 asthma-related deaths in the placebo group were in patients older than 60 years of age, with 1 death listed as being due to COPD. In contrast, only 2 of the 13 asthma-related deaths in the salmeterol group were in patients older than 60 years of age, with 1 considered to be due to COPD. If

Figure 3. **Effect of long-acting β-agonists compared with placebo on odds ratio of life-threatening asthma exacerbations.**



SMART = Salmeterol Multi-center Asthma Research Trial.

the reported COPD deaths were excluded from the analysis, salmeterol would be associated with a 6-fold increase in relative risk for asthma-related deaths.

To put these risks in perspective, it is necessary to understand the benefits that these agents provide. Unfortunately, all the trials evaluated allowed as-needed short-acting β-agonist use in both groups; thus, they were in effect comparing regular with as-needed β-agonist use. Some trials reported a reduction in asthma exacerbations associated with long-acting β-agonists (8, 9, 39, 42, 77). However, these trials used a definition of exacerbation that included clinical symptoms as well as a decrease in peak flows below a specified level in asymptomatic patients. The use of a short-acting β-agonist causes peak flows to regularly decrease below baseline levels as the effect of the medication wears off (77). Therefore, patients in the placebo group who are using intermittent short-acting β-agonists may be expected to have asymptomatic decreases in peak flow that would be called an exacerbation. This could explain why a reduction in exacerbations could be seen with long-acting β-agonists if this definition is used, even though the drug may actually increase true clinical exacerbations that are associated with hospitalization, intubation, or death.

Inhaled β-agonists are also widely used to treat COPD, although inhaled anticholinergics such as ipratropium and tiotropium have been shown to have equal or superior efficacy compared with β-agonists (78, 79). A recent meta-analysis pooled the results of 22 randomized trials, which followed more than 15 000 participants with COPD, and found that inhaled anticholinergics reduced respiratory deaths by 70% (relative risk, 0.3 [CI, 0.1 to 0.8]) while β-agonists increased respiratory deaths by more than 2-fold (relative risk, 2.5 [CI, 1.1 to 5.5]) compared with placebo (80).

Long-acting β-agonists may worsen asthma control by means of a negative feedback mechanism of the β-adrenergic system that is an adaptive response to stimulation of receptors (21). Stimulation results in uncoupling and internalization of receptors, which is known as *desensitization*, followed by a decrease in receptor density and receptor gene expression, which is known as *downregulation* (21). Regular use of β-agonists has been shown to increase bronchial hyperreactivity despite maintenance of some degree of bronchodilation (15, 65, 73, 81). These effects, along with a reduction in response to subsequent rescue β-agonist use, may worsen asthma control without giving any warning of increased symptoms (15, 51, 73, 82).

Inhaled corticosteroids have been shown to reduce bronchial inflammation and asthma exacerbations and to partially protect against the adverse effects seen with regular β-agonist use (9, 18, 83–86). Despite this protective effect, regular β-agonist use with concomitant inhaled corticosteroids still results in substantial tolerance over time (15, 87, 88). For example, in this meta-analysis, we separately evaluated trials in which more than 75% of participants were receiving concomitant inhaled corticosteroids (mean, 90%) and found that the risk for hospitalizations was still increased 2-fold (OR, 2.1 [CI, 1.3 to 3.4]). For this reason, the FDA has required strong warning labels on both salmeterol preparations, with and without an inhaled corticosteroid (26).

In this meta-analysis, the risks for severe exacerbations and asthma-related deaths were increased by 2- to 4-fold. However, we must also look at the absolute risk increase to put this into clinical perspective. We found that the absolute increase in asthma-related deaths was estimated to be 0.06% to 0.07% over 6 months, indicating that long-acting β-agonists cause an excess of approximately 1 death per 1000 patient-years of use. Salmeterol is one of the most widely prescribed medications in the world, with an estimated 3.5 million adults treated in the United States in 2004 (89, 90). This indicates that salmeterol may be responsible for approximately 4000 of the 5000 asthma-related deaths that occur in the United States each year (91). The SMART findings indicated that African Americans may be at especially high risk for asthma-related deaths associated with salmeterol, which may reflect an increase in asthma severity in general (23, 91).

Asthma mortality rates increased worldwide in the 1960s, when inhaled β-agonists were introduced on the market (92). We have seen another increase in mortality rates in the United States over the past 10 years, since long-acting β-agonists were introduced (92). Similar increases in mortality were seen in New Zealand when the strong inhaled β-agonist fenoterol was introduced; mortality decreased rapidly when use of the drug was severely curtailed and widespread use of inhaled corticosteroids was instituted (92, 93). If long-acting β-agonists were removed from the market in the United States, we might witness a reduction in asthma mortality rates here.

If long-acting β-agonists were removed from the market, the main treatment options for asthma would be inhaled corticosteroids and anticholinergic agents. Inhaled corticosteroid use is the treatment of choice for asthma and has been shown to increase peak flows and reduce asthma exacerbations (94). Observational studies have consistently shown that the risks for life-threatening and fatal asthma exacerbations are reduced with the use of inhaled corticosteroids and increased with the use of β-agonists (95–99). Treatment with anticholinergic agents results in bronchodilation and protection against bronchoconstrictive agents without evidence of tolerance to its effects over time (54, 100–103). Short-term use in acute asthma exacerbations improves peak flows by 15% and reduces the need for hospitalization by 30% in both children and adults (104). Treatment of chronic asthma with anticholinergic agents is associated with a 15% improvement in symptom scores and a 7% increase in peak flows compared with placebo (105). Compared with β-agonists, inhaled anticholinergics have been shown to reduce bronchial hyperresponsiveness

and result in slightly more favorable symptom scores (81, 105).

Our analysis has several limitations. Standard meta-analytic results for ORs and risk differences can be uncertain when the numbers of events per study are small, as is the case with asthma-related deaths. The accurate assessment of asthma-related deaths in this analysis was further hindered by the fact that many trials did not provide this information, and also by the difficulty inherent in ascertaining the true cause of death. The OR for deaths in this analysis was obtained solely from SMART. However, the increased OR found in this trial was statistically significant. In addition, the absolute increase in risk was estimated by pooling all trials with and without deaths through the use of exact statistical methods; this finding was also statistically significant. Our analysis was based mainly on published literature and therefore may be subject to publication bias. However, we also included unpublished trials listed on the FDA Web site, and funnel plots of effect size versus standard error found no evidence for bias. Finally, it is unfortunate that no true placebo-controlled trials of long-acting β-agonist use in asthma have been published. Despite these limitations, we believe that this meta-analysis provides valuable information on the effect of long-acting β-agonist use on severe adverse clinical outcomes.

In summary, long-acting β-agonist use increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. Similar risks are found with salmeterol and formoterol and in children and adults. Concomitant inhaled corticosteroids do not adequately protect against the adverse effects. The use of long-acting β-agonists could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions, and deaths each year. Black box warnings on the labeling for these agents clearly outline the increased risk for asthma-related deaths associated with their use, but these warnings have not changed prescribing practices of physicians (25). This information could be used to reassess whether these agents should be withdrawn from the market.

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Potential Financial Conflicts of Interest: None of the authors have had any relationships with a pharmaceutical company that manufactures a β-agonist or other respiratory medications. Dr. Shelley Salpeter has consulted on legal cases involving β-agonists but has never given expert testimony and has no contracts with law firms.

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