Safety of long-acting β agonists for the treatment of asthma: clearing the air

Gustavo J Rodrigo,1 José A Castro-Rodríguez2

ABSTRACT
Concerns about the safety of long-acting β2-agonist (LABA) therapy, has led to the appearance of multiple publications and recommendations. This review critically examines the available clinical evidence and safety requirements for LABA use. On the basis of nearly 20 systematic reviews and databases, the authors conclude that LABA monotherapy significantly increases the risk of asthma-related adverse effects. We also conclude that the use of LABAs concomitantly with inhaled corticosteroids (ICS) significantly reduces asthma hospitalisations and is not associated with life-threatening events and asthma-related deaths, especially when concurrent use of LABAs and ICS can be reasonably assured (use of a single inhaler device). An appropriate clinical study would require an extremely large sample, making it impractical. Finally, some of the new US Food and Drug Administration (FDA) recommendations have caused confusion and do not appear to be fully evidence based. Although limited by low statistical power, the evidence supports the use of LABAs plus ICS in a single inhaler device (to increase adherence and reduce the potential use of LABA monotherapy) for all patients (not only children) with moderate to severe asthma.

INTRODUCTION
Short-acting β agonists (SABAs) have been used for decades as bronchodilators in the treatment of both chronic and acute asthma. Their therapeutic profile has generally been good, although safety concerns have persisted since SABAs were implicated in two epidemics of asthma deaths in the 1960s and 1970s.1 The question of whether these epidemics effectively resulted from the use of SABAs has been the subject of intense and persisting controversy. The introduction of long-acting β2 agonists (LABAs) in the 1990s was considered a major advance in bronchodilator therapy, with evidence that their use led to improved lung function and quality of life. However, concerns about the possible risks associated with LABA therapy appeared soon after its introduction, with the suggestion that regular use has the potential to reduce bronchodilator sensitivity to β agonists, and induce tolerance to their bronchoprotective effects.2 It also became evident that patients with asthma using LABAs may be at risk of increased morbidity and mortality if the symptom control achieved with LABA use led to a discontinuation of inhaled corticosteroid (ICS) therapy.3 Contrary to previous hypotheses, recent prospective data have shown no evidence of a pharmacogenetic effect of β-receptor variation on salmeterol response.4

Given the serious concerns about the use of LABAs for asthma, the following review critically examines the available clinical evidence and the different safety requirements for the use of LABAs.

CLINICAL EVIDENCE
The Serevent Nationwide Surveillance study
GlaxoSmithKline (GSK, Brentford, Middlesex, UK) sponsored the Serevent Nationwide Surveillance (SNS) study in which patients with asthma were recruited throughout the UK.5 It was a randomised, double-blind study in parallel groups over 16 weeks, comparing inhaled salmeterol (50 μg, twice daily) to salbutamol (200 μg four times daily). A total of 25 180 patients were randomised to salmeterol and 8395 to salbutamol. The only significant difference between the two groups was the number of medical withdrawals because of asthma, which were fewer with salmeterol than with salbutamol (table 1). Approximately 70% of patients received ICS concomitantly. The investigators reported 12 deaths caused by asthma in the salmeterol group (7.1 per 10 000 patients) and two in the salbutamol group (2.4 per 10 000 patients). This threefold increased risk did not reach statistical significance. Because the number of events was very small, it is not possible to determine if this difference is a chance finding. Moreover, bias may have been introduced by the higher proportion of withdrawals in the salbutamol group. Finally, the authors considered that a number of deaths could have been prevented by more appropriate use of ICS.

The Salmeterol Multicenter Asthma Research Trial (SMART)
The US Food Drug Administration (FDA) required GSK to obtain additional data in a large new trial.6 This study was designed to evaluate the effects of salmeterol on respiratory and asthma-related deaths or life-threatening events. It was a multicentre, randomised, double-blind, parallel-group, placebo-controlled study conducted in the USA. Patients with asthma who were aged 12 years and over were assigned to receive either salmeterol 50 μg twice daily via metered-dose inhalers or placebo for 28 weeks in addition to their usual therapy. Initially, patients were recruited via print, radio, and television advertising from 1996 to 1999 (phase 1). When recruitment decreased, the advertising campaign was stopped and patients were recruited by the study investigators from 2000 to 2003 (phase 2). However, following an interim analysis of 26 355 patients, the sponsor decided to terminate the study due to preliminary findings in African Americans and difficulties in enrolment. This trial was planned for 60 000 patients, or 238

1Department of Emergency, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay
2Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Correspondence to
Gustavo J Rodrigo, Department of Emergency, Hospital Central de las Fuerzas Armadas, Av. 8 de Octubre 3020, Montevideo 11600, Uruguay; gurodrig@adinet.com.uy

Received 12 November 2010
Accepted 13 January 2011
primary events, but was terminated when approximately half the target number of patients had been enrolled, subsequently providing 86 primary events.

Baseline ICS use was reported by 47% of the overall population, with 49% in white patients and 38% among African–American patients. Data indicate greater disease severity at baseline among the African–American subgroup compared with white patients. For the primary endpoint, there were no significant differences between treatment groups in the number of respiratory-related deaths or life-threatening events (figure 1). However, the number of combined asthma deaths and life-threatening events, and the number of asthma deaths alone were significantly higher in patients receiving salmeterol. There was one excess asthma death every 1318 salmeterol-treated patients (95% CI 734 to 23666). Most asthma deaths occurred during phase 1 (13 of 16).

There were statistically significant differences among the African–American population in the primary endpoint and for one of the secondary endpoints (figure 1). Although SMART was not designed to assess the effect of ICS use on the endpoints, post hoc analyses showed that the number of events for the primary and all secondary endpoints was similar for patients reporting baseline use of ICS in both treatment groups (figure 1). In contrast, the number of primary and secondary outcome events for patients reporting no baseline ICS use was significantly greater in the salmeterol group compared with the placebo group.

Overall, the results of SMART have been controversial. There were differences in baseline asthma characteristics between white patients and African–American patients (lower baseline peak expiratory flow, more nocturnal symptoms, more emergency department visits and hospitalisations, and more intubations in their lifetimes among the latter group). In the previous 12 months there were higher numbers of hospitalisations and emergency department visits in the African–American patients. There were also baseline differences in the use of ICS. Finally, the finding of more deaths with salmeterol use contrasts with national statistical data in the USA on asthma deaths and prescriptions for salmeterol and salmeterol plus ICS combinations. Extrapolation of the mortality data from SMART suggests that in 2004 there would have been twofold to threefold more asthma deaths than were reported in the national statistics.

### Formoterol studies

The use of formoterol was approved in the USA in a 12 μg formulation based on two 12-week studies7 8 and one 1-year study in children aged 5–12 years.9 Clinical studies caused concern about a possible relationship between the use of higher doses (24 μg twice daily) and an increase in serious asthma exacerbations.10 As a consequence, the FDA asked the manufacturer (Novartis Pharmaceuticals Basel, Switzerland) to conduct a phase IV post-marketing clinical trial to investigate the relative safety of the two different doses of formoterol.11 This trial, which enrolled 2083 patients with stable mild-to-moderate persistent asthma (64% received regular concomitant ICS), showed five (0.9% of all patients) severe asthma-related complications in the group receiving 24 μg formoterol compared with two (0.4%) in the 12 μg group, and only one (0.2%) in the placebo group, suggesting that formoterol 24 μg twice daily was associated with an increase in serious asthma exacerbations. Likewise, tabular data from Novartis12 showed an increased incidence of serious asthma-related events in patients taking formoterol. Although the FDA confirmed the availability of both salmeterol and formoterol, black box warnings were required on their product labels.13

### The FDA meta-analysis

This meta-analysis was in response to the recommendations from the Paediatric Advisory Committee meeting (28 November 2007) to continue assessing the risks and benefits of LABAs.14 It explored possible associations of LABAs with asthma hospitalisations, intubations, and deaths. It was based on data from 110 randomised, parallel controlled clinical trials (60 954 patients) that the sponsors submitted to the FDA. The meta-analysis considered four products that contain a LABA and are approved in the USA for the treatment of asthma: salmeterol plus fluticasone, formoterol, salmeterol, and formoterol plus budesonide. The majority of patients (>70% of total sample) were from salmeterol trials. SMART6 provided a substantial percentage (45%) of the total sample. For the overall analysis, 77% of patients were aged between 18 and 64 years, 11% between 12 and 17 years, 7% 65 years and over, and only 6% between 4 and 11 years. The majority of patients were white (72%), female (57%), and from trials with treatment durations of 12 weeks or more (94%).

Overall, data showed that LABAs were associated with an increased risk difference (RD) of asthma-related events relative to non-LABA treatment as measured by the asthma composite endpoint consisting of asthma deaths, asthma intubations, and

### Table 1 Summary of data from the Serevent Nationwide Surveillance study (adapted from Castle et al5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salmeterol (n = 16787)</th>
<th>Salbutamol (n = 8393)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>54 (0.31%)</td>
<td>20 (0.24%)</td>
<td>1.35 (0.81 to 2.25)</td>
<td>0.25</td>
</tr>
<tr>
<td>Respiratory and asthma deaths</td>
<td>12 (0.07%)</td>
<td>2 (0.02%)</td>
<td>3.00 (0.67 to 13.4)</td>
<td>0.105</td>
</tr>
<tr>
<td>Hospitalisations and life-threatening asthma</td>
<td>193 (1.1%)</td>
<td>102 (1.2)</td>
<td>0.95 (0.74 to 1.20)</td>
<td>0.74</td>
</tr>
<tr>
<td>Withdrawals due to asthma</td>
<td>488 (2.9%)</td>
<td>318 (3.8%)</td>
<td>0.77 (0.67 to 0.88)</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

#### Figure 1 Pooled relative risk RR with 95% CI of primary and secondary endpoints during the 28-week study period in the Salmeterol Multicenter Asthma Research Trial (SMART) (n, number of events; N, total sample) (adapted from Nelson et al6).
asthma hospitalisations (figure 2). Non-LABA treatments included ICS, SABAs, other non-LABA treatments, placebo, or a combination of treatments. This overall finding was supported by a significant increase in the asthma composite endpoint, but not in the individual endpoints.

Interestingly, RDs for the asthma composite endpoint only increased when LABAs without randomly assigned ICS were compared with non-LABA treatment (figure 3). In contrast, the comparison of LABAs with randomised ICS versus randomised ICS alone (same ICS and dose) was not statistically significant. Three of the four products (formoterol, salmeterol, and formoterol plus budesonide) showed non-significant increases in the RD for the asthma composite endpoint; only salmeterol had a statistically significant estimate. There were 20 asthma-related deaths, 16 of which were in the LABA group (all occurred among salmeterol-treated patients) and four in the non-LABA group. It should be noted that the majority of trials submitted by AstraZeneca (Lund, Sweden) for the formoterol plus budesonide combination were not included in the FDA analysis (38 studies with 22240 patients) for different reasons (non-US-approved doses and age (4–11 years).

In contrast to the FDA analysis (four trials with 1270 patients), which showed a non-significant increased risk of asthma-related hospitalisations (RD=7.49 per 1000 patients), the analysis of the 44 trials (23 510 patients) submitted by AstraZeneca showed a non-significant decreased risk (RD=−4.5 per 1000 patients) for formoterol plus budesonide (figure 5). There was a general trend among age, with higher RD among the younger age groups. RDs for all age groups, except the 65 and over age group, were positive and statistically significant. Women and African Americans showed significant increases in RD.

In summary, LABAs were associated with an increased risk of an asthma composite endpoint. Of 44 deaths and intubations in the LABA-exposed population, 43 occurred among 22 286 patients (0.19%) in trials in which ICS use was not mandatory, four in the LABA group (all occurred among salmeterol-treated patients) and four in the non-LABA group. It should be noted that the majority of trials submitted by AstraZeneca (Lund, Sweden) for the formoterol plus budesonide combination were not included in the FDA analysis (38 studies with 22240 patients) for different reasons (non-US-approved doses and age (4–11 years). In contrast to the FDA analysis (four trials with 1270 patients), which showed a non-significant increased risk of asthma-related hospitalisations (RD=7.49 per 1000 patients), the analysis of the 44 trials (23 510 patients) submitted by AstraZeneca showed a non-significant decreased risk (RD=−4.5 per 1000 patients) for formoterol plus budesonide (figure 5). There was a general trend among age, with higher RD among the younger age groups. RDs for all age groups, except the 65 and over age group, were positive and statistically significant. Women and African Americans showed significant increases in RD.

In summary, LABAs were associated with an increased risk of an asthma composite endpoint. Of 44 deaths and intubations in the LABA-exposed population, 43 occurred among 22 286 patients (0.19%) in trials in which ICS use was not mandatory compared with one death among 7862 patients (0.01%) in trials with mandatory ICS therapy. No deaths or intubations were reported for patients treated with single-device combinations of ICS and LABAs.

**Systematic reviews with meta-analyses based on randomised controlled trials and clinical databases**

Because of the rarity of death in asthma clinical trials, one useful approach is to analyse systematic reviews using a meta-analysis based on randomised controlled trials (RCTs). The authors examined 16 meta-analyses: three compared LABAs with placebo,16–18 eight compared LABAs plus ICS with ICS alone,19–26 and three presented both comparisons.27–29 Additionally, we evaluated two databases of RCTs submitted by the sponsors to the FDA.30 31

Of the six reviews comparing LABAs with placebo (table 2), four17 27 29 showed significant increases in asthma deaths in the LABA group, with one excess asthma death every 1127–1824 LABA patients. The majority of deaths recorded in these reviews were from SMART. The only review that examined exclusively the effect of formoterol19 presented only one asthma death in the LABA group. LABA monotherapy increased the risk of life-threatening asthma and asthma hospitalisation events, although in some reviews the effect was not statistically significant.17 27 29 Clearly, analysis of these data confirms previous concerns arising from studies such as SNS or SMART. An important limitation was the low number of paediatric studies.

Reviews comparing LABAs plus ICS versus ICS alone showed quite a different picture (table 3). All reviews, except two,28 29 presented the same dose of ICS in both arms, and one included trials exclusively in children.22 Overall, asthma deaths and life-threatening events were very rare, and patients treated with LABAs plus ICS presented a reduced risk of asthma hospitalisations. The only paediatric review22 did not show asthma deaths or life-threatening events. However, it presented a non-significant increased risk of asthma hospitalisations.

These findings differ markedly from the Salpetter et al review.20 These authors selected RCTs (≥3 months) that compared LABAs with placebo or LABAs plus ICS with ICS alone. The primary outcome was catastrophic events, defined as asthma-related intubation or death. Using data from six trials and one database provided by GSK (7253 patients), the authors concluded there was a surprisingly threefold increase in catastrophic events among patients treated with LABAs plus ICS compared with those treated with ICS alone (table 3). Nevertheless, this finding appears problematic because of different

---

**Table 2**

<table>
<thead>
<tr>
<th>Product Combinations</th>
<th>Asthma Composite</th>
<th>Asthma Death</th>
<th>Asthma Death/Intubation</th>
<th>Asthma Hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LABAs plus ICS</td>
<td>(95% CI)</td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td>LABAs alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 2**

Pooled risk difference (RD) with 95% CI of asthma endpoints in the US Food and Drug Administration (FDA) meta-analysis (n, number of events; N, total sample; LABAs, long-acting β2 agonists) (adapted from Levenson14).

**Figure 3**

Pooled risk difference (RD) with 95% CI of asthma composite by subgroups in the FDA meta-analysis (n, number of events; N, total sample; LABAs, long-acting β2 agonists; LABAs wo/R ICS versus No LABAs, LABAs without randomised ICS versus no LABAs; LABAs wo/R ICS versus R ICS, LABAs with randomised ICS versus randomised ICS).

*RD from 4 (n=1270) of 42 (n=23 510) studies included in the FDA analysis; **RD from 42 (n=23 510) studies (adapted from Levenson14).
### Table 2: Data from a meta-analysis of randomised, controlled trials comparing long-acting β2 agonists with placebo

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Number of patients</th>
<th>Number of studies</th>
<th>Comparison analysis</th>
<th>Duration of trials (range)</th>
<th>All-cause death effect estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodrigo GJ, Castro-Rodríguez JA.</td>
<td>16 22 (17/5)</td>
<td>8032</td>
<td>Formoterol vs placebo</td>
<td>12–52 weeks</td>
<td>RR = 1.27 (0.86 to 1.88)</td>
</tr>
<tr>
<td>Cates</td>
<td>40 (31/9)</td>
<td>36303</td>
<td>LABA vs placebo</td>
<td>4–56 weeks</td>
<td>NS</td>
</tr>
<tr>
<td>Rodrigo GJ.</td>
<td>54</td>
<td>33286</td>
<td>LABA vs placebo</td>
<td>3–12 months</td>
<td>NS</td>
</tr>
<tr>
<td>Salpeter</td>
<td>19 (14/5)</td>
<td>26935</td>
<td>LABA vs placebo</td>
<td>3–13 months</td>
<td>NS</td>
</tr>
</tbody>
</table>

#### Notes
- LABA, long-acting β2 agonist; NNTH, number need to treat for harm; NS, not stated.
- Non-statistically significant (p > 0.05).
- Subgroup analysis of data from studies comparing LABAs with placebo.

#### Summary

- There were no asthma-related deaths, and the FDA asthma mortality review included only one asthma death among formoterol-treated patients.

### ARE NEW DATA NEEDED?

Although mortality is a very rare event in the use of LABAs with mandatory ICS trials, estimates of risk should be interpreted with caution, given that such trials were not powered on these events. Accordingly, the FDA is requiring the manufacturers of LABAs to conduct additional studies to evaluate their safety. Likewise, some authors have issued a call for a very...
<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Number of trials (adults/children)</th>
<th>Number of patients</th>
<th>Comparison analysed</th>
<th>Duration of trials (range)</th>
<th>All-cause deaths effect estimate (95% CI)</th>
<th>Asthma-related deaths effect estimate (95% CI)</th>
<th>Life-threatening asthma effect estimate (95% CI)</th>
<th>Asthma-related hospitalisations effect estimate (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bateman1^13</td>
<td>66 (60/6)</td>
<td>20966</td>
<td>Salmeterol + ICS vs ICS</td>
<td>1–52 weeks</td>
<td>NS</td>
<td>1 event (salmeterol + ICS)</td>
<td>1 event (salmeterol + ICS)</td>
<td>OR=0.94 (0.52 to 1.73)</td>
<td>Subgroup analysis of data from studies with same dose of ICS</td>
</tr>
<tr>
<td>Cates20</td>
<td>14 (7/7)</td>
<td>10816</td>
<td>Formoterol + ICS vs ICS</td>
<td>4–12 months</td>
<td>1 event (formoterol + ICS)</td>
<td>1 event (formoterol + ICS)</td>
<td>OR=0.68 (0.39 to 1.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cates21</td>
<td>33 (30/3)</td>
<td>12046</td>
<td>Salmeterol + ICS vs ICS</td>
<td>4–14 months</td>
<td>OR=1.05 (0.32 to 3.47)</td>
<td>No events</td>
<td>OR=0.91 (0.50 to 1.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ni Chroinin22</td>
<td>16 (0/16)</td>
<td>4625</td>
<td>LABAs + ICS vs ICS</td>
<td>4–26 weeks</td>
<td>No events</td>
<td>No events</td>
<td>NS</td>
<td>OR=1.65 (0.83 to 3.25)</td>
<td>Subgroup analysis of data from studies with same dose of ICS in both arms</td>
</tr>
<tr>
<td>Ni Chroinin23</td>
<td>24 (20/4)</td>
<td>8163</td>
<td>LABAs + ICS vs ICS</td>
<td>4–52 weeks</td>
<td>No events</td>
<td>No events</td>
<td>NS</td>
<td>RR=1.13 (0.70 to 1.82)</td>
<td>Steroid-naive patients. Same dose of ICS in both arms</td>
</tr>
<tr>
<td>Ducharme24</td>
<td>77 (61/16)</td>
<td>21248</td>
<td>LABAs + ICS vs ICS</td>
<td>12–54 weeks</td>
<td>RR=2.46 (0.48 to 12.65)</td>
<td>NS</td>
<td>NS</td>
<td>RR=1.13 (0.70 to 1.82)</td>
<td>Subgroup analysis of data from studies with same dose of ICS in both arms</td>
</tr>
<tr>
<td>Jaescheke25</td>
<td>36</td>
<td>15372</td>
<td>LABAs + ICS vs ICS</td>
<td>NS</td>
<td>OR=1.34 (0.53 to 3.35)</td>
<td>2 events (LABA + ICS)</td>
<td>1 event (LABA + ICS)</td>
<td>OR=0.66 (0.41 to 1.05)</td>
<td>Subgroup analysis of data from studies with same dose of ICS in both arms</td>
</tr>
<tr>
<td>Jaescheke26</td>
<td>10</td>
<td>5334</td>
<td>Formoterol + ICS vs ICS</td>
<td>NS</td>
<td>4 events (formoterol + ICS)</td>
<td>1 event (formoterol + ICS)</td>
<td>No events</td>
<td>OR=0.46 (0.23 to 0.93)</td>
<td>Subgroup analysis of data from studies with same dose of ICS in both arms</td>
</tr>
<tr>
<td>Rodrigo27</td>
<td>32 (26/6)</td>
<td>18999</td>
<td>LABAs + ICS vs ICS</td>
<td>6–54 weeks</td>
<td>NS</td>
<td>3 events (LABA + ICS)</td>
<td>RR=1.44 (0.60 to 3.43)</td>
<td>RR=0.75 (0.52 to 1.09)</td>
<td>Subgroup analysis of data from studies with same dose of ICS in both arms</td>
</tr>
<tr>
<td>Salpeter28</td>
<td>7</td>
<td>7253</td>
<td>LABAs + ICS vs ICS</td>
<td>NS</td>
<td>NS</td>
<td>OR=3.65 (1.39 to 9.55)</td>
<td>NNTH=395 (208 to 9152)</td>
<td>NS</td>
<td>Studies with different comparisons and doses of ICS in both arms</td>
</tr>
<tr>
<td>Weatherall29</td>
<td>63</td>
<td>22600</td>
<td>LABA + ICS vs ICS</td>
<td>NS</td>
<td>OR=0.6 (0.2 to 2.4)</td>
<td>No events</td>
<td>No events</td>
<td>OR=1.0 (0.6 to 1.7)</td>
<td>Subgroup analysis of data from studies with same or higher dose of ICS</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; NNTB, number needed to benefit; NNTH, number needed to treat for harm; NS, not stated.
large randomised clinical study. The appropriate next step could be to conduct an adequately powered, well designed, prospective study to define the magnitude of the result resulting from treating patients with asthma with LABAs plus ICS versus the same dose of ICS alone. Kazani et al\(^38\) proposed that 50,000 patients with moderate or severe asthma should be enrolled in a randomised double-blind trial, with half of the patients treated with ICS and the other half treated with ICS plus LABAs. Enrolled patients should be followed until 20 severe asthma episodes or asthma deaths have occurred in the entire cohort. However, this proposed study would not have the power to definitively rule out a relative risk of less than fourfold because the sample size was based on data from LABA studies that did not mandate ICS use. In contrast, Sears\(^38\) states that a large trial is neither practicable nor necessary and will not provide any more useful data about adverse asthma events than those presently available. Based on data from the FDA meta-analysis,\(^4\) Sears has estimated the large sample sizes necessary for different outcomes (Table 5). The use of the FDA composite outcome of deaths, intubations and hospitalisations would introduce major difficulties in interpretation because data have shown that LABA use with concomitant randomised ICS is either neutral in risk for exacerbations (dominantly hospitalisations), or reduces risk.\(^5\)\(^23\)\(^25\)\(^27\) Therefore, using the composite outcome would produce results opposing those suggested by the worst-case interpretation of the mortality data.

### Observational studies

With rare outcomes of treatment, such as asthma mortality, the failure of different designs to detect associations may represent type II error, and so indicate a lack of statistical power rather than the absence of an association. Researchers should very cautiously interpret evidence of safety for a rare adverse event, such as asthma death with LABA use, based on the traditional categories of evidence. It has been established that in a real scenario, meta-analyses of RCTs and single large RCTs lack statistical power to detect or rule out this association.\(^39\) Case–control methodology may be a better approach because it requires a smaller sample size. However, the risks of bias are higher than those of a well designed RCT, or a properly conducted meta-analysis of RCTs.

### FDA 2010 NEW SAFETY REQUIREMENTS FOR LABAs

A case–control study of 552 patients who died from asthma found an association between asthma deaths and use of SABAs in the period 1–5 years prior to death\(^30\) without evidence of any positive association of LABAs in any period (3, 4–12 months and 1–5 years before death). Another case–control study used the UK’s General Practice Research Database (GPRD) (96,258 patients) to assess respiratory mortality and found the strongest association with heavy use of SABAs.\(^4\) Lanes et al\(^4\) performed an open cohort study with a nested case–control analysis in the UK based on the GPRD (14,657 patients). The authors concluded that salmeterol use was not associated with an increase in short-term mortality compared with the use of ipratropium and theophylline. Finally, Lang et al\(^4\) looked at data on asthma hospitalisations in Philadelphia from 1995 to 1999 and prescription rates for LABAs and other asthma drugs. The authors found that asthma hospitalisation was significantly associated with increased SABA prescriptions, poverty, area of residence, and African–American identity. By contrast, LABAs appeared to be protective, with lower rates of hospitalisation. However, asthma deaths are highly related to health behaviour, psychosocial factors,\(^44\) poor adherence, and the underuse of primary care services,\(^4\) and it is unlikely that sufficient information will be available in epidemiological datasets to deal completely with these biases. Finally, ecological analysis of asthma-related events and ICS dispensing observational data have shown a gradual reduction in asthma mortality in the USA since 2000, in the setting of a marked increase in LABA use predominantly in combination therapy.\(^46\)

A novel approach has recently been developed to describe the patterns of hazard rates of asthma outcomes with changes in exposures.\(^47\) This pattern analysis focuses on the convergence or divergence of hazard rates rather than on estimating relative rates. The objectives of this study were to describe the patterns of risk of death and asthma outcomes with exposure to different asthma medications in general practice, and to statistically compare these patterns of risk among LABAs, inhaled SABAs and ICS. The study population included patients receiving \(\beta\)-agonist treatment aged 18 years and over in the UK GPRD (507,966 patients), which is linked to the national registry of hospitalisations. The mortality rate increased with the least and most severe treatment steps. Higher relative rates of outcomes were found in patients who had recently started treatment and in those receiving long-term LABA, SABA and ICS treatment. The relative death rate was statistically similar over time between LABAs and ICS despite differences in exposure. There were no statistically significant increases in the risk of death and asthma outcomes with LABAs compared with other asthma medications.

### Table 4 Risk differences per 10,000 patients for asthma-related deaths and intubations (adapted from GlaxoSmithKline\(^30\))

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Salmeterol vs placebo (no ICS)</th>
<th>Salmeterol + ICS vs ICS</th>
<th>Salmeterol + LABA vs ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n N</td>
<td>n N</td>
<td>n N</td>
</tr>
<tr>
<td>Salmeterol vs placebo (no ICS)</td>
<td>8 9463</td>
<td>0 8932</td>
<td>0 8932</td>
</tr>
<tr>
<td>Salmeterol + ICS vs ICS</td>
<td>5 10264</td>
<td>3 10135</td>
<td>10 10264</td>
</tr>
<tr>
<td>Salmeterol + LABA vs ICS</td>
<td>1 2841</td>
<td>0 3040</td>
<td>20 10264</td>
</tr>
<tr>
<td>Salmeterol Comparator Asthma-related deaths</td>
<td>8.79 (6.23 to 5.80)</td>
<td>2.03 (12.17 to 16.22)</td>
<td>4.64 (28.77 to 38.04)</td>
</tr>
<tr>
<td>Salmeterol Comparator Asthma-related intubations</td>
<td>5.42 (13.67 to 24.52)</td>
<td>7.16 (10.08 to 24.39)</td>
<td>8.21 (25.91 to 42.33)</td>
</tr>
</tbody>
</table>

### Table 5 Sample sizes calculations for a new study comparing long-acting \(\beta\)2 agonists plus mandatory inhaled corticosteroids versus ICS alone (adapted from Kazani\(^38\))

<table>
<thead>
<tr>
<th>Risk difference</th>
<th>Clinical outcomes</th>
<th>Sample size (number of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 \times 1.00</td>
<td>1 excess asthma death</td>
<td>4384000</td>
</tr>
<tr>
<td>0.25 \times 1.00</td>
<td>1 excess asthma death or intubation</td>
<td>77000</td>
</tr>
<tr>
<td>0.25 \times 1.00</td>
<td>5 excess asthma deaths or intubations</td>
<td>770000</td>
</tr>
<tr>
<td>0.15 \times 1.00</td>
<td>5 excess asthma deaths or intubations</td>
<td>1200000</td>
</tr>
</tbody>
</table>

BK, background; ICS, inhaled corticosteroid; n, number of events; N, total sample; RD, risk difference; SD, single device; SP, separate inhaler devices.
implemented new recommendations about how LABAs should be used in the treatment of asthma.\(^4\) The specific label changes were:

1. the use of LABAs without the use of an asthma controller medication such as an ICS is contraindicated (absolutely advised against) in the treatment of asthma;
2. LABAs should only be used as additional therapy for patients with asthma who are currently taking a long-term asthma control medication, such as an ICS, but whose symptoms are not adequately controlled;
3. LABAs should be used for the shortest period of time required to achieve control of asthma symptoms and then discontinued, if possible, once asthma control is achieved; patients should then be maintained on asthma controller medication;
4. paediatric and adolescent patients who require the addition of an LABA to an ICS should use a combination product containing both an ICS and a LABA to ensure adherence to both medications.

These changes are based on FDA analyses of studies showing an increased risk of severe adverse effects in paediatric and adult patients using LABAs for the treatment of asthma.

These recommendations appropriately emphasize the risk associated with the use of LABA monotherapy (largely based on findings of SNS and SMART trials \(^6\) and meta-analysis).\(^7\)\(^8\)\(^9\)\(^10\)

Also, the FDA’s reminder that LABAs are not recommended as adjunct therapy in patients whose asthma is adequately controlled with low-dose ICS agrees with the National Asthma Education and Prevention Program’s Expert Panel Report-3 (EPR-3) guidelines.\(^11\) However, some of the new recommendations have caused confusion and do not appear to be fully evidence based.\(^12\)\(^13\)\(^14\) For example, the change proposed by the FDA in point 3 implies that once adequate control is achieved after the addition of an LABA to ICS therapy, initial consideration should be given to stepping down therapy by discontinuing the LABA. However, the EPR-3 and the Global Initiative for Asthma’s guidelines recommend that care is stepped down only after asthma control is achieved and maintained for a sufficient length of time (several months). The idea of stopping LABA use ‘once control is achieved’ suggests a quick or sudden withdrawal of therapy (LABAs) as soon as control is achieved. We must keep in mind that the concept of asthma control includes two different domains (impairment and risk), and that medications might affect the two in different ways, particularly in patients with severe asthma. In fact, evidence suggests that stopping LABAs after the achievement of asthma control results in the patient’s asthma becoming less controlled.\(^15\)

Recently, Reddel et al\(^16\) showed that patients with well-controlled asthma who are taking high doses of ICS plus LABAs can safely reduce the ICS dose to levels that are lower than advisable with ICS alone, without loss of asthma control or evidence of disease activity.

The FDA’s recommendation against LABA use in patients whose asthma is controlled with a low—medium dose of ICS is also controversial. Therefore, the EPR-5\(^17\) considers the choice of either increasing the dose of an ICS or adding a LABA as equal options for preferred step-up therapy. This recommendation is the result of weighing the benefits of combining LABAs and low-dose ICS therapy and the infrequent risk of serious adverse events. In effect, there is a large body of evidence that supports the superior effectiveness of adding LABAs to low-dose ICSs rather than increasing the dose of ICSs, even in preschoolers and school children with moderate to severe asthma, and in adults with asthma.\(^18\)\(^19\)\(^20\) Finally, it is difficult to understand why the FDA recommended the use of combination products in a single device only in children and adolescents. The difficulty of ensuring compliance might apply to all age groups. Actually, there are no data to indicate a higher risk exclusively in the paediatric population. Compliance to treatment is a crucial issue of the therapeutic process that can increase the risk of serious adverse effects. It has been suggested that adherence profiles of ICS plus LABAs in a single inhaler are significantly better when compared with the controller regimens in separate inhalers.\(^21\)

**Conclusions**

Based mainly on the safety concerns arising from the SNS and SMART\(^22\)\(^6\)\(^7\) studies, some authors have suggested withdrawing LABA use for asthma therapy. However, these serious events have been infrequent and appeared when LABAs were used as monotherapy. By contrast, evidence from RCTs, meta-analysis of RCTs and observational studies, although limited by low statistical power, have indicated that the use of combination therapy (LABAs plus ICS) is associated with a decreased risk of serious asthma-related events. This is particularly true when the concomitant use of LABAs plus ICS can be reasonably assured (combined in a single inhaler). Therefore, the use of separate inhalers could result in periods of LABA monotherapy because of poor compliance with ICS use. Combination therapy could reduce asthma mortality by increasing the prescription and increasing compliance with ICS in the community. Furthermore, combination therapy should be applied to all patients with moderate to severe asthma, and not just paediatric and adolescent patients, as suggested by the FDA guidelines.

**Funding**

This study came from salary support for Drs Rodrigo and Castro-Rodriguez.

**Competing interests**

This study came from salary support for Drs Rodrigo and Castro-Rodriguez. They have received consultation fees for work on this project from Almirall. JCR received consultation fees from Almirall. JCR has received support for presentations at scientific meetings and some honoraria, and is a member of the scientific advisory board of Bial, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and the International Study Group on Formoterol. JCR is a member of the scientific advisory board of Bial, Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and the International Study Group on Formoterol. JCR has received presentation fees and expense reimbursement for work on this project. JCR has received honoraria for serving on the editorial board of Asthma, Allergy & Lung Health. JCR has received presentation fees for work on this project.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**References**

Review


Safety of long-acting β agonists for the treatment of asthma: clearing the air

Gustavo J Rodrigo and José A Castro-Rodríguez

Thorax published online April 21, 2011

Updated information and services can be found at: http://thorax.bmj.com/content/early/2011/04/21/thx.2010.155648

These include:

Supplementary Material
Supplementary material can be found at: http://thorax.bmj.com/content/suppl/2011/01/20/thx.2010.155648.DC1

References
This article cites 42 articles, 9 of which you can access for free at: http://thorax.bmj.com/content/early/2011/04/21/thx.2010.155648#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Asthma (1782)
- Child health (843)
- Medicines regulation (22)
- Drugs: respiratory system (526)

Notes

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: http://group.bmj.com/subscribe/