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REVIEW

The safety of long-acting β_2-agonists in the treatment of stable chronic obstructive pulmonary disease

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Background: Inhaled long-acting bronchodilators are the mainstay of pharmacotherapy for chronic obstructive pulmonary disease (COPD). Both the twice-daily long-acting β_2-adrenoceptor agonists (LABAs) salmeterol and formoterol and the once-daily LABA indacaterol are indicated for use in COPD. This review examines current evidence for the safety of LABAs in COPD, focusing on their effect on exacerbations and deaths.

Methods: We searched PubMed for placebo-controlled studies evaluating long-term (≥24 weeks) use of formoterol, salmeterol, or indacaterol in patients with stable COPD, published between January 1990 and September 2012. We summarized data relating to exacerbations and adverse events, particularly events related to COPD.

Results: From 20 studies examined (8774 LABA-treated patients), there was no evidence of an association between LABA treatment and increased exacerbations, COPD-related adverse events, or deaths. Where analyzed as an efficacy outcome, LABA treatment was generally associated with significant or numerical reductions in COPD exacerbations compared with placebo. Incidences of COPD-related adverse events were similar for active and placebo treatments. The incidence of adverse events typically associated with the β_2-agonist drug class such as skeletal muscle tremors and palpitations was low (often <1% of patients), and there were no reports of increased incidence of cardiac arrhythmias. The systemic effects of β_2-adrenoceptor stimulation, such as high glucose and potassium levels, were considered minor.

Conclusion: Current evidence from clinical studies of the safety and tolerability profile of LABAs supports their long-term use in COPD.

Keywords: LABA, formoterol, salmeterol, indacaterol, bronchodilator, COPD

Background

Chronic obstructive pulmonary disease (COPD) affects more than 200 million people worldwide, is currently the third-leading cause of mortality in the USA,[1] and is predicted to become the third most frequent cause of death globally by 2030.[2] COPD is characterized by alveolar destruction, loss of alveolar attachments, loss of elastic recoil, and increased airway resistance, which leads to expiratory flow limitation and inadequate lung emptying on expiration, resulting in lung hyperinflation.[3] Static hyperinflation occurs during resting breathing, and dynamic hyperinflation is brought about by increased ventilation, such as occurs during exercise.[4]

Current guidelines for the treatment of patients with moderate or more severe COPD recommend the use of one or more long-acting bronchodilators.[5] These agents are central to the management of COPD and are used on a regular basis for maintenance treatment. The inhaled long-acting bronchodilators include the long-acting

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β_2-agonists (LABAs). LABAs act primarily to relax airway smooth muscle by stimulating β_2-adrenergic receptors and providing functional antagonism to bronchoconstriction.[6] The resulting bronchodilation leads to increased functional lung capacity (via lung deflation), lessening the dyspnea and the limitations placed upon patients' ability to undertake everyday activities.[7–11]

In COPD, LABAs have been shown to provide significant improvements to airway obstruction and patient-reported outcomes.[7,12–14] Currently available inhaled LABAs include salmeterol and formoterol, which have a 12-hour duration of effect and are administered twice daily, and indacaterol, which provides 24-hour bronchodilation on once-daily dosing. While the older agents, salmeterol and formoterol, are indicated for use in both asthma and COPD,[6,15–18] indacaterol (currently approved for use in all major markets, including the US) is indicated for use as monotherapy in COPD only.[19] The position of LABAs in asthma and COPD therapy differs. In asthma, LABAs are used only as add-on therapy to inhaled corticosteroids (ICSs) in patients who are not well controlled on ICSs alone. In COPD, the use of long-acting bronchodilators, including LABA monotherapy, is considered as a first-line maintenance treatment option. Correct diagnosis is clearly important in determining the appropriate management strategy.[20] The choice of treatment strategy should also take into consideration that the COPD population tends to be older and multiple comorbidities are common.[21]

In contrast to the treatment of COPD, first-line maintenance pharmacotherapy for asthma is ICSs, which, unlike in COPD, have been shown to reduce disease progression in asthma.[22] Asthma is characterized by reversible bronchoconstriction[6] and bronchodilators are used with the aim of reversing bronchoconstriction to provide symptom relief, as well as blocking the bronchoconstrictor effects of common triggers such as allergens and exercise.[23] While undoubtedly effective in this role, there is evidence that LABA monotherapy (ie, without ICSs) in asthma may increase the risk of life-threatening exacerbations and respiratory-related death.[24–26] This led to the warning by the US Food and Drug Administration (FDA) that LABAs should be used in asthma only in combination with an ICS.[27] A warning to this effect was added to the labels of formoterol and salmeterol, which have common labeling for the two conditions. Not surprisingly, this has led to some confusion about whether the warning applies to COPD as well.

While the warnings about the use of LABA monotherapy in asthma have triggered concerns over the safety of LABAs in patients with COPD, the differences in etiology, pathophysiology, disease progression, and outcomes mean that the safety of LABAs in COPD and asthma needs to be evaluated separately. Further, the newer once-daily LABA indacaterol is indicated only in COPD. It is therefore timely to review the available literature on the safety of LABAs in patients with COPD, with the principal aim of determining if LABA use is associated with an increased level of COPD exacerbations or COPD-related adverse events in comparison with placebo.

Methods

To provide the basis for a comprehensive narrative review, we searched the literature to retrieve full-length articles published from January 1990 to date (end of September 2012) relating to randomized, placebo-controlled clinical studies with a LABA (formoterol, salmeterol, or indacaterol) treatment arm and of at least 24 weeks' duration. The limit of 24 weeks was chosen to provide the most robust data for the assessment of treatment effect on COPD exacerbations[28] and drug safety, and will likely better reflect drug use in clinical practice. Other treatment arms in the studies were not considered. Initially, a search of the PubMed database was performed then confirmatory database searches were made of Web of Science, Embase, and Biosis Previews. Results were checked against the PubMed results and duplicates deleted. Remaining results were checked manually for relevance. Articles were selected for inclusion based on the relevance of their abstracts. Studies meeting the criteria were not screened further for eligibility.

The publications were scrutinized for deaths, all adverse events, and serious adverse events, with the focus on events related to COPD. We included data for exacerbations of COPD recorded as an efficacy outcome and for adverse events related to COPD. "COPD exacerbations" are usually rigorously defined as an efficacy endpoint in clinical studies, although definitions vary between studies. The most commonly used definition is a worsening of symptoms for 2 or more days and requiring additional treatment (eg, oral corticosteroids and/or antibiotics). They can be graded for severity – for example, in terms of the need for emergency treatment or hospitalization. Episodes of "COPD-related adverse events", including exacerbations captured as adverse events, may be self-reported or judged by clinicians on the basis of patient diaries. A "serious event" is formally defined in a clinical trial, for example, as an event that is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a birth defect, requires inpatient hospitalization or prolongation of existing hospitalization,

or is medically significant. We also considered the adverse events that may be regarded as typical of the β_2-agonist class and the question of cardiovascular safety of these agents, given that patients with COPD often have cardiovascular comorbidities.[29]

Data were summarized and not subjected to further analysis. No calculations were performed for this narrative review, and all reported data are from the cited source material.

Results

The search strategy yielded 21 studies from PubMed (Table 1). The additional databases did not yield further articles of interest. One of the studies was excluded because of very small patient numbers (six patients treated with LABA).[30] The studies included in this analysis (Table 2) had similar patient populations; that is, predominantly male (>60%), mean age between 60 and 64 years, and with moderate-to-severe COPD (defined as forced expiratory volume in 1 second [FEV_1] of ≥30%–80% of predicted value).

Mortality

In the 3-year Towards a Revolution in COPD Health (TORCH) study,[7] mortality in subjects taking the LABA was not significantly different from that in patients on placebo, with reported hazard ratios versus placebo of 0.88 (95% confidence interval [CI] 0.73–1.06) for all-cause mortality and 1.01 (95% CI 0.76–1.35) for respiratory-related death. Causes of death (LABA vs placebo) were cardiovascular (5% vs 3% of patients), pulmonary (5% vs 5%), and cancer (3% vs 3%). Similar mortality results were observed for the LABA plus ICS combination versus placebo.[7] A similar pattern was observed in most of the studies reviewed (Table 3), although not all publications reported causes of death. Only one study appeared to show an excess of deaths with LABA (formoterol) treatment compared with placebo (13 versus five deaths);[31] the authors stated that most of these events were related to COPD, and that investigation into individual causes of death did not explain the apparent difference between the groups.

Elsewhere, there are reports of modest and occasionally significant reductions in mortality with LABA treatment in COPD. A meta-analysis of published mortality data (including many of the studies reviewed here) reported a nonsignificant reduction for LABA versus placebo (hazard ratio 0.9 [95% CI 0.77–1.06]),[32] indicating that there was no increased risk of death associated with LABA therapy in COPD. Similar findings were reported by Donohue et al[33] in an analysis of pooled data from the indacaterol clinical-trial database, with statistically significant or numerical reductions in relative risk with LABAs versus placebo.

Lee and colleagues analyzed a large cohort of outpatients with COPD (over 32,000 treated patients and 320,501 control patients) and reported that LABAs were associated with a significant reduction in all-cause mortality compared with no treatment or with short-acting β_2-agonists alone (odds ratio 0.92 [95% CI 0.88–0.96]).[34] A smaller analysis of longitudinal data from a US health care database also found significantly improved survival among 531 patients using a LABA alone compared with a cohort of 1832 patients using only a short-acting bronchodilator.[35]

Table 1 Study selection[a]

	FOR	SLM	IND
Retrieved (total)	154	225	42
Excluded	144	216	38
Acute (eg, single dose)	30	30	6
Already listed (eg, pooled studies)	2	1	–
No LABA as single treatment arm	–	10	–
No LABA as single treatment, no placebo	–	5	–
No placebo	9	20	–
Not relevant	50	65	7
Of other interest (eg, meta-analysis)	1	2	2
Other (eg, journal club)	1	2	–
Review	9	9	7
Secondary study report	–	20	–
Too short	23	28	14
Too short, no single treatment arm, no placebo	–	1	–
Too short, no placebo	19	23	2
Included	10	9	4[b]

Notes: [a]Only single reasons included here although articles may have qualified for exclusion for multiple reasons; [b]two of these studies also feature in the FOR and SLM columns.

Abbreviations: FOR, formoterol; SLM, salmeterol; IND, indacaterol; LABA, long-acting β_2-agonist.

COPD exacerbation as efficacy outcome and adverse event

Treatment effects on COPD exacerbations as an efficacy outcome are summarized in Table 2. Formoterol had some significant beneficial effects compared with placebo on outcomes defining milder exacerbations, with little difference versus placebo for more severe exacerbations. In the large 3-year TORCH study, salmeterol significantly reduced the rate of all grades of exacerbations relative to placebo, including those requiring hospitalization;[7] most of the other studies showed similar effects between active and placebo treatment or numerical reduction with salmeterol over placebo. Indacaterol treatment was associated with significant or numerical reductions in exacerbations versus placebo.

COPD-related adverse events were the most commonly reported adverse events in the studies reviewed (Table 3).

Table 2 Effect of treatment on COPD exacerbations (as efficacy outcome)

Reference	Exclusion criteria for asthma	ICS allowed[a] (% of patients)	n (LABA/PBO)	Exacerbations (LABA vs PBO)
FOR 9, 10, or 12 µg bid				
Rossi et al[68]	Current or childhood asthma according to American Thoracic Society criteria	Y (47)	211/220	~32% vs ~41% of days (mild)[b] 7% vs 8% of days (moderate) 32% vs 34% of pts (additional therapy) 10 vs 20 hospitalizations
Szafranski et al[69]	History of asthma and/or seasonal allergic rhinitis before the age of 40 years	N	201/205	1.84 vs 1.87 per pt-yr (severe)
Calverley et al[31]	History of asthma/seasonal allergic rhinitis before the age of 40 years	N	255/256	154 vs 96 days (time to first exacerbation) 1.85 vs 1.80 per pt-yr (total) 0.91 vs 1.14 per pt-yr (oral steroids)
Campbell et al[70]	History of asthma or seasonal allergic rhinitis	Y (47)	215/217	16.3% vs 15.7% of pts (≥1 severe)
Tashkin et al[71]	History of asthma or seasonal allergic rhinitis before the age of 40 years	N	284/300	1.098 vs 1.110 per pt-yr (all) 1.104 vs 1.068 per pt-yr (oral steroids)
Vogelmeier et al[72]	Not stated	Y	210/209	24.9% vs 33.9% "bad days"[b] 2.4% vs 4.7% "exacerbation days"[b] 8.1% vs 14.4% of pts (additional therapy) 0.5% vs 1.4% (hospitalizations)
Rennard et al[73]	History of asthma or seasonal allergic rhinitis before the age of 40 years	N	495/481	~0.75 vs ~0.88 per pt-yr
Dahl et al[39]	History of asthma	Y (51)	435/432	31.5% vs 36.3% of pts (≥1 exacerbation) 0.56 vs 0.74 per yr[b]
Doherty et al[74]	Current diagnosis of asthma	N	243/236	40% vs 46% of pts (total) 18% vs 25% of pts (moderate/severe as first event)
Tashkin et al[75]	Current diagnosis of asthma; increase in FEV_1 ≥400 mL post-salbutamol	N	209/212	ND
FOR 24 µg bid				
Rossi et al[68]	Current or childhood asthma according to American Thoracic Society criteria	Y (47)	214/220	~34% vs ~41% "bad days"[b] 4% vs 8% of days (moderate)[b] 23% vs 34% of pts (additional therapy) 5 vs 20 hospitalizations
SLM 50 µg bid				
Mahler et al[76]	Current diagnosis of asthma	N	160/181	No significant difference (time to first)
Chapman et al[77]	Not stated	Y (68)	201/207	26% vs 33% of pts (>1 exacerbation) 13% vs 18% of pts (oral steroids)
Calverley et al[78]	Not stated	N	372/361	1.04 vs 1.30 per pt-yr (total)[b] 0.54 vs 0.76 per pt-yr (oral steroids)[b]

Brusasco et al[79]	Patients with a history of asthma, allergic rhinitis, atopy, or with an increased total eosinophil count	ND	405/400	35% vs 39% of pts (≥1 exacerbation) 24.1 vs 25.0 "exacerbation days" per pt-yr 13.8% vs 14.5% of pts (oral steroids) 5% vs 5% of pts (hospitalization) 1.23 vs 1.49 per pt-yr (total) 0.17 vs 0.15 per pt-yr (hospitalization)
Hanania et al[80]	Current diagnosis of asthma	N	177/185	No significant differences (number or time to first)
Stockley et al[81]	Not stated	Y (54)	316/318	0.58 vs 0.83 per pt-yr (moderate/severe)[b]
Calverley et al[7]	Increase in FEV_1 with salbutamol <10% of predicted value; diagnosis of asthma	N	1521/1524	0.97 vs 1.13 per pt-yr (moderate/severe)[b] 0.64 vs 0.80 per pt-yr (systemic steroids)[b] 0.16 vs 0.19 per pt-yr (hospitalization)[b]
Kornmann et al[40]	History of asthma	Y (46)	333/335	34.1% vs 38.1% "days of poor COPD control"
IND 150 µg od				
Donohue et al[41]	History of asthma	Y (38)	416/418	17.3% vs 21.8% of pts (≥1 exacerbation) Hazard ratio 0.69[b] (time to first) 0.50 vs 0.72 per pt-yr[b]
Kornmann et al[40]	History of asthma	Y (45)	330/335	34.1% vs 38.1% "days of poor COPD control"
Chapman et al[42]	History of asthma	Y (34)	144/124	0.39 vs 0.54 per pt-yr[b]
IND 300 µg od				
Dahl et al[39]	History of asthma	Y (56)	437/432	32.8% vs 36.3% of pts (≥1 exacerbation) Hazard ratio 0.77[b] (time to first) IND 300, 0.60 vs 0.74 per pt-yr
Donohue et al[41]	History of asthma	Y (37)	416/418	18.3% vs 21.8% of pts (≥1 exacerbation) Hazard ratio 0.74 (time to first) 0.53 vs 0.72 per pt-yr
Chapman et al[42]	History of asthma	Y (34)	146/124	0.38 vs 0.54 per pt-yr[b]
IND 600 µg od				
Dahl et al[39]	History of asthma	Y (53)	428/432	29.3% vs 36.3% of pts (≥1 exacerbation) Hazard ratio 0.69[b] (time to first) 0.57 vs 0.74 per pt-yr[b]

Notes: [a]Patients permitted to continue on stable doses of inhaled corticosteroids; [b]significant difference favoring active over placebo treatment. "~" = estimated from graphical data.
Abbreviations: bid, twice daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FOR, formoterol; ICS, inhaled corticosteroids; IND, indacaterol; LABA, long-acting β_2-agonist; N, no; ND, not disclosed; od, once daily; PBO, placebo; pt, patient; SLM, salmeterol; Y, yes; yr, year.

Table 3 Reported safety outcomes (LABA versus PBO)

Study	Deaths (n)	SAEs[a]		AEs	
		All	COPD	All	COPD
FOR 9, 10 or 12 µg bid					
Rossi et al[68]	3 vs 0	11% vs 15%	ND	66% vs 67%	16% vs 15%
Szafranski et al[69]	6 vs 9	18% vs 18%	ND	ND	19% vs 26%
Calverley et al[31]	13 vs 5	85 vs 66 events	55 vs 38 events (29% vs 31%)	6 vs 5 events/1000 days	ND
Campbell et al[70]	2 vs 1	13 vs 9 pts	ND	3.8 vs 4.5 events/1000 days	ND
Tashkin et al[71]	1 vs 1	8% vs 8%	4% vs 4%	57% vs 51%	18% vs ND
Vogelmeier et al[72]	0 vs 1	8%–10% vs ND	2% vs 3%	34% vs 39%	10% vs 16%
Rennard et al[73]	4 vs 4	18% vs 12%	8% vs 6%	60% vs 56%	17% vs 16%
Dahl et al[39]	3 vs 4	16% vs 11%	7% vs 5%	65% vs 62%	31% vs 35%
Doherty et al[74]	4 vs 2	8% vs 9%	2% vs 5%	38% vs 40%	ND
Tashkin et al[75]	3 vs 1	8% vs 6%	3% vs 3%	34% vs 32%	ND
FOR 24 µg bid					
Rossi et al[68]	1 vs 0	7% vs 15%	ND	64% vs 67% pts	12% vs 15%
SLM 50 µg bid					
Mahler et al[76]	0 vs 3	4%–7% overall	ND	73% vs 69%	ND
Chapman et al[77]	ND	ND	ND	72% vs 71%	20% vs 22%
Calverley et al[78]	ND	ND	ND	78%–81% overall	ND
Brusasco et al[b,44,79]	6 vs 5	12% vs 14%	6% vs 6%	75% vs 77%	37% vs 41%
Hanania et al[80]	0 vs 0	3% vs 6%	ND	69% vs 64%	ND
Stockley et al[81]	6 vs 5	10% vs 12%	ND	45% vs 51%	ND
Calverley et al[7]	14 vs 15	40% vs 41%	ND	90% vs 90%	0.76 vs 0.92 per yr
Kornmann et al[40]	0 vs 3	6% vs 8%	1% vs 3%[c]	46% vs 47%	15% vs 19%
IND 150 µg od					
Donohue et al[41]	1 vs 0	8% vs 8%	3% vs 2%	67% vs 64%	18% vs 22%
Kornmann et al[40]	1 vs 3	9% vs 8%	2% vs 3%[c]	51% vs 47%	18% vs 19%
Chapman et al[42]	0 vs 1	10% vs 11%	3% vs 2%	76% vs 68%	24% vs 27%
IND 300 µg od					
Dahl et al[39]	1 vs 4	14% vs 11%[c]	4% vs 5%[c]	71% vs 62%	32% vs 35%
Chapman et al[77]	1 vs 1	12% vs 11%	3% vs 2%	77% vs 68%	27% vs 27%
Donohue et al[41]	0 vs 0	8% vs 8%	2% vs 2%	66% vs 64%	18% vs 22%
IND 600 µg od					
Dahl et al[39]	0 vs 4	12% vs 11%[c]	3% vs 5%[c]	65% vs 62%	28% vs 35%

Notes: Percentages are % of patients. [a]Defined variably between the studies, eg, the studies with indacaterol include deaths; [b]additional safety data from FDA.[82] [c]data supplied by Novartis Pharma AG.

Abbreviations: AE, adverse event; bid, twice daily; COPD, chronic obstructive pulmonary disease; FOR, formoterol; IND, indacaterol; LABA, long-acting β_2-agonist; ND, not disclosed; od, once daily; PBO, placebo; pt, patient; SAE, serious adverse event; SLM, salmeterol; yr, year.

The incidence of COPD-related adverse events was either very similar between active and placebo treatments or numerically higher with placebo than with a LABA in those studies that disclosed this information. The same pattern was observed for COPD-related serious adverse events, apart from in one study in which there were more events with formoterol (85 vs 66 events per year), although the incidence was similar with formoterol and placebo (29% vs 31% of patients, respectively).[31]

Most (17/20) of the clinical studies reviewed here were included in a formal meta-analysis by Wang et al,[36] who adopted similar search criteria (≥6-month studies, LABA versus placebo) to evaluate the effect of LABAs on frequency of exacerbation, although the largest and longest study, TORCH, was excluded from the analysis. Results showed a significant reduction in exacerbations with individual LABAs versus placebo and for LABAs overall (odds ratio 0.81 [95% CI 0.75–0.88]). Donohue et al[33] examined a database of pooled clinical-trial data (all data from studies ≥12 weeks' duration) with indacaterol and LABA comparators salmeterol and formoterol and found that the incidence of COPD-related adverse events with all LABAs was significantly lower than with placebo. Similarly, rates of COPD exacerbations (as an efficacy outcome) were significantly reduced with all LABAs compared with placebo.[33]

Cardiovascular safety

The studies reviewed here were inconsistent in their level of detail and do not provide a useful overview of

the cardiovascular safety profile of LABA treatment in COPD, although this has been the subject of separate investigations. In a secondary analysis of the TORCH study data,[37] the investigators found that the occurrence of a new cardiovascular event was no more frequent with a LABA than with placebo. In that analysis, for salmeterol and placebo respectively, similar proportions of patients had serious cardiovascular events (11% vs 11%), any cardiovascular event (18% vs 19%), and ischemic cardiovascular events (11% vs 11%). Fewer deaths with salmeterol were due to cardiovascular causes (3% vs 5% with placebo). The study population included 7% of patients who reported a history of previous myocardial infarction and 41% were taking cardiovascular medications.

The cerebro- and cardiovascular (CCV) safety of the once-daily LABA indacaterol was reviewed, using pooled 6-month data from four clinical studies with 3035 patients treated with indacaterol and the twice-daily LABAs.[38] Many patients (20%) had pre-existing CCV conditions, and CCV risk factors such as hypertension (50%) and high body mass index (23%) were common. Relative to placebo, no significant increase was detected in the risk of CCV adverse events or serious CCV adverse events with indacaterol. Electrocardiogram measurements of QTc interval were also reported, since QTc interval prolongation is an indication of possible arrhythmogenic effects. With all the LABAs, the incidence of notable values was low and similar to placebo. Increases of >60 ms occurred in 0.1%–0.3% of patients receiving indacaterol and 0.3% of placebo patients.[38] An analysis of major cardiovascular adverse events (all terms relating to myocardial infarction, cerebrovascular events, and nervous system hemorrhages) with indacaterol and the twice-daily LABAs, using pooled data from all studies of ≥12 weeks' duration, reported a nonsignificant reduction with all LABAs relative to placebo.[33]

Other adverse events

The overall proportion of patients experiencing all-cause adverse events was 60%–80% for the majority of studies, with a similar incidence between treatment groups for overall adverse events and serious adverse events (Table 3). Many of the other most common adverse events, when reported, may also be considered disease related and typically included respiratory tract infections, nasopharyngitis, and cough, although there was some variability, even between studies evaluating the same agents.

The adverse events typically associated with β_2-adrenoceptor agonists were reported in very few of the studies reviewed. Although tremors, tachycardia, and palpitations are considered the more common adverse events associated with β_2-agonists, they occurred at very low rates when reported, often in <1% of patients in each treatment group. Headache and muscle spasms were occasionally reported in approximately 5% of patients but were not a consistent feature of LABA treatment.

The clinical studies with indacaterol consistently reported the effects of all three LABAs on plasma potassium and blood glucose,[39–42] so provide a useful basis for comparison (as with the majority of studies in this analysis, patients with cardiac disorders judged to be clinically significant or uncontrolled were excluded from these studies). The incidence of clinically notable low levels of plasma potassium (<3.0 mmol/L) was 0%–0.7% of patients treated with indacaterol (at daily doses up to 600 µg, several times higher than licensed), 0% with formoterol, 0.6% with salmeterol, and 0%–0.7% with placebo. High blood glucose (>9.99 mmol/L) occurred in 6%–13% of patients treated with indacaterol, 7% with formoterol, 9% with salmeterol, and 6%–8% with placebo.

Discussion

This overview suggests that long-term LABA treatment in patients with COPD is well tolerated and has an acceptable safety profile. Overall, in the clinical trials reviewed, there were few deaths during the studies and no indication that LABAs were associated with increased mortality in these controlled settings. Further, the majority of studies reviewed reported reductions in exacerbations or exacerbations requiring hospitalization or additional medication during LABA treatment compared with placebo.

In the studies reviewed here, death was a primary outcome in only one. In the 3-year TORCH study,[7] mortality with the LABA was not significantly different from placebo, and the overall causes of death (pulmonary and cardiovascular events and lung cancer) are typical of any population of patients with COPD, in whom deaths are primarily related to cardiovascular diseases, lung cancer, and, in more severe COPD, respiratory failure,[43] a pattern that reflects the common comorbidities. Many of the reported deaths in the studies reviewed fall into the cardiovascular or respiratory categories. However, to investigate overall mortality, studies of longer duration than most of those considered here are required, and the small numbers of reported deaths prevent a clear picture emerging. Overall, from the clinical study data reviewed, we detected no indication of increased mortality with LABA treatment in patients with COPD.

Although some of the studies reviewed here did not disclose the cause of death, in those that did, the incidence of

cardiovascular deaths was low. The subject of cardiovascular safety is important, since concerns have been raised that β_2-agonists may precipitate ischemia, congestive heart failure, arrhythmias, and sudden death via β_2-adrenoceptor stimulation,[44–46] especially because of the common occurrence of cardiovascular disease as a comorbidity in COPD.[29] Data provided by the TORCH study[37] and pooled clinical-trial databases[33,38] suggest that LABAs incur little if any additional cardiovascular safety signal compared with placebo in the treatment of COPD. However, a retrospective cohort case-control analysis of elderly (≥67 years) patients with COPD who developed severe cardiac arrhythmia (cases) compared with those who did not (controls) found that rate of arrhythmia was modestly elevated with use of the LABAs salmeterol or formoterol (rate ratio 1.47; 95% CI, 1.01–2.15),[47] emphasizing the importance of considering comorbidities when treating patients with COPD.[5]

Furthermore, the more recent clinical studies with LABAs, unlike earlier studies, included patients with pre-existing cardiovascular morbidity.[33,37,38] Nevertheless, LABAs should always be used with caution in patients with pre-existing cardiovascular disease. Many of the studies reviewed here did not separate out causes of serious adverse events. In the few that did, COPD-related serious adverse events (ie, including exacerbations leading to hospitalization) generally occurred in similar or slightly smaller proportions of patients treated with LABAs compared with placebo. COPD-related adverse events were, in nearly every study reviewed here, less common with LABA treatment than with placebo. Additional evidence may be gained from considering COPD exacerbations analyzed as an efficacy outcome, with many of the studies reviewed here reporting significant reductions in exacerbations with LABA treatment. One of the main objectives of COPD management is to reduce the severity and the frequency of exacerbations, which are among the commonest causes of hospital admission and death in patients with COPD.[7,48,49] We could not detect any evidence of any association between LABA treatment and increased risk of COPD exacerbations in the clinical studies reviewed.

The difference in risk associated with LABA treatment in asthma and COPD remains to be explained but is perhaps not surprising, given that the two diseases differ in many aspects, including causes, sites, inflammatory cells, mediators, and inflammatory consequences. With so many differences between asthma and COPD, it also should not be surprising that they differ in their response to treatment. A key characteristic of asthma is the increased volume of airway smooth muscle,[50,51] and the hyperresponsiveness to bronchoconstrictor mediators is more prominent in asthma than COPD.[52] One important difference between asthma and COPD, which could also help explain the difference in safety, is the difference in mechanisms of progression of exacerbations. Exacerbations typically progress with a gradually increasing degree of airflow obstruction and need for rescue bronchodilator therapy in asthma, whereas a typical COPD exacerbation is associated with increased mucus production. A bronchodilator such as a LABA could therefore hide the early symptoms of an asthma exacerbation, delaying patients from intensifying their use of anti-inflammatory preventive medications. In the worst case scenario, the microenvironmental concentration of bronchoconstrictor mediators associated with the asthma attack could override the effects of the therapeutic bronchodilators, leading to catastrophic bronchoconstriction.[53] This could also explain the protective effect of ICSs when given with LABA treatment in asthma. Another possible factor implicated in the negative effects of β_2-agonist use in asthma is β_2-adrenoceptor sub-sensitivity, which may become clinically important during conditions of increased bronchomotor tone such as an exacerbation.[54] In contrast, in COPD, the benefits of β_2-agonists may more largely depend on bronchodilator-induced reduction in hyperinflation rather than bronchodilation per se,[55] and COPD exacerbations are not associated with excessive bronchoconstrictor mediators in the bronchial microenvironment.

Another hypothesis for the different risk associated with LABA treatment in asthma and COPD is that it is persistent activation (rather than desensitization) of the β_2-adrenergic receptor that leads to the development of airway hyperresponsiveness and allergic inflammation, which are cardinal features of asthma but not of COPD. A study in transgenic mice overexpressing the airway smooth muscle β_2-adrenoceptor found that chronic β_2-activation led to cross-talk with the bronchoconstrictor pathway and a gain in contractile signaling, leading to enhanced airway responsiveness to bronchoconstrictor stimuli.[56] In addition, in a mouse model, β_2-adrenoceptor signaling was required for the development of an asthma phenotype.[57] In further support of this hypothesis, chronic dosing with non-selective β-blockers in mice and in patients with mild asthma led to a reduction in airway hyperresponsiveness to methacholine challenge.[58,59]

In a clinical trial setting, inclusion criteria are very specific when studying either COPD or asthma, thus such studies exclude patients with mixed asthma and COPD,

estimated to coexist in approximately 10% of the COPD population,[20] particularly in older patients.[60] Given the lack of data for this small patient population, and considering the concerns over the safety of LABA monotherapy in asthma, patients with "true" mixed disease should not be managed solely with LABA monotherapy but should have background ICS therapy. Differential diagnosis of each condition is important for treatment.[20] The use of ICSs in combination with LABAs in COPD is recommended for high-risk patients with severe airflow limitation and repeated exacerbations, on the basis of established efficacy in preventing exacerbations in patients with more severe disease.[5] More widespread use is not recommended in patients with COPD, given that these agents are not effective anti-inflammatories in COPD and that the often-elderly population of patients with COPD may be more prone to suffer serious ICS-induced side effects such as pneumonia.[7,48,49,61] Long-acting bronchodilators alone have been shown to provide effective protection against exacerbations in patients with COPD.[7,61–63]

Certain adverse events may be associated with β_2-agonists as a class. Clinically notable reductions in plasma potassium were very rare in the studies reviewed here, suggesting little if any risk for hypokalemia-mediated adverse events with LABA treatment. Clinically notable high levels of blood glucose were more common but occurred at similar rates in LABA and placebo treatment groups and may simply reflect the common association between type II diabetes and COPD.[64] Adverse events such as tremor and palpitations appeared to be relatively rare with LABAs in the studies reviewed and may reflect perceptions of the safety profile of older, short-acting β_2-agonists.

This review may have several limitations. "Exacerbations" were defined in different ways by different studies, ranging from periods of worsening symptoms to the need to use oral steroids and hospitalization. However, all definitions reflect some degree of COPD worsening and our interest was in providing an overview of the effect of a LABA compared with placebo, rather than presenting a formal analysis of a consistently defined outcome. The outcomes reviewed here were rarely primary outcomes of the individual studies, although again this would be more of a limitation for a formal analysis. The amount and level of detail of safety information disclosed varied widely among the included studies, leading us to supplement the review with data from analyses specifically directed at questions such as cardiovascular safety. Finally, the studies varied in whether they permitted concomitant ICS treatment. We observed similar trends in the effect of LABAs on exacerbations and COPD-related adverse events in both types of study; indeed, some have pointed out that any beneficial effect of combined ICS and LABA treatment on mortality in COPD is due to the LABA component.[65–68] This is a narrative review, so no attempt at meta-analysis or statistics was made.

Conclusion

LABAs provide an important means of improving symptoms and health status of patients with COPD.[5,7,12–14] They may also have a useful effect in reducing COPD exacerbations, as observed here and by others.[33,36] Our overview suggests that LABA treatment is not associated with an increased incidence of COPD-related adverse events. It will be important to continue to evaluate the safety of LABA treatment in patients with COPD and this will require assessment of all available data from many sources.

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Authors' contributions

All authors contributed to the concept, design, and writing of this manuscript and approved the final contents. All authors are responsible for the decision to submit.

Disclosure

MD has been part of advisory boards for Boehringer-Pfizer, GlaxoSmithKline (GSK), Nycomed, and Altana. He has performed consulting work for Boehringer-Pfizer, GSK, AstraZeneca, and Dompé. He also received lecture fees from these companies. All of the above amounted to less than €10,000 per annum. He received a research grant of €45,000/year from AstraZeneca.

NAH has received honoraria for serving on the speakers' bureau of GSK and Boehringer Ingelheim, as a member of advisory boards or as a consultant for GSK, Novartis, Forest Labs, Dey, and Pfizer. He has also received research grant support that went to his institution from GSK, Novartis, Pfizer, Boehringer Ingelheim, and Sunovion.

JL has received honoraria for consultations and lectures from AstraZeneca, GSK, Merck, Novartis, Oriel Pharmaceutics, and UCB. JL/University of Gothenburg has received financial support for clinical studies and research from Actelion, AstraZeneca, GSK, and Novartis, as well as different contract research organizations and related commercial entities.

BPY has served as a consultant and on advisory boards for Novartis, Boehringer Ingelheim, Pfizer, Merck, and GSK in the areas of asthma and COPD. She has research funding from Boehringer Ingelheim, Novartis, Merck, the Agency for Healthcare Research and Quality, and the National Heart, Lung, and Blood Institute in the areas of asthma and COPD. She does not serve on any speakers' bureaus.

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