
Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis

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Background: Although several published studies have suggested that formoterol fumarate could be equivalent to short-acting β_2 -agonists (SABAs) for the treatment of asthma exacerbations, its role in acute asthma treatment remains undefined.

Objective: To evaluate the efficacy and safety of inhaled formoterol (compared with SABAs) for the emergency department treatment of patients with acute asthma.

Methods: Systematic searches were conducted in MEDLINE, EMBASE, the Cochrane Controlled Trials Register, and manufacturers' trial registers, without language restriction. The primary outcomes were spirometric measures. The secondary outcomes included final serum potassium level, heart rate, electrocardiographic QT interval corrected for heart rate, and total withdrawals.

Results: Nine randomized controlled trials (including 576 participants) were selected. No significant difference could be detected between formoterol and SABAs for any of the selected time points: at 30 to 40 minutes after the first administration of study drugs (standardized mean difference, -0.19 ; 95% confidence interval, -0.56 to 0.17 ; $I^2=75\%$), at the end of treatment (standardized mean difference, -0.25 ; 95% confidence interval, -0.72 to 0.13 ; $I^2=89\%$), and at 60 to 90 minutes after the last dose (standardized mean difference, -0.13 ; 95% confidence interval, -0.55 to 0.28 ; $I^2=80\%$). Similarly, there were no significant differences between formoterol and SABAs regarding final serum potassium level, heart rate, QT interval, hospitalization rate, and total withdrawals.

Conclusions: This review suggests that high-dose formoterol administered via dry powder inhaler is well tolerated and provides rapid and effective bronchodilation, similar to high-dose salbutamol or terbutaline via metered-dose inhaler or nebulizer. Formoterol may be used in the treatment of acute asthma in the emergency department setting.

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INTRODUCTION

The treatment of acute asthma includes the repetitive administration of inhaled short-acting β_2 -agonists (SABAs), often in combination with inhaled anticholinergic agents, systemic corticosteroids, and supplemental oxygen.^{1,2} Although clinical experience with long-acting β_2 -agonists is approaching 25 years, their applicability in acute asthma has only recently been explored. Thus, several studies^{3,4} have suggested that formoterol fumarate could be equivalent to salbutamol or terbutaline for the treatment of acute asthma. The rationale

for using formoterol as a substitute to SABAs in the acute care setting relates to its duration of action and potential for reducing the need for repeated administration of bronchodilator therapy. Thus, formoterol is a selective long-acting β_2 -agonist with a rapid onset of effect (1–3 minutes) and a long duration of action (12 hours).^{5,6} However, the role of formoterol for the treatment of patients with acute asthma is unclear. Thus, among main asthma guidelines, only the Global Initiative for Asthma⁷ suggests that inhaled formoterol could be equally effective to salbutamol in the treatment of

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acute asthma. The current systematic review is an attempt to compare the efficacy and safety of inhaled formoterol with the efficacy and safety of SABAs for the emergency department treatment of patients with acute asthma.

METHODS

Search Strategy and Selection Criteria

We identified studies from MEDLINE, EMBASE (January 1980–October 2009), and the Cochrane Controlled Trials Register (CENTRAL) (third quarter 2009) databases using the following Medical Subject Headings, full text, and keywords: (“Formoterol” or “Oxis” or “Foradil”) and (“emergency” or “acute asthma” or “status asthmaticus” or “severe asthma” or “wheeze”). Also, we performed a search of relevant files from the AstraZeneca (available at: <http://www.astrazenecaclinicaltrials.com>) and Novartis (available at: <http://www.novartisclinicaltrials.com>) databases. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.

The specific inclusion criteria were as follows: (1) children (aged <18 years) and adults (aged ≥18 years) with short-term exacerbations of asthma who presented to an emergency department or equivalent-care setting; (2) single or repeated doses of inhaled formoterol alone or in combination with inhaled corticosteroids as the intervention arm compared with an SABA alone delivered via dry powder inhaler (DPI), metered-dose inhaler, or nebulizer; (3) randomized (parallel-group) controlled trials without language restriction; and (4) primary outcomes (spirometric measures [forced expiratory volume in 1 second {FEV₁} or peak expiratory flow {PEF}]) as absolute or predicted values or change from baseline at 30 to 40 minutes after the first administration of the study drugs, at the end of treatment, and at 60 to 90 minutes after the last dose. Secondary outcome measures were as follows: final serum potassium level, heart rate, electrocardiographic results, QT interval corrected for heart rate, and total withdrawals.

Data Abstraction and Assessment of Risk of Bias

This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.⁸ Titles, abstracts, and citations were independently analyzed by all reviewers. From full text, they independently assessed all studies for inclusion based on the criteria for population, intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. Two of us (G.J.R. and J.A.C.-R.) were independently involved in all stages of study selection, data extraction, and quality assessment. We selected the following markers of validity for randomized trials: appropriate generation of random allocation sequence, concealment of the allocation sequence, blinding of participants, and data collection.⁹ Disagreements were resolved by group consensus. In case of multiple published or unpublished reports for a particular study, data from the most recent version were extracted.

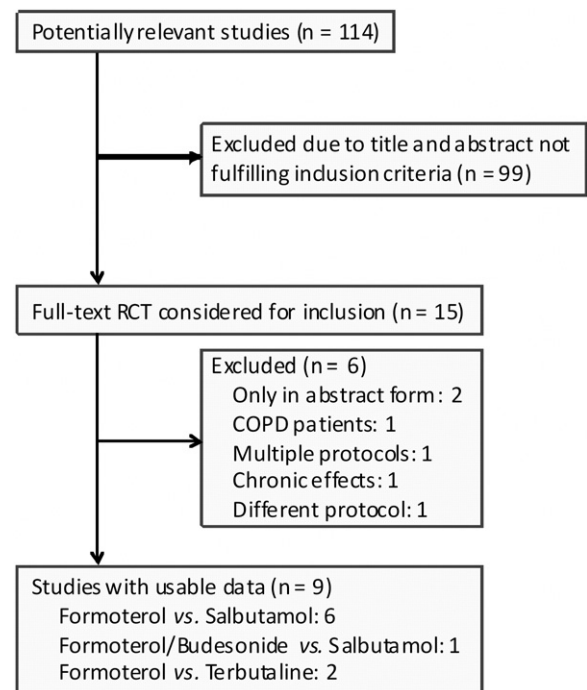


Figure 1. Flowchart for the identification of studies. COPD indicates chronic obstructive pulmonary disease; RCT, randomized controlled trial.

Data Analysis

For continuous outcomes, the standardized mean difference (SMD) or weighted mean difference and the 95% confidence intervals (CIs) were calculated. Binary outcomes were pooled using common odds ratios (ORs) and 95% CIs. If pooled effect estimates were significantly different between groups, we calculated the number needed to treat. Heterogeneity was measured by the I^2 test.¹⁰ Because selected studies differed in the mixes of participants (by participant age and acute asthma severity) and in the implementation of interventions (ie, doses and devices), there may be different effect sizes underlying different studies. Consequently, a random-effects meta-analysis was performed to address this variation across studies in all outcomes.¹¹ The publication bias of primary outcomes was evaluated by visual inspection of funnel plots.¹² A predefined sensitivity analysis of the primary outcome (ie, spirometric measures at the end of treatment) was conducted to explore the influence of the following factors: the ratio (<50 vs ≥50) of SABA to formoterol dose (in micrograms), the age of patients (children vs adults), acute asthma severity (mild to moderate vs severe), and pharmaceutical industry sponsorship (yes vs no). We also tested the influence of the statistical model (fixed vs random effects) on the primary outcome. Subgroups were compared using the interaction test.¹³ $P < .05$ (using a 2-tailed test) was considered significant. Meta-analysis was performed with commercially available software (Review Manager 5.0.21; Copenhagen, Denmark) (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009).

Table 1. Characteristics of Included Studies

Source	Location/ Design/ Duration	No. of Patients (% of Males) by Treatment	Age, Mean (Range), y	Baseline % Predicted FEV ₁ , Mean (Range)	Intervention (Active Drugs)	SABA to Formoterol Fumarate Ratio	Pharmaceutical Industry Sponsorship
Malolepszy et al, ¹⁴ 2001	Single center/ R, DB, PG/ 3 h	F: 24	46 (20-64)	32 (20-50)	F: 4.5 µg × 20 (0, 30, 60, 120, 180 min) (total dose, 90 µg) DPI	111	Yes
		T: 24	44	35	T: 0.5 mg × 20 (0, 30, 60, 120, 180 min) (total dose, 10 mg) DPI		
Boonswat et al, ¹⁵ 2003	5 Centers/ R, DB, PG/ 4 h	F: 44 (32)	45 (18-67)	44 (30-60)	F: 18 µg × 3 (0, 30, 60 min) (total dose, 54 µg) DPI	44	Yes
		S: 44 (23)	43	44	S: 800 µg × 3 (0, 30, 60 min) (total dose, 2400 µg) MDI plus spacer		
Ávila-Castañón et al, ¹⁶ 2004	Single center/ R, DB, PG/ 60 min	F: 18 (61)	8.9 (5-15)	75.2	F: 12 µg × 1 DPI	17	No
		S: 18 (61)	8.7	78.5	S: 200 µg × 1 DPI		
Balanag et al, ¹⁷ 2006	Multicenter/ R, DB, PG/ 3 h	F: 55 (42)	47 (13-80)	42 (30-60)	F/B: 18/640 µg × 2 (-5, 0 min) (total dose, 36/1280 µg) DPI	44	Yes
		S: 48 (40)	42	45	S: 800 µg × 2 (-5, 0 min) (total dose, 1600 µg) DPI		
Rubinfeld et al, ¹⁸ 2006	Single center/ R, DB, PG/ 4 h	F: 38 (42)	36 (18-70)	57 (≥30)	F: 18 µg × 2 (0, 30 min) (total dose, 36 µg) DPI	44	Yes
		S: 40 (25)	37	60	S: 800 µg × 2 (0, 30 min) (total dose, 1600 µg) MDI plus spacer		
Najafzadeh et al, ³ 2007	Single center/ R, DB, PG/ 45 min	F: 32 (50)	56 (>18)	119.3 L/min*	F: 12 µg × 2 (0, 20 min) (total dose, 24 µg) DPI	25	No
		S: 28 (40)	53	100.8 L/min	S: 200 µg × 3 (0, 20, 40 min) (total dose, 600 µg) MDI plus spacer		
Lee-Wong et al, ⁴ 2008	Single center/ R, DB, PG/ 60 min	F: 15 (21)	47 (18-65)	49 (40-60)*	F: 12 µg × 2 (0, 30 min) (total dose, 24 µg) DPI	208	No
		S: 19 (20)	41	44	S: 2.5 mg × 2 (0, 30 min) (total dose, 5 mg) nebulized		
Rodriguez et al, ¹⁹ 2008	Single center/ R, DB, PG/ 60 min	F: 25	(5-12)	58	F: 24 µg nebulized	312	No
		S: 25	(5-12)	56	S: 2.5 × 3 (0, 20, 40 min) (total dose, 7.5 mg) nebulized		
Bussamra et al, ²⁰ 2009	Single center/ R, DB, PG/ 60 min	F: 41	10.2 (6-20)	63	F: 12 µg × 3 (0, 20, 40 min) (total dose, 36 µg) DPI	42	No
		T: 38	9.5	61	T: 0.5 mg × 3 (0, 20, 40 min) (total dose, 1.5 mg) DPI		

Abbreviations: B, budesonide; DB, double-blind; DPI, dry powder inhaler; F, formoterol; FEV₁, forced expiratory volume in 1 second; MDI, metered-dose inhaler; PG, parallel group; R, randomized; S, salbutamol; SABA, short-acting β_2 -agonist; T, terbutaline.

* Peak expiratory flow.

RESULTS

Nine randomized controlled trials^{3,4,14–20} fulfilled the inclusion criteria (total patients, 576) (Figure 1). Six studies^{4,14,15,17} compared inhaled formoterol with inhaled salbutamol, 2 studies^{14,20} compared formoterol with terbutaline, and 1 study¹⁷ compared the combination formoterol and budesonide with salbutamol (Table 1). In 8 trials,^{3,4,14–18,20} formoterol was administered via a DPI; in the remaining study,¹⁹ formoterol was nebulized. The mean dose of formoterol was 37.3 µg (range, 12-90 µg). Three studies^{16,19,20} included children. In 4 studies,^{4,14,15,17} most of the patients showed severe acute asthma (FEV₁ or PEF <50% of predicted). Regarding the validity assessment of selected trials, only 1 study³ met the 4 selected markers (Table 2). Four trials^{14,15,17,18} were sponsored by the pharmaceutical industry.

Primary Outcomes

All studies reported data on spirometric measures (FEV₁ or PEF). No significant difference could be detected between

the formoterol and SABA group at any of the selected time points. Thus, there were no significant differences between both groups at 30 to 40 minutes after the first administration of study drugs, at the end of treatment, and at 60 to 90 minutes after the last dose (Figure 2). However, the analysis showed evidence of statistical heterogeneity among trials; this was related to 2 studies.^{3,15} The exclusion of these trials completely removed the statistical heterogeneity and did not affect the finding of no evidence in spirometric measures between groups at 30 to 40 minutes after the first dose (SMD, 0.09; 95% CI, -0.12 to 0.30; I² = 0%; P = .38), at the end of treatment (SMD, 0.03; 95% CI, -0.16 to 0.22; I² = 0%; P = .79), and at 60 to 90 minutes after the last dose (SMD, -0.06; 95% CI, -0.27 to 0.15; I² = 0%; P = .56). The excluded studies^{3,15} were the only ones that showed significant greater increases in FEV₁ or PEF at 30 to 40 minutes after the first administration of study drugs and at the end of treatment in the formoterol group compared with the SABA group.

Table 2. Validity of the Eligible Studies

Source	Sequence Generation	Allocation Concealment	Patients Blinded	Data Collection Blinded
Malolepszy et al, ¹⁴ 2001	No	No	Yes	Yes
Boonswat et al, ¹⁵ 2003	No	No	Yes	Yes
Ávila-Castañón et al, ¹⁶ 2004	No	No	Yes	Yes
Balanag et al, ¹⁷ 2006	No	No	Yes	Yes
Rubinfeld et al, ¹⁸ 2006	Yes	No	Yes	Yes
Najafizadeh et al, ³ 2007	Yes	Yes	Yes	Yes
Lee-Wong et al, ⁴ 2008	Yes	No	No	No
Rodriguez et al, ¹⁹ 2008	Yes	No	Yes	Yes
Bussamra et al, ²⁰ 2009	No	No	Yes	No

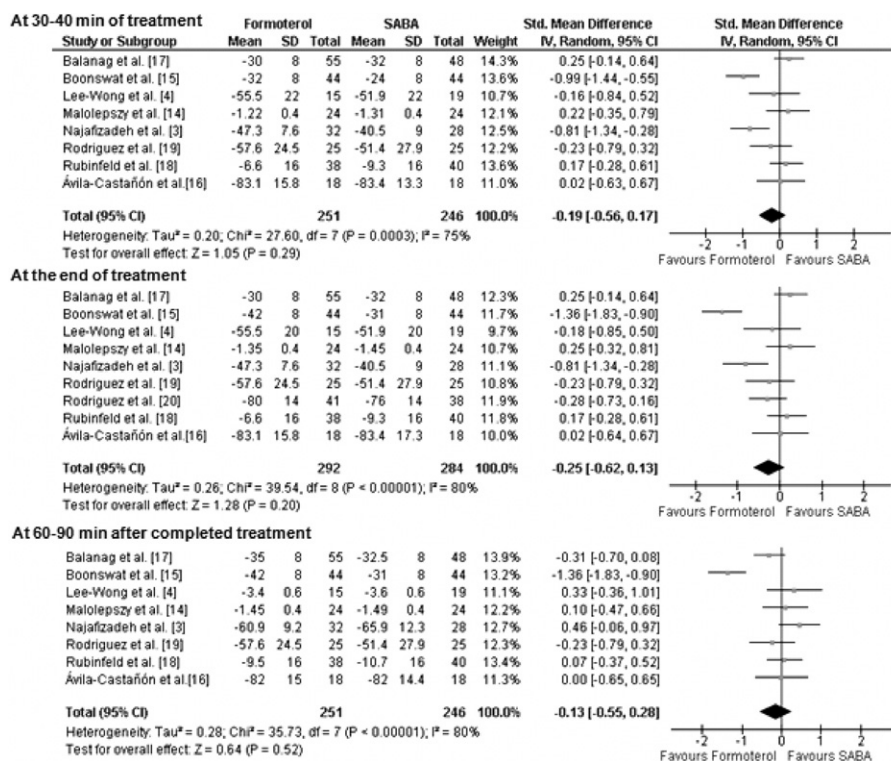


Figure 2. Standardized mean differences for spirometric measures (at 30-40 minutes after the first administration of treatment, at the end of treatment, and at 60-90 minutes after completed treatment) with 95% confidence intervals (CIs) of eligible studies comparing inhaled formoterol fumarate with short-acting β_2 -agonists (SABAs).

Both studies^{3,15} were also characterized by the cumulative administration of inhaled formoterol with an SABA to formoterol dose (in micrograms) ratio of less than 50 in patients with severe acute asthma.

A visual inspection of the funnel plot of spirometric measures at the end of treatment did not reveal any asymmetry, suggesting the absence of publication bias. Because 1 study¹⁷ used the formoterol and budesonide combination, we excluded it in a new analysis limited to the remaining 8 trials. However, this exclusion did not change the primary conclusions on spirometric measures at 30 to 40 minutes after the first dose (SMD, -0.27 ; 95% CI, -0.66

to 0.12 ; $I^2 = 72\%$; $P = .17$), at the end of treatment (SMD, -0.32 ; 95% CI, -0.72 to 0.09 ; $I^2 = 78\%$; $P = .12$), and at 60 to 90 minutes after the last dose (SMD, -0.10 ; 95% CI, -0.60 to 0.39 ; $I^2 = 84\%$; $P = .68$). In the same way, the meta-analysis of the 8 trials^{3,4,14-18,20} that administered formoterol via a DPI device found similar results (SMD, -0.25 ; 95% CI, -0.67 to 0.18 ; $I^2 = 82\%$; $P = .25$). Finally, the predefined post hoc subgroup analysis did not show significant differences in FEV₁ or PEF at the end of treatment regarding statistical model, SABA to formoterol dose ratio, age of patients, acute asthma severity, and pharmaceutical industry sponsorship (Table 3).

Table 3. Sensitivity Analysis*

Subgroup Comparisons	SMD (95% CI)	Difference (95% CI)	P Value
Fixed vs random effects	−0.24 (−0.41 to −0.06; I ² =82%) vs −0.25 (−0.67 to 0.18; I ² =82%)	−0.01 (−0.46 to 0.44)	.96
SABA to formoterol dose (μg) ratio (<50 ^{3,15–18,20} vs ≥50 ^{4,14,19})	−0.34 (−0.86 to 0.19; I ² =86%) vs 0.04 (−0.39 to 0.30; I ² =0%)	0.38 (−0.24 to 1.00)	.23
Children ^{16–20} vs adults ^{3,4,14,15,17,18}	−0.20 (−0.51 to 0.10; I ² =0%) vs −0.28 (−0.85 to 0.29; I ² =87%)	−0.08 (−0.72 to 0.56)	.80
Acute asthma severity (mild to moderate ^{4,16,18–20} vs severe ^{3,14,15,17})	−0.09 (−0.33 to 0.14; I ² =0%) vs −0.42 (−1.23 to 0.39; I ² =91%)	−0.33 (−1.17 to 0.51)	.36
Pharmaceutical industry sponsorship (yes ^{14,15,17,18} vs no ^{3,4,16,19,20})	−0.18 (−0.95 to 0.60; I ² =91%) vs −0.33 (−0.59 to −0.06; I ² =13%)	−0.15 (−0.96 to 0.66)	.71

Abbreviations: CI, confidence interval; SABA, short-acting β_2 -agonist; SMD, standardized mean difference.

* Comparisons for the SMD in pulmonary function at the end of treatment were stratified by statistical model (fixed vs random effects), SABA to formoterol dose (in micrograms) ratio (<50 vs ≥50), age of patients (children vs adults), acute asthma severity (mild to moderate vs severe), and pharmaceutical industry sponsorship (yes vs no).

Secondary Outcomes

The meta-analysis did not show significant differences between the formoterol and SABA groups regarding final serum potassium level, heart rate, electrocardiographic QT interval corrected for heart rate, hospitalization rate, and total withdrawals (Table 4). Only 1 of the 5 analyzed variables (ie, final heart rate) showed evidence of statistical heterogeneity between studies.

DISCUSSION

In the present study (ie, to our knowledge, the first systematic review designed to evaluate the safety and efficacy of use of inhaled formoterol compared with SABAs in patients with mild to severe acute asthma in the emergency department setting), we found that formoterol via DPI was at least equally effective as SABAs in terms of spirometric measure assessment. Thus, formoterol was equivalent to SABAs as early as 30 to 40 minutes after treatment, at the end of the protocol, and at 60 to 90 minutes after the last dose. This equivalence was independent of the statistical model, SABA to formoterol dose ratio, the age of patients, the severity of the asthma exacerbation, and pharma-

ceutical industry sponsorship. On the other hand, there were no significant differences between formoterol and SABA treatments on serum potassium level, heart rate, electrocardiographic QT interval corrected for heart rate, and hospitalization rate. Furthermore, there was no significant difference on total withdrawals, suggesting that formoterol via DPI is safe in patients with acute asthma.

Previous studies^{21,22} in asthmatic patients and healthy volunteers suggested that a dose of formoterol of 36.00 μg via DPI would be the nearest equivalent dose to salbutamol, 1.60 μg (SABA to formoterol dose ratio, <50). In our systematic review, the mean formoterol and SABA doses were 37.00 and 2.25 μg, respectively, suggesting that a total dose of formoterol of 36.00 μg (12.00 μg administered each 30 minutes) via DPI constitutes a therapeutic alternative to SABA treatment.

This review was performed according to the methodological criteria suggested for scientific reviews.⁸ However, our meta-analysis presented several potential limitations that come from the validity of reported data. Overall, the quality of the studies was low. Of 9 studies, only 1 adequately concealed allocation; 5 did not report an appropriate generation of random allocation

Table 4. Analysis of Secondary Outcomes (Formoterol vs SABAs)

Outcome	References	Formoterol	SABAs	Measure (95% CI)	P Value	I ² , %
Final serum potassium level, mmol/L	4, 14, 15, 17, 18	176	175	WMD = −0.00 (−0.15 to 0.14)	.96	34
Final heart rate/min	4, 14, 15, 17, 18, 20	217	213	WMD = −2.97 (−7.32 to 1.30)	.17	55
ECG QTc interval, ms	15, 17, 18	137	132	WMD = −8.10 (−19.79 to 3.58)	.17	0
Hospitalizations	3, 4, 20	9/88*	16/85*	OR = 0.50 (0.21 to 1.22)	.13	0
Withdrawals	3, 14, 15, 17–19	14/232*	22/230*	OR = 0.64 (0.31 to 1.34)	.24	0

Abbreviations: CI, confidence interval; ECG, electrocardiographic; OR, odds ratio; QTc, QT interval corrected for heart rate; SABA, short-acting β_2 -agonist; WMD, weighted mean difference.

* Data are given as number/total.

concealment. On the other hand, the finding of a symmetrical funnel plot in the main outcome suggests the absence of publication bias. Regarding consistency, the meta-analysis of primary outcomes showed evidence of statistical heterogeneity as the result of differences between studies. This heterogeneity was completely explained by 2 studies.^{3,15} Both studies showed the superiority of formoterol and were characterized by the use of high and cumulative doses of formoterol in a short period (range, 20–30 minutes) in patients with severe acute asthma. This suggested that high doses could obtain additional benefits. In addition, the fact that all selected studies excluded patients at the most severe end of the spectrum of acute asthma (patients with an FEV₁ or PEF of <20% of predicted or who required intensive care unit admission) indicates that our results do not apply to patients with life-threatening acute asthma.

The results of this systematic review support the efficacy and safety of formoterol as an alternative to SABA (salbutamol or terbutaline) as reliever therapy in mild to severe acute asthma exacerbations. The review suggests that high-dose formoterol, administered via DPI, is well tolerated and provides similar rapid and effective bronchodilation as high- and repetitive-dose salbutamol or terbutaline, administered via metered-dose inhaler or nebulizer, in the treatment of acute asthma. The fact that formoterol required less repeated rescue medication to balance it is probably the cost difference. Therefore, formoterol could replace conventional SABAs as reliever medication in the acute care setting. Future trials are needed to assess the comparison of formoterol with SABAs in patients with acute life-threatening asthma and to examine the use of formoterol plus inhaled corticosteroids in acute asthma treatment.

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