Original Article Efficacy and safety of vilanterol and fluticasone furoate/vilanterol in the treatment of asthma: a systematic review and meta-analysis

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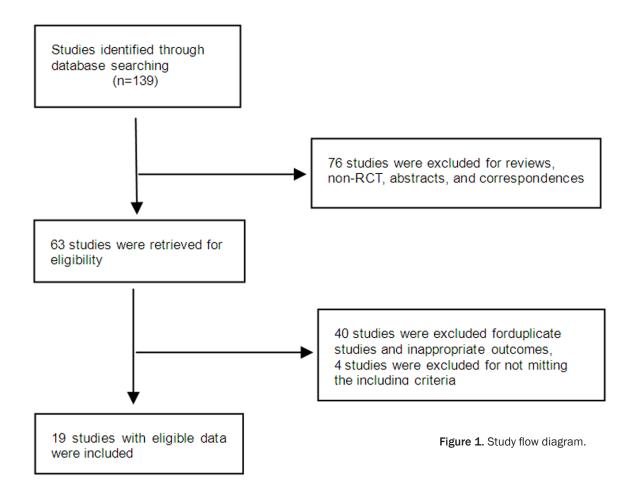
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Abstract: Objective: This is a meta-analysis of the efficacy and safety of vilanterol and fluticasone furoate/vilanterol in the treatment of asthma. Methods: Randomized controlled trials were identified from CENTRAL, MEDLINE, EMBASE, CNKI, and Wanfang, ClinicalTrials.gov, GSK databases, and manual searches. Pulmonary function indices (trough FEV1, wmFEV1 and PEF), exacerbation rates, symptom-free and rescue-free 24-hour periods, quality of life scores and adverse effects were evaluated by meta-analysis. Results: The bronchodilation effect of vilanterol was rapid and sustained. Once-daily vilanterol (VI) or fluticasone furoate/vilanterol (FF/VI) significantly improved trough FEV1 (140 ml, P<0.001 and 170 ml respectively), wmFEV1 (160 ml, P<0.001 and 240 ml, P<0.001 respectively), and PEF values relative to placebo. Fluticasone furoate/vilanterol treatment significantly improved the pulmonary function indices (trough FEV1 90 ml, P<0.001, wmFEV1 120 ml, P<0.001, PEF 28.03 L/m, P<0.001) and reduced the asthma exacerbation and rescue drug use relative to fluticasone furoate alone. Combined treatment was also superior to fluticasone propionate in improving of trough FEV1 (210 ml, P<0.001), wmFEV1 (210 ml, P=0.002) and PEF (32.62 L/m, P<0.001). Once-daily dual regimen administration was as effective as twice-daily fluticasone propionate/salmeterol in improving pulmonary function indices and quality of life. Trough FEV1, symptom-free and rescue-free 24-hour periods were similar between FF/VI and fluticasone furoate/umeclidinium (FF/UMEC). Treatment-related adverse events were tolerable in most of the asthma patients. Conclusion: Vilanterol and fluticasone furoate/vilanterol are effective and generally well tolerated for patients with asthma.

Keywords: Efficacy, safety, vilanterol, asthma

Introduction

Asthma is a serious global health problem, which is characterized by wheeze, chest tightness, shortness of breath, and cough, together with variable airflow obstruction [1]. It is a heterogeneous respiratory tract disease composed of chronic airway inflammation, airway hyper-responsiveness, and airway remodeling [2]. Affecting more than 300 million people all over the world, it has a high prevalence among children younger than 18 years (9.3%) [3] and among adults (1% to 21%) [4]. It is reported that about 200,000 people die from asthma per year, and there may be an additional 100 million people affected by asthma by 2025 [5]. Combination inhalers with an ICS and a LABA continue to be the preferred choice in the treatment of asthma for those patients who are symptomatic on ICS treatment alone [6]. The majority of available ICS are taken twice daily, and once daily inhalation may be suitable for some patients without uncontrolled symptoms [7]. Fluticasone furoate (FF), along with vilanterol (VI), have been developed as a novel, singleinhaler, once-daily ICS/LABA combination for patients with COPD. It is a new combination drug not previously indicated for asthma and recently is approved in the Europe for the treatment of asthma [8]. At present it is the only once-daily ICS/LABA available for the management of asthma. This systematic review and



meta-analysis will aim to investigate systematically efficacy and safety of VI and FF/VI in the treatment of asthma.

Materials and methods

Study selection

A comprehensive literature search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EM-BASE, China National Knowledge Internet (CNKI), Wanfang database, GSK database and ClinicalTrials database, with the most recent search being conducted in September, 2015. The searching words included "vilanterol" or "fluticasone furoate" or "Breo" or "GW685698" or "GW642444" and "asthma". Additional references were checked in the reference lists of all primary studies and review articles.

Inclusion criteria

There was no language restriction. Relevant RCTs were included according to the following inclusive criteria: (1) the study was a random-

ized controlled trial (RCT); (2) the study was designed to evaluate the efficacy and safety of VI and FF/VI treatment in adults or children with asthma; (3) VI and FF/VI were studied versus placebo or other bronchodilators; (4) the duration of treatment was more than 7 days; (5) the dose of VI was more than 12.5 μ g; (6) the Jadad score of each study was equal or more than two points.

Data extraction

Two reviewers collected data from each trial independently using a standardized data extraction form and reached agreement on all items. The extracted data included: first author, publication date, study design, type of disease, country, number of patients, duration of therapy, patient characteristics (age, percentage of males, ethnicity), and end-point outcomes.

Statistical analysis

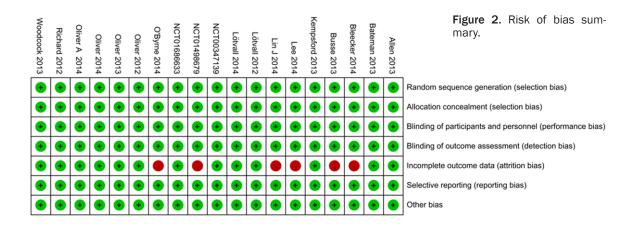
This meta-analysis was performed by Review Manager 5.3. To measure the effects of VI and

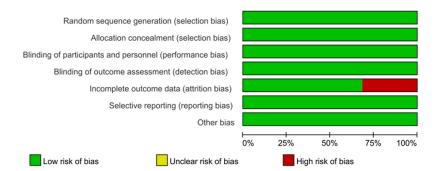
Table 1. Characteristics of the studies inc	cluded in the meta-analysis
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Study	Year	Study design	Type of disease	Country	Ethnicity	Age (y)	Male (%)	Pa- tients (n)	Jada score	Experimental group	Control group	Duration of treat- ment	Outcomes
Richard [9]	2012	multicentre, ran- domised, double-blind, placebo-controlled, five- period crossover study	persistent asthma	USA	White, African American, Asian	38.9± 14.37	37.3	75	5	VI 12.5 µg qd, 25 µg qd	placebo	7 days	trough FEV1, wmFEV1, AE
NCT00347139 [10]	2007	randomised, double- blind, placebo-con- trolled, four-way incom- plete block crossover study	persistent asthma	Germany, Russia, Sweden, New Zealand, UK	White, Asian	43.8± 15.0	72.7	55	4	VI 25 μg qd, 100 μg qd	SAL 50 µg bid, placebo	14 days	trough FEV1, pharmaco- kinetic parameters, blood glucose, blood potassium, AE
Lötvall [11]	2012	multicentre, ran- domised, double-blind, placebo-controlled study	persistent asthma	Germany, Hungary, South Africa, Russian Federation, et al.	White, Asian, African, American	42.4± 14.72	44.3	607	5	VI 12.5 µg qd, 25 µg qd, 50 µg qd	placebo	28 days	trough FEV1, wmFEV1, PEF, symptom-free period, rescue-free period, AE
Lötvall [18]	2014	double-blind, double- dummy, randomised, placebo-controlled study	persistent asthma	Germany, Peru, Poland, Ukraine, USA	White, African American, American Indian, Asian	41.3± 17.06	41.2	347	5	VI 25 µg qd	SAL 50 µg bid, placebo	12 weeks	wmFEV1, symptom-free period, rescue-free period, FEV1, PEF, AE
Oliver [25]	2014	multi-center, random- ized, double-blind, placebo-controlled, two- way crossover study	persistent asthma	USA	White, African American	8 (5- 11)	64.3	28	4	VI 25 µg qd	placebo	14 days	AE, PEF, blood pressure, heart rate, pharmacoki- netic parameters, blood glucose, blood potassium
Bleecker [12]	2014	a randomized, double- blind, parallel-group study	persistent asthma	USA, Poland, Ukraine	White, Asian, African Ameri- can, mixed	39.7± 16.56	42	609	5	FF/VI 100/25 µg qd, FF 100 µg qd	placebo	12 weeks	trough FEV1, serial (0-24 hours) wmFEV1, symptom free 24-h periods, rescue- free 24-h periods, AE
Lee [13]	2014	double-blind, three- period cross-over, incomplete-block study	uncon- trolled asthma	Argentina, Chile, Russia, Thailand, USA	White, Asian, African, American	47.5± 13.84	31.4	421	5	FF/VI 100/25 µg qd	FF/UMEC 100/125 μg qd, 100/250 μg qd; FF 100 μg qd	14 days	trough FEV1, PEF, rescue-free 24-h periods, symptom-free 24-h peri- ods, AE
NCT01686633 [14]	2013	multicenter, random- ized, double-blind, stratified, parallel group study	moderate to severe, persistent asthma	multicenter	White, African American, American, Indian, Asian	45.7± 15.60	65.4	1039	5	FF/VI 100/25 µg qd, FF/VI 200/25 µg qd	FF 100 µg qd	12 weeks	wmFEV1, trough FEV1, rescue-free 24-h periods, symptom-free 24-h peri- ods, PEF, AE
0'Byrne [15]	2014	randomised, multi- centre, double-blind, double-dummy, parallel- group study	Moderate to severe, persistent- asthma	Germany, Japan, Poland, Roma- nia, Russia, USA	White, African American, American, Indian, Asian	46.2± 14.51	41.1	586	5	FF/VI 200/25 µg qd	FP 500 µg bid, FF 200 µg qd	24 weeks	trough FEV1, wmFEV1, rescue-free 24-h periods, symptom-free 24-h peri- ods, AQLQ, PEF, ACT
Bateman [16]	2013	randomised, multi- centre, double-blind, parallel-group study	uncon- trolled asthma	USA, Russia, Mexico, Ukraine, Germany, et al.	White, Asian, African, American, mixed	41.7± 16.96	33	2019	5	FF/VI 100/25 µg qd	FF 100 µg qd	24-78 weeks	time to first severe exac- erbation, severe asthma exacerbations, trough FEV1, ACQ7, AE
Woodcock [17]	2013	multicenter, random- ized, double-blind, double-dummy, parallel group study	persistent asthma	multicenter	White, Asian, African, American	42.8± 16.41	39.3	806	5	FF/VI 100/25 µg qd	FP/SAL 250/50 µg bid	24 weeks	wmFEV1, serial FEV, time to onset of bronchodila- tion, trough FEV1, AE, AQLQ, ACT

Oliver [19]	2013	randomized, double-blind, placebo- controlled, four-way crossover study	mild asthma	Sweden, Austra- lia, New Zealand	White, Asian, mixed	30.8± 7.46	70.4	27	5	FF/VI 100/25 μg qd, FF 100 μg qd, VI 25 μg qd	placebo	21 days	wmFEV1, AHR, AE
Oliver [20]	2012	multi-centre, ran- domised, double-blind, placebo-controlled, 3-period crossover study	mild asthma	UK, Germany, New Zealand	White, African American, Asian	35.4± 8.63	65.4	52	5	FF/VI 100/25 μg qd, FF 100 μg qd	placebo	28 days	decrease of wmFEV1 0-2 h after allergen challenge, maximum percentage de- crease of FEV1, minimum FEV1 absolute change from baseline, AE
Kempsford [21]	2013	double-blind, placebo- controlled, randomised, three-way crossover study	persistent asthma	New Zealand	White	38.1± 11.30	69.2	26	5	FF/VI 100/25 µg qd	placebo	14 days	wmFEV1, trough FEV1, mean pre-treatment PEF
NCT01498679 [22]	2013	randomised, double- blind, placebo con- trolled, parallel group, multi-centre study	persistent asthma	China, Korea, Philippines	Asian	47.2± 13.94	44.3	307	4	FF/VI 100/25 µg qd	placebo	12 weeks	PEF, rescue-free 24-h pe- riods, symptom-free 24-h periods, AQLQ, AE
Lin J [23]	2014	double-blind, double- dummy, active-com- parator, parallel-group, multicenter study	persistent asthma	China, South Ko- rea, Philippines	Asian	47.9± 13.19	41.1	309	5	FF/VI 200/25 µg qd	FP 500 µg bid	12 weeks	daily evening PEF, daily morning PEF, rescue-free 24-h periods, symptom- free 24-h periods, AQLQ, AE
Busse [24]	2013	randomised, multi- centre, double-blind, double-dummy, active comparator, parallel group study	asthma	USA, Germany, Ukraine, Thai- Iand	White, Asian, African, American, mixed	39.0± 15.77	37.2	503	5	FF/VI 100/25 µg qd, FF/VI 200/25 µg qd	FP 500 µg bid	52 weeks	severe exacerbations, 24-h urinary cortisol, laboratory assessments, AE
Allen [26]	2013	randomised, multi- centre, double-blind, parallel-group, double- dummy, placebo-con- trolled study	persistent asthma	Germany, Po- land, USA	White, African American, American, Indian, Asian	35.1± 14.82	53	185	5	FF/VI 100/25 μg qd, 200/25 μg qd	placebo	42 days	wmSC, PK, PD, FEV1, AE
Oliver A [27]	2014	randomized, double- blind, repeated-dose, 2-period, crossover, phase IIa study	mild to moderate, persistent, asthma	United kingdom	White, African American, mixed	8.1± 1.97	57.7	26	4	FF/VI 100/25 μg qd	FF 100 µg qd	14 days	AE, clinical laboratory mea- surements, PEF, maximum heart rate, blood pressure, ECG parameters, PK, PD, serum cortisol, glucose

FEV1: forced expiratory volume in one second; wmFEV1: weighted mean FEV1; PEF: peek expiratory flow; AE: adverse event; AQLQ: asthma quality of life questionnaire; ACT: asthma control test; ACQ: asthma control questionnaire; wmSC: weighted mean serum cortisol; SAL: salmeterol; PK: pharmacokinetics; PD: pharmacodynamics; FP: fluticasone propionate; FP/SAL: fluticasone propionate/salmeterol.







Trough FEV1: Trough FEV1 is defined as the mean of the 23 hour and 24 hour post-dose assessments at the end of the treatment period. The data from nine studies were collected [9-17]. Compared with placebo, monotherapy with VI and combined FF/VI treatment significantly incre-

Figure 3. Risk of bias graph.

FF/VI treatments on asthmatic patients, standardized mean difference (SMD) or weighed mean difference (WMD) was used. The heterogeneities of the enrolled studies were assessed by I^2 test and P<0.1 was considered as significant. A random-effects model was applied regardless of statistical heterogeneity. Differences were considered significant when P<0.05.

Results

Study characteristics

One hundred and thirty nine studies were retrieved after the initial search and seventy six studies were excluded because they are reviews, non-RCT, abstracts or correspondences (Figure 1). Sixty-three studies were identified for full-text review. Forty studies were excluded for duplicate studies and inappropriate outcomes. Four studies were excluded for not mitting the including criteria. Finally, 19 studies were included in this meta-analysis. The characteristics of included studies are summarized in Table 1 and qualities of the included studies are assessed (Figures 2 and 3). ased trough FEV1 with an improvement of 140 ml (95% Cl: 0.11-0.18, P<0.001) [9-11] and 170 ml (95% Cl: 0.09-0.26, P<0.001) respectively [12] (**Figure 4**). FF/VI was more potent than FF (95% Cl: 0.06-0.11, P<0.001) [12-16] and FP (95% Cl: 0.13-0.29, P<0.001) [15] and had similar potency to fluticasone furoate/umeclidinium (FF/UMEC) (95% Cl: 0.00-0.06, P=0.03) [13] and fluticasone propionate/salmeterol (FP/SAL) (95% Cl: -0.07-0.03, P=0.48) [17] in improving trough FEV1 (**Figure 5**).

wmFEV1: Changes from baseline in weighted mean for 24-h serial FEV1 (wmFEV1) were assessed and nine studies were included [9, 11, 12, 14, 15, 17-20]. VI and FF/VI significantly improved wmFEV1 with an increase of 160 ml (95% CI: 0.13-0.19, P<0.001) [9, 11, 18] and 240 ml (95% CI: 0.14-0.34, P<0.001) respectively compared to placebo [12, 19, 20] (Figure 6). Data from three studies showed a greater effect of FF/VI versus FF (95% CI: 0.08-0.16, P<0.001) [12, 14, 15] and FP (95% CI: 0.07-0.34, P=0.002) [15]. No superiority of FF/VI to FP/SAL was found (95% CI: -0.09-0.02, P=0.17) [17] (Figure 7).

	Exp	eriment	al	c	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 VI trough FEV1 vs place	ebo								
Richard 2012 12.5µg 7d	0.161	0.189	73	0.059	0.19	74	21.6%	0.10 [0.04, 0.16]	
Richard 2012 25µg 7d	0.184	0.189	73	0.059	0.19	74	21.6%	0.13 [0.06, 0.19]	
NCT00347139 25µg 14d	0.218	0.292	34	-0.02	0.288	58	6.8%	0.24 [0.12, 0.36]	
NCT00347139 100µg 14d	0.235	0.304	37	-0.02	0.288	58	6.8%	0.26 [0.13, 0.38]	
Lötvall 2012 12.5µg 28d	0.278	0.355	97	0.147	0.351	95	9.9%	0.13 [0.03, 0.23]	
Lötvall 2012 25µg 28d	0.269	0.348	99	0.147	0.351	95	10.1%	0.12 [0.02, 0.22]	
Lötvall 2012 50µg 28d	0.309	0.35	100	0.147	0.351	95	10.1%	0.16 [0.06, 0.26]	
Subtotal (95% CI)			513			549	87.0%	0.14 [0.11, 0.18]	•
Heterogeneity: Tau ² = 0.00; Ch	i² = 7.86	, df = 6	(P = 0.1	25); l² =	24%				
Test for overall effect: Z = 7.43	(P < 0.0	0001)							
1.1.2 FF/VI trough FEV1 vs pl	acebo								
Bleecker 2014 100/25µg 12w	0.368	0.43	200	0.196	0.431	193	13.0%	0.17 [0.09, 0.26]	
Subtotal (95% CI)			200			193	13.0%	0.17 [0.09, 0.26]	
Heterogeneity: Not applicable									
Test for overall effect: Z = 3.96	(P < 0.0	001)							
Total (95% CI)			713			742	100.0%	0.15 [0.11, 0.18]	•
Heterogeneity: Tau ² = 0.00; Ch	i² = 8.36	. df = 7	(P = 0.3	30); l ² =	16%				
Test for overall effect: Z = 8.56				,					-0.2 -0.1 0 0.1 0.2
Test for subgroup differences:		,	1 (P =	0.56), I	² = 0%				Favours [control] Favours [Experimental]

Figure 4. Monotherapy with VI and combined FF/VI treatment significantly increased trough FEV1 with an improvement of 140 ml (P<0.001) and 170 ml (P<0.001) respectively.

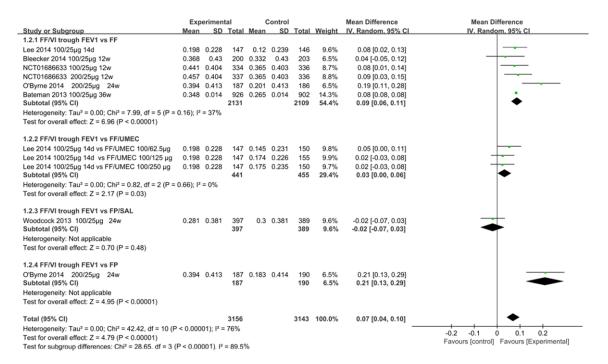


Figure 5. FF/VI was more potent than FF (P<0.001), FP (P<0.001) and FF/UMEC (P=0.03) and had similar potency to FP/SAL (P=0.48) in improving trough FEV1.

PEF: Compared to placebo, patients with VI and FF/VI administration had overall obvious improvements from baseline in morning or evening PEF rate [11, 12, 18, 21, 22]. FF/VI had an overall statistical significant effect on PEF relative to FF (95% CI: 24.61-31.45, P<0.001) [13-15], FP (95% CI: 26.71-8.52, P<0.001) [15, 23], and FF/UMEC (95% CI: 1.68-10.01, P=0.006) [13] (**Figure 8**).

AQLQ score: The total asthma quality of life questionnaire (AQLQ) score is used to evaluate the impact of asthma treatments on the quality of life of asthma patients. Five studies reported AQLQ scores. FF/VI administration could significantly improve the life quality relative to placebo (95% CI: 0.19-0.59, P<0.001) [12, 22] (**Figure 9**), but there was no significant difference between FF/VI and FF (95% CI: -0.01-

Experimental Control	Mean Difference	Mean Difference
		N/ D 1 050/ 01
Study or Subgroup Mean SD Total Mean SD Total W	Veight IV. Random, 95% Cl	IV. Random. 95% CI
2.1.1 VI wmFEV1 vs placebo		
	25.8% 0.17 [0.11, 0.22]	
	25.8% 0.18 [0.13, 0.24]	
Lötvall 2012 12.5µg 28d 0.292 0.318 99 0.149 0.322 101 1	10.4% 0.14 [0.05, 0.23]	
Lötvall 2012 25µg 28d 0.315 0.31 100 0.149 0.322 101 1	10.7% 0.17 [0.08, 0.25]	
Lötvall 2012 50µg 28d 0.321 0.31 100 0.149 0.322 101 1	10.7% 0.17 [0.08, 0.26]	
Lötvall 2014 25µg 12w 0.359 0.418 101 0.289 0.418 95	6.1% 0.07 [-0.05, 0.19]	
Subtotal (95% CI) 546 546 8	89.5% 0.16 [0.13, 0.19]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 3.32, df = 5 (P = 0.65); I ² = 0%		
Test for overall effect: Z = 10.89 (P < 0.00001)		
2.1.2 FF/VI wmFEV1 vs placebo		
Oliver 2013 100/25µg 21d -0.297 0.475 27 -0.56 0.443 22	1.3% 0.26 [0.01, 0.52]	
Oliver 2012 100/25µg 28d -0.227 0.373 46 -0.372 0.374 45	3.6% 0.14 [-0.01, 0.30]	
Bleecker 2014 100/25µg 12w 0.513 0.447 108 0.212 0.444 95	5.6% 0.30 [0.18, 0.42]	
	10.5% 0.24 [0.14, 0.34]	
Heterogeneity: Tau ² = 0.00; Chi ² = 2.45, df = 2 (P = 0.29); l ² = 18%		
Test for overall effect: $Z = 4.57$ (P < 0.00001)		
Total (95% CI) 727 708 10	00.0% 0.17 [0.14, 0.20]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 8.42, df = 8 (P = 0.39); l ² = 5%		
Test for overall effect: $Z = 11.47$ (P < 0.00001)		-0.5 -0.25 0 0.25 0.5
Test for subgroup differences: $Chi^2 = 1.92$. df = 1 (P = 0.17). $I^2 = 47.8\%$		Favours [control] Favours [Experimental]

Figure 6. VI and FF/VI significantly improved wmFEV1 with an increase of 160 ml (P<0.001) and 240 ml (P<0.001) respectively compared to placebo.

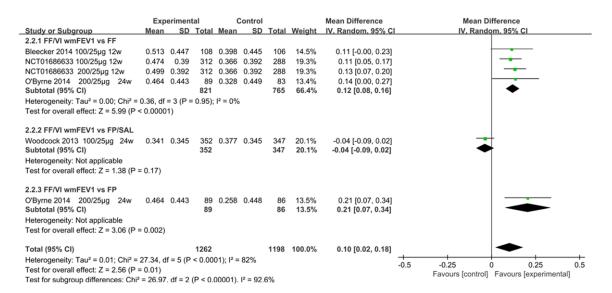


Figure 7. FF/VI was more potent than FF (P<0.001) and FP (P=0.002) and had similar potency to FP/SAL (P=0.17) in improving wmFEV1.

0.23, *P*=0.07) [12, 15], FP (95% CI: -0.07-0.20, *P*=0.33) [15, 23] and FP/SAL (95% CI: -0.03-0.21, *P*=0.14) [17] (**Figure 10**).

Severe exacerbations: A severe asthma exacerbation is a deterioration of asthma symptoms unresponsive to standard bronchodilators or corticosteroids, which requires systemic corticosteroids or an admission to hospital or emergency department visit. Only two studies reported numbers of severe asthma exacerbations. Compared to FF, FF/VI could significantly reduce rate of asthma deterioration [16], but was non-superior to FP [24].

Percentage of symptom-free 24-h periods: VI and FF/VI significantly reduced occurrence of affecting asthma symptoms compared with placebo with the confidence interval (95% CI: 7.58-21.55, P<0.001) [11, 18] and (95% CI: 12.57-21.28, P<0.001) [12, 22] respectively. Subgroup analysis showed that a duration of 28 days of VI treatment markedly relieved the asthma symptoms (I²=9%, 95% CI: 12.21-

	Exp	erimen	tal	c	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% C	I IV. Random, 95% CI
4.2.1 FF/VI PEF vs FF									
Lee 2014 100/25µg 14d	24.1	32.26	156	-2.9	33.37	159	11.2%	27.00 [19.75, 34.25]	
NCT01686633 100/25µg 12w	44.3	41.8	345	19.2	41.85	346	11.4%	25.10 [18.86, 31.34]	
NCT01686633 200/25µg 12w	47.7	41.8	345	19.2	41.85	346	11.4%	28.50 [22.26, 34.74]	
O'Byrne 2014 200/25µg 24w	51.8	41.26	197	18.2	41.26	193	10.9%	33.60 [25.41, 41.79]	
Subtotal (95% CI)			1043			1044	44.9%	28.03 [24.61, 31.45]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 2.72, df = 3 (P =	0.44); I ²	= 0%							
Test for overall effect: Z = 16.05 (P < 0.00001)									
4.2.2 FF/VI PEF vs FF/UMEC									
Lee 2014 100/25µg 14d vs FF/UMEC 100/62.5µg	24.1	32.26	156	15.7	33.14	155	11.1%	8.40 [1.13, 15.67]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/125 µg	24.1	32.26	156	20	32.37	158	11.2%	4.10 [-3.05, 11.25]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/250 µg	24.1	32.26	156	19	33.28	159	11.2%	5.10 [-2.14, 12.34]	
Subtotal (95% CI)			468			472	33.5%	5.84 [1.68, 10.01]	◆
Heterogeneity: Tau ² = 0.00; Chi ² = 0.74, df = 2 (P =	0.69); l ²	= 0%							
Test for overall effect: Z = 2.75 (P = 0.006)									
4.2.3 FF/VI PEF vs FP									
Lin J 2014 200/25µg 12w	46.2	38.1	154	14	38.22	152	10.8%	32.20 [23.65, 40.75]	
O'Byrne 2014 200/25µg 24w	51.8	41.26	197	18.8	41.2		10.9%	33.00 [24.84, 41.16]	
Subtotal (95% CI)			351			347	21.6%		•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.02, df = 1 (P =	0.89); l ²	= 0%							
Test for overall effect: Z = 10.83 (P < 0.00001)									
Total (95% CI)			1862			1863	100.0%	21.81 [13.89, 29.73]	
Heterogeneity: Tau ² = 132.67; Chi ² = 85.30, df = 8 (f	2 < 0.00	001)- 12							
Test for overall effect: $Z = 5.40$ (P < 0.00001)	- 0.00	001), I ²	- 3170						-50 -25 0 25 50
Test for subgroup differences: $Chi^2 = 81.81$. df = 2 (f	P < 0.00	001) 12	= 97.69	16					Favours [control] Favours [experimental]
rescrue sougroup unerences. Chir = 61.61. 01 = 2 (i	- 0.00	001).1-	- 01.0	10					

Figure 8. FF/VI was more potent than FF (P<0.001), FP (P<0.001) and FF/UMEC (P=0.006) in improving PEF.

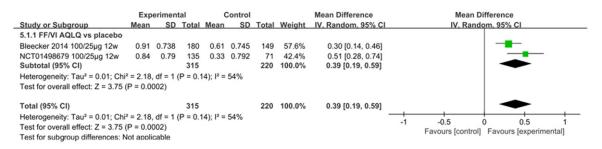


Figure 9. FF/VI administration could significantly improve the life quality relative to placebo (P<0.001).

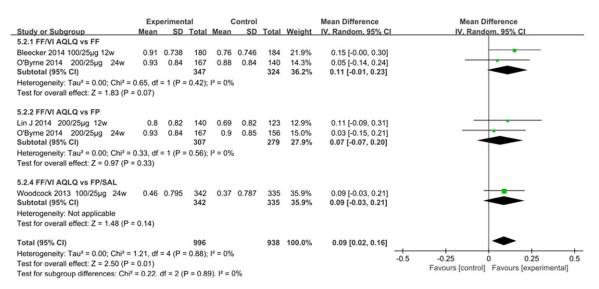


Figure 10. AQLQ scores were similar between FF/VI and FF (P=0.07), FP (P=0.33) and FP/SAL (P=0.14).

23.10, *P*<0.001) (**Figure 11**). But FF/VI was non-superior to FF (95% CI: -2.75-11.78, *P*= 0.22) [12, 13, 15], FP (95% CI: -7.74-8.5, *P*=0.93) [15, 23] or FF/UMEC (95% CI: -3.43-2.24, *P*=0.68) [13] in relieving asthma symptoms (**Figure 12**). Percentage of rescue-free 24-h periods: The number of rescue albuterol/salbutamol aerosol inhalations reflects the severity of asthma disease. Eight studies reported the impact of VI and FF/VI on the percentage of rescue-free 24-h periods. Less rescue drug use were found

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	Exper	rimental		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV. Random. 95% CI [%]	IV. Random, 95% CI [%]
7.1.1 VI symptom-free periods	s vs placebo								
Lötvall 2012 12.5µg 28d	26.8	32.27	98	14.2	32.27	98	13.6%	12.60 [3.56, 21.64]	
Lötvall 2012 25µg 28d	36.4	32.26	101	14.2	32.27	98	13.8%	22.20 [13.23, 31.17]	
Lötvall 2012 50µg 28d	32.3	32.42	102	14.2	32.27	98	13.8%	18.10 [9.13, 27.07]	
Lötvall 2014 25µg 12w	19.4	27.35	115	12.7	27.67	115	17.9%	6.70 [-0.41, 13.81]	
Subtotal (95% CI)			416			409	59.1%	14.56 [7.58, 21.55]	-
Heterogeneity: Tau ² = 31.97; Cl	hi ² = 8.15, df	= 3 (P =	0.04); 1	^e = 63%					
Test for overall effect: Z = 4.09	(P < 0.0001)								
7.1.2 FF/VI symptom-free peri	iods vs place	ebo							
NCT01498679 100/25µg 12w	24.8	28.57	153	9	28.54	154	19.8%	15.80 [9.41, 22.19]	
Bleecker 2014 100/25µg 12w	32.5	30.34	201	14.6	30.56	202	21.1%	17.90 [11.95, 23.85]	
Subtotal (95% CI)			354			356	40.9%	16.93 [12.57, 21.28]	•
Heterogeneity: Tau ² = 0.00; Chi	i ² = 0.22, df =	1 (P = 0	.64); 12	= 0%					
Test for overall effect: Z = 7.62	(P < 0.00001)							
Total (95% CI)			770			765	100.0%	15.38 [11.16, 19.60]	•
Heterogeneity: Tau ² = 12.76; Cl	hi² = 9.37, df	= 5 (P =	0.10); P	2 = 47%					
Test for overall effect: Z = 7.14	(P < 0.00001)							-20 -10 0 10 20
Test for subgroup differences: 0	Chi ² = 0.32. d	f = 1 (P =	0.57).	$I^2 = 0\%$					Favours [control] Favours [experimental]

Figure 11. Compared with placebo, VI and FF/VI significantly reduced occurrence of affecting asthma symptoms (P<0.001). Subgroup analysis showed that a duration of 28 days of VI treatment markedly relieved the asthma symptoms (I^2 =9%, 95% CI: 12.21-23.10, P<0.001).

	Exper	imental		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV. Random. 95% CI [%]	IV. Random, 95% CI [%]
7.2.1 FF/VI symptom-free periods vs FF									
Lee 2014 100/25µg 14d	7.3	21.9	154	5.8	22.43	158	13.9%	1.50 [-3.42, 6.42]	
Bleecker 2014 100/25µg 12w	32.5	30.34	201	20.4	30.42	204	12.1%	12.10 [6.18, 18.02]	
O'Byrne 2014 200/25µg 24w	21	32.56	197	21	32.23	193	11.3%	0.00 [-6.43, 6.43]	
Subtotal (95% CI)			552			555	37.3%	4.52 [-2.75, 11.78]	
Heterogeneity: Tau ² = 32.57; Chi ² = 9.64, df = 2 (P =	0.008); I ² =	79%							
Test for overall effect: Z = 1.22 (P = 0.22)									
7.2.2 FF/VI symptom-free periods vs FF/UMEC									
Lee 2014 100/25µg 14d vs FF/UMEC 100/62.5µg	7.3	21.9	154	8.6	22.27	154	13.9%	-1.30 [-6.23, 3.63]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/125 µg	7.3	21.9	154	8.2	22.02	155	14.0%	-0.90 [-5.80, 4.00]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/250 µg	7.3	21.9	154	6.9	22.23	159	14.0%	0.40 [-4.49, 5.29]	
Subtotal (95% CI)	1.0	2110	462	0.0	22.20	468	41.9%	-0.60 [-3.43, 2.24]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 0.25, df = 2 (P =	0.88 : $I^2 = 0\%$								
Test for overall effect: Z = 0.41 (P = 0.68)									
7.2.3 FF/VI symptom-free periods vs FP									
Lin J 2014 200/25µg 12w	25.4	34.11	155	20.6	34.15	152	9.5%	4.80 [-2.84, 12.44]	
O'Byrne 2014 200/25µg 24w	21	32.56	197	24.5	32.17	194	11.3%	-3.50 [-9.92, 2.92]	
Subtotal (95% CI)			352			346	20.8%	0.38 [-7.74, 8.50]	
Heterogeneity: Tau ² = 21,50; Chi ² = 2,66, df = 1 (P =	0.10); I ² = 6	2%							
Test for overall effect: Z = 0.09 (P = 0.93)	,,								
Total (95% CI)			1366			1369	100.0%	1.49 [-1.70, 4.67]	+
Heterogeneity: Tau ² = 12.60; Chi ² = 17.89, df = 7 (P	= 0.01); l ² =	61%							-20 -10 0 10 20
Test for overall effect: Z = 0.92 (P = 0.36)									Favours [control] Favours [experimental]
Test for subgroup differences: Chi ² = 1.66. df = 2 (P	= 0.44). I ² =	0%							ravous (control) ravous (experimental)

Figure 12. FF/VI was non-superior to FF (P=0.22), FP (P=0.93) or FF/UMEC (P=0.68) in relieving asthma symptoms. Due to different observation periods in the FF/VI group compared with FF, subgroup analysis was unavailable.

in patients with VI treatment relative to placebo (95% CI: 7.98-26.12, P<0.001) [11, 18]. Subgroup analysis found that a duration of 28 days of VI treatment substantially reduced the rescue drug use (l²=56%, 95% Cl: 12.71-28.66, P<0.001). FF/VI reduced the number of rescue drug use significantly compared with placebo (95% CI: 15.65-25.10, P<0.001) [12, 22] (Figure 13). FF/VI was more effective than FF in reducing rescue drug use (95% CI: 5.44-14.19, P<0.001) [12-15], with similar potency to FP (95% CI: -1.59-9.38, P=0.16) [15, 23] and FF/ UMEC (95% CI: -1.63-4.16, P=0.39) [13]. Subgroup analysis showed that compared with FF, a duration of 12 weeks of FF/VI treatment remarkably reduced the rescue drug use $(I^2=0\%)$. 95% CI: 9.04-15.30, P<0.001) (Figure 14).

Safety: Respiratory infections, nasopharyngitis, oral candidiasis, headaches and palpations are common adverse events with ICS/LABA administration. Ten studies reported detailed information of adverse events of VI and FF/ VI treatment compared to placebo. Adverse events occurred during VI and FF/VI treatment were similar compared with placebo with the confidence interval (95% CI: 0.65-1.00, P=0.05) [9-11, 18, 19, 25] and (95% CI: 0.94-1.37, P=0.20) [12, 19, 20, 22, 26] respectively (Figure 15). Six studies compared FF/VI with FF and found that once-daily FF/VI 100/25 µg produced similar adverse events compared with FF 100 µg once per day (95% CI: 0.91-1.21, P=0.49) [12-14, 16, 20, 27]. FF/VI was superior to FP (95% CI: 0.79-0.95, P=0.002) [23, 24]

	Expe	rimental		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV. Random. 95% CI [%]	[] IV. Random. 95% CI [%]
8.1.1 VI rescue-free 24-hour p	periods vs pl	acebo							
Lötvall 2012 12.5µg 28d	29.6	33.06	98	15	33.13	99	15.0%	14.60 [5.36, 23.84]	
Lötvall 2012 25µg 28d	43.4	32.96	101	15	33.13	99	15.1%	28.40 [19.24, 37.56]	· · · · ·
Lötvall 2012 50µg 28d	34	33.13	102	15	33.13	99	15.1%	19.00 [9.84, 28.16]	
Lötvall 2014 25µg 12w	21.7	28.74	115	14.6	29.06	115	17.5%	7.10 [-0.37, 14.57]	
Subtotal (95% CI)			416			412	62.8%	17.05 [7.98, 26.12]	-
Heterogeneity: Tau ² = 65.70; C	hi² = 12.99, d	if = 3 (P =	0.005)	; l ² = 77%					
Test for overall effect: Z = 3.68	(P = 0.0002)								
8.1.2 FF/VI rescue-free 24-ho	ur periods v	s placebo	,						
Bleecker 2014 100/25µg 12w	37.1	32.04	201	17.8	32.12	202	19.3%	19.30 [13.04, 25.56]	· · · · ·
NCT01498679 100/25µg 12w	30.1	32.16	153	8.3	32.14	154	17.9%	21.80 [14.61, 28.99]	
Subtotal (95% CI)			354			356	37.2%	20.38 [15.65, 25.10]	•
Heterogeneity: Tau ² = 0.00; Ch	i ² = 0.26, df =	= 1 (P = 0.	61); l2	= 0%					
Test for overall effect: Z = 8.46	(P < 0.00001)							
Total (95% CI)			770			768	100.0%	18.24 [12.63, 23.84]	•
Heterogeneity: Tau ² = 32.19; C	hi² = 14.93, d	f = 5 (P =	0.01);	l ² = 67%					-50 -25 0 25 5
Test for overall effect: Z = 6.38									
Test for subgroup differences:	Chi ² = 0.41. d	f = 1 (P =	0.52).	$I^2 = 0\%$					Favours [control] Favours [experimental]

Figure 13. VI and FF/VI reduced the number of rescue drug use significantly compared with placebo (P<0.001). Subgroup analysis found that a duration of 28 days of VI treatment substantially reduced the rescue drug use (I^2 =56%, 95% CI: 12.71-28.66, P<0.001).

	Exper	imental		Co	ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV. Random. 95% CI [%]	IV. Random, 95% CI [%]
8.2.1 FF/VI rescue-free 24-hour periods vs FF									
Lee 2014 100/25µg 14d	8.6	22.51	153	6.5	22.5	158	10.9%	2.10 [-2.90, 7.10]	
Bleecker 2014 100/25µg 12w	37.1	32.04	201	26.5	32.14	204	9.7%	10.60 [4.35, 16.85]	
NCT01686633 100/25µg 12w	34.8	34.36	345	22.6	34.23	346	10.8%	12.20 [7.09, 17.31]	
NCT01686633 200/25µg 12w	35.8	34.41	346	22.6	34.23	346	10.8%	13.20 [8.09, 18.31]	
O'Byrne 2014 200/25µg 24w	38.2	40	197	26.6	34.04	193	8.6%	11.60 [4.23, 18.97]	
Subtotal (95% CI)			1242			1247	50.8%	9.81 [5.44, 14.19]	-
Heterogeneity: Tau ² = 16.33; Chi ² = 11.91, df = 4 (P	= 0.02); 12 = 1	66%							
Test for overall effect: Z = 4.40 (P < 0.0001)									
8.2.2 FF/VI rescue-free 24-hour periods vs FF/UM	IEC								
Lee 2014 100/25µg 14d vs FF/UMEC 100/62.5µg	8.6	22.51	153	6.8	22.51	153	10.9%	1.80 [-3.24, 6.84]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/125 µg	8.6	22.51	153	7.9	22.43	157	10.9%	0.70 [-4.30, 5.70]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/250 µg	8.6	22.51	153	7.3	22.5	158	10.9%	1.30 [-3.70, 6.30]	
Subtotal (95% CI)			459			468	32.8%	1.26 [-1.63, 4.16]	*
Heterogeneity: Tau ² = 0.00; Chi ² = 0.09, df = 2 (P = 0	0.95); l ² = 0%	5							
Test for overall effect: Z = 0.86 (P = 0.39)									
8.2.3 FF/VI rescue-free 24-hour periods vs FP									
Lin J 2014 200/25µg 12w	32.4	36.73	155	31.5	36.74	152	7.8%	0.90 [-7.32, 9.12]	
O'Byrne 2014 200/25µg 24w	38.2	40	197	31.9	34.12	194	8.6%	6.30 [-1.07, 13.67]	
Subtotal (95% CI)			352			346	16.4%	3.89 [-1.59, 9.38]	-
Heterogeneity: Tau ² = 0.00; Chi ² = 0.92, df = 1 (P = 0	0.34); $I^2 = 0\%$	5							
Test for overall effect: Z = 1.39 (P = 0.16)									
Total (95% CI)			2053			2061	100.0%	6.02 [2.61, 9.44]	•
Heterogeneity: Tau ² = 21.24; Chi ² = 31.70, df = 9 (P	$= 0.0002$): l^2								
Test for overall effect: $Z = 3.46$ (P = 0.0005)	0.0002/, 1	. 270							-20 -10 0 10 20
Test for subgroup differences: $Chi^2 = 10.20$. df = 2 (F									Favours [control] Favours [experimental]

Figure 14. FF/VI was more effective than FF in reducing rescue drug use (P<0.001), with similar potency to FP (P=0.16) and FF/UMEC (P=0.39). Subgroup analysis showed that compared with FF, a duration of 12 weeks of FF/VI treatment remarkably reduced the rescue drug use (I^2 =0%, 95% CI: 9.04-15.30, P<0.001).

and had comparable adverse events relative to FP/SAL (95% CI: 0.94-1.22, *P*=0.32) [17], with relatively more adverse events than FF/UMEC (95% CI: 1.03-1.63, *P*=0.02) [13] (Figure 16).

Discussion

GINA guideline recommends a 5-step approach for the treatment of asthma [6]: SABA for mild asthma (step 1), regular therapy with inhaled corticosteroids (ICS) or leukotriene modifier (step 2), low-dose ICS and add-on drugs (step 3), ICS with LABA or addition of another control drug for persistent asthma (step 4), and oral steroids or anti-IgE therapy (step 5). ICS remains the first choice in asthma management with evident effect and acceptable tolerance [6]. Upper respiratory tract infection, pneumonia, nasopharyngitis, dysphonia, oral candidiasis, headache, abdominal pain, changes in serum glucose are common adverse events of ICS [28]. LABA has longer durations of action of about 12 hours in comparison with short-acting relievers. Common adverse events of LABAs include cardiac arrhythmias, agitation, headache, nasopharyngitis, upper respiratory tract infection and tremor. Monotherapy with LABA increased the mortality rates of asthma patients in SMART study [29]. Combination therapy with ICS/LABA in one inhaler is pre-

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H. Random, 95% Cl
9.1.1 VI adverse effects vs pla	acebo						
Richard 2012 12.5µg 7d	4	73	13	74	1.9%	0.31 [0.11, 0.91]	
Richard 2012 25µg 7d	6	73	13	74	2.5%	0.47 [0.19, 1.16]	
Oliver 2014 25µg 14d	9	27	6	26	2.7%	1.44 [0.60, 3.49]	
NCT00347139 25µg 14d	16	34	29	52	7.3%	0.84 [0.55, 1.30]	
NCT00347139 100µg 14d	14	37	29	52	6.5%	0.68 [0.42, 1.10]	
Oliver 2013 25µg 21d	22	26	19	27	10.4%	1.20 [0.90, 1.61]	-
Lötvall 2012 12.5µg 28d	25	100	37	102	7.4%	0.69 [0.45, 1.06]	
Lötvall 2012 25µg 28d	23	101	37	102	7.1%	0.63 [0.40, 0.98]	
Lötvall 2012 50µg 28d	31	102	37	102	8.2%	0.84 [0.57, 1.24]	-+
Lötvall 2014 25µg 12w	27	115	27	116	6.7%	1.01 [0.63, 1.61]	
Subtotal (95% CI)		688		727	60.8%	0.81 [0.65, 1.00]	•
Total events	177		247				
Heterogeneity: Tau ² = 0.05; Ch	i ² = 17.14, (if = 9 (P	= 0.05);	$ ^2 = 47\%$	6		
Test for overall effect: Z = 1.92	(P = 0.05)						
9.1.2 FF/VI adverse effects vs	placebo						
Oliver 2013 100/25µg 21d	20	27	19	27	9.5%	1.05 [0.76, 1.47]	+
Oliver 2012 100/25µg 28d	18	51	20	51	6.1%	0.90 [0.54, 1.49]	
Allen 2013 100/25µg 42d	23	56	16	58	5.8%	1.49 [0.88, 2.51]	
Allen 2013 200/25µg 42d	21	56	16	58	5.6%	1.36 [0.79, 2.33]	
Bleecker 2014 100/25µg 12w	29	201	22	203	5.9%	1.33 [0.79, 2.24]	
NCT01498679 100/25µg 12w	26	151	27	151	6.3%	0.96 [0.59, 1.57]	
Subtotal (95% CI)		542		548	39.2%	1.13 [0.94, 1.37]	•
Total events	137		120				
Heterogeneity: Tau ² = 0.00; Ch	i² = 3.33, di	= 5 (P =	= 0.65); l ²	= 0%			
Test for overall effect: Z = 1.29	(P = 0.20)						
Total (95% CI)		1230		1275	100.0%	0.93 [0.80, 1.09]	•
Total events	314		367				
Heterogeneity: Tau ² = 0.04; Ch	i ² = 25.14, 0	if = 15 (P = 0.05).	l ² = 40)		
Test for overall effect: Z = 0.89							0.01 0.1 1 10 1
Test for subgroup differences: 0	. /	df = 1 (P = 0.02	$l^2 = 81$	0%		Favours [experimental] Favours [control]

Figure 15. Adverse events occurred during VI and FF/VI treatment were similar compared with placebo.

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% C	M-H. Random, 95% Cl
9.2.1 FF/VI adverse effects vs FF							
Lee 2014 100/25µg 14d	43	172	25	187	3.4%	1.87 [1.20, 2.92]	
Dliver A 2014 100/25µg 14d	4	25	1	25	0.2%	4.00 [0.48, 33.33]	
Dliver 2012 100/25µg 28d	18	51	23	51	3.0%	0.78 [0.48, 1.26]	
Bleecker 2014 100/25µg 12w	29	201	21	205	2.6%	1.41 [0.83, 2.39]	
VCT01686633 100/25µg 12w	131	346	130	347	9.9%	1.01 [0.83, 1.22]	+
VCT01686633 200/25µg 12w	124	346	130	347	9.7%	0.96 [0.79, 1.16]	+
Bateman 2013 100/25µg 36w	677	1009	681	1010	16.3%	1.00 [0.94, 1.06]	t
Subtotal (95% CI)		2150		2172	45.0%	1.05 [0.91, 1.21]	•
Fotal events	1026		1011				
Heterogeneity: Tau ² = 0.01; Chi ² = 12.30, df = 6 (P =	0.06); 12 =	51%					
Test for overall effect: Z = 0.69 (P = 0.49)							
0.2.2 FF/VI adverse effects vs FF/UMEC							
ee 2014 100/25µg 14d vs FF/UMEC 100/62.5µg	43	172	30	180	3.8%	1.50 [0.99, 2.28]	
ee 2014 100/25µg 14d vs FF/UMEC 100/125 µg	43	172	38	176	4.3%	1.16 [0.79, 1.70]	
Lee 2014 100/25µg 14d vs FF/UMEC 100/250 µg	43	172	36	186	4.2%	1.29 [0.87, 1.91]	
Subtotal (95% CI)	10	516	00	542	12.2%	1.30 [1.03, 1.63]	•
Fotal events	129		104				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.81, df = 2 (P = 0		0.0%	104				
First for overall effect: $Z = 2.24$ (P = 0.02)	<i></i> , r = (0 70					
9.2.3 FF/VI adverse effects vs FP							
in J 2014 200/25µg 12w	41	155	43	154	4.6%	0.95 [0.66, 1.36]	+
Busse 2013 100/25µg 52w	142	201	80	100	12.8%	0.88 [0.77, 1.01]	-
Busse 2013 200/25µg 52w	135	202	80	100	12.5%	0.84 [0.73, 0.96]	-
Subtotal (95% CI)	155	558	00	354	29.9%	0.87 [0.79, 0.95]	•
Fotal events	318	550	203	554	20.070	0.07 [0.73, 0.35]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.62, df = 2 (P = 0		0.0/	203				
Test for overall effect: $Z = 3.07$ (P = 0.002)	J.73), I ² = (076					
0.2.4 FF/VI adverse effects vs FP/SAL							
Noodcock 2013 100/25µg 24w	217	403	203	403	12.8%	1.07 [0.94, 1.22]	+
Subtotal (95% CI)	217	403	203	403	12.8%	1.07 [0.94, 1.22]	•
Total events	217	403	203	403	12.0 %	1.07 [0.04, 1.22]	ſ
	217		203				
Heterogeneity: Not applicable							
Fest for overall effect: Z = 0.99 (P = 0.32)							
Fotal (95% CI)	100000	3627		3471	100.0%	1.02 [0.93, 1.12]	t
Fotal events	1690		1521				
Heterogeneity: Tau ² = 0.01; Chi ² = 30.71, df = 13 (P	= 0.004); I	² = 58%					0.01 0.1 1 10
Test for overall effect: Z = 0.45 (P = 0.65)							Favours [experimental] Favours [control]
Test for subgroup differences: Chi ² = 15.40. df = 3 (F	= 0.002	12 - 90.6	10/				avous feybenmental Lavous foontiol

Figure 16. Once-daily FF/VI 100/25 μ g produced similar adverse events compared with FF 100 μ g once per day (*P*=0.49). FF/VI was superior to FP (*P*=0.002), non-superior to FP/SAL (*P*=0.32) and had relatively more adverse events than FF/UMEC (*P*=0.02).

ferred, which can improve lung function and reduce deterioration [7].

Compared with fluticasone propionate (FP), FF has a longer duration of action, greater receptor affinity and is more potent in the respiratory cells, allowing for its once-daily use in asthma control [30, 31]. Vilanterol trifenatate is a longacting β_2 agonist inhaled once a day. Compared with salmeterol, VI has a faster onset and longer duration of action, with a much higher selectivity for β_2 receptors [32]. Simplifying the dosing regimen, FF/VI can potentially increase patient adherence and thereby control of asthma symptoms [26].

In our meta-analysis, when pulmonary function indices (trough FEV1, wmFEV1 and PEF) were assessed in adolescents and adults with persistent or uncontrolled asthma, VI was more effective than placebo. Compared with placebo, once-daily FF/VI 100/25 µg was more effective in improving pulmonary function with a significant increase in trough FEV1, 0-24 h serial wmFEV1 and PEF. The percentages of symptom-free and rescue-free 24-h periods were also increased in patients with FF/VI inhalation versus controls. Greater improvement was found in the health-related quality of life of patients inhaling FF/VI 100/25 µg relative to controls.

Comparing FF/VI with FF alone, greater improvements in trough FEV1, 0-24 h serial wmFEV1 and PEF were found with dual regimen. In an exacerbation study, once-daily FF/VI 100/25 μ g for 24-78 weeks delayed the time to first severe asthma exacerbation and reduced the rate of exacerbation, compared with once-daily FF 100 μ g alone [16]. FF/VI was also associated with a significantly greater percentage of rescue-free 24-h periods than FF.

In trials enrolling patients with moderate to severe persistent asthma receiving FF/VI for 12 to 24 weeks, once-daily FF/VI 200/25 μ g was more effective than FP 500 μ g twice daily in improving trough FEV1, 0-24 h serial wmFEV1 and PEF [15, 23], but it was non-superior to FP when AQLQ, exacerbation, symptom-free 24-h

periods and rescue-free 24-h periods were concerned.

No significant differences were observed when patients receiving once-daily 100/25 µg FF/VI or twice-daily 250/50 µg FP/SAL in terms of change from baseline in trough FEV1 and wmFEV1 at 24 weeks [17]. Both treatments produced a sustained duration of bronchodilator effect over 24 h which was assessed by serial hourly measurement of FEV1. There was no significant difference between two treatments in terms of health-related quality of life, as measured by the AQLO scores for usual activities, asthma symptoms, self-care, discomfort and emotion. FF/VI was generally well tolerated in patients with asthma and the adverse events were generally similar between two treatments [17].

FF/VI had similar potency to FF/UMEC when trough FEV1, symptom-free 24-h periods and rescue-free 24-h periods were concerned, although moderately weaker in improvement of drug tolerability [13].

This meta-analysis has several limitations: (1) The enrolled numbers of patients in several included studies were relatively small, which might impair the strength of evidence. (2) Moderate to high heterogeneity was found in some studies evaluating endpoints of symptom-free 24-hour periods and rescue-free 24hour periods, which may due to the different publication date and different observing periods. Subgroup analyses revealed that different duration of treatment may account for the high heterogeneity. (3) In some studies, a significant discontinuation rate ranging from 15.4% to 36.75% was found, which may reduce the persuasiveness of the results. (4) All trials were funded by the manufacturer of VI and FF/VI. which might contribute to a potential source of conflict of interest.

In summary, once-daily vilanterol or fixed-dose combination of fluticasone furoate and vilanterol is effective and well tolerated in asthma patients. More studies are still required to determine the relative position of fluticasone furoate and vilanterol to other current available ICS/LABA drugs.

Disclosure of conflict of interest

None.

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