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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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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, single-inhaler, 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

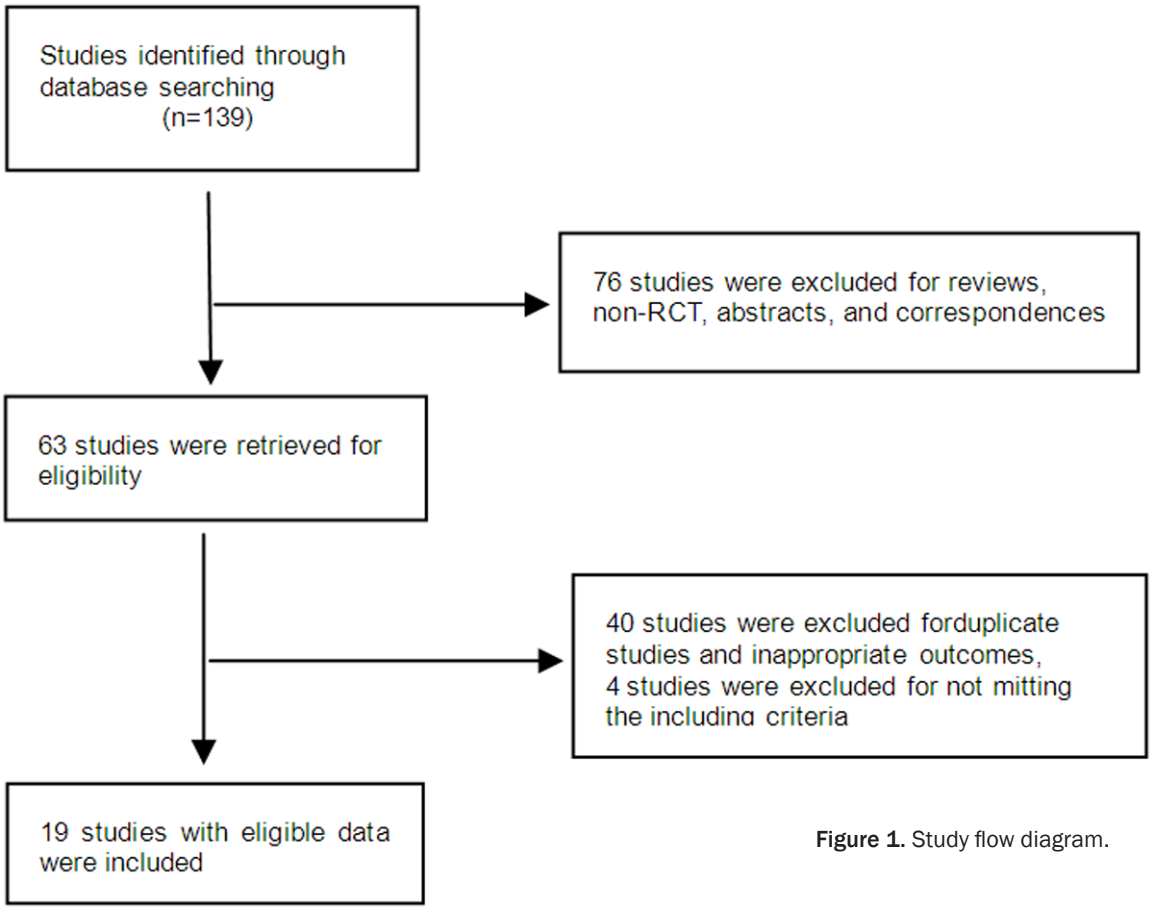

Figure 1. Study flow diagram.

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, EMBASE, 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 randomized 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 μg; (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 included in the meta-analysis

Study	Year	Study design	Type of disease	Country	Ethnicity	Age (y)	Male (%)	Patients (n)	Jada score	Experimental group	Control group	Duration of treatment	Outcomes
Richard [9]	2012	multicentre, randomised, 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-controlled, four-way incomplete 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, pharmacokinetic parameters, blood glucose, blood potassium, AE
Lötvall [11]	2012	multicentre, randomised, 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, randomized, 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, pharmacokinetic parameters, blood glucose, blood potassium
Bleecker [12]	2014	a randomized, double-blind, parallel-group study	persistent asthma	USA, Poland, Ukraine	White, Asian, African American, 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	uncontrolled 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 periods, AE
NCT01686633 [14]	2013	multicenter, randomized, 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 periods, PEF, AE
O'Byrne [15]	2014	randomised, multicentre, double-blind, double-dummy, parallel-group study	Moderate to severe, persistent-asthma	Germany, Japan, Poland, Romania, 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 periods, AQLQ, PEF, ACT
Bateman [16]	2013	randomised, multicentre, double-blind, parallel-group study	uncontrolled 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 exacerbation, severe asthma exacerbations, trough FEV1, ACQ7, AE
Woodcock [17]	2013	multicenter, randomized, 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 bronchodilation, trough FEV1, AE, AQLQ, ACT

Oliver [19]	2013	randomized, double-blind, placebo-controlled, four-way crossover study	mild asthma	Sweden, Australia, 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, randomised, 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 decrease 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 controlled, 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 periods, symptom-free 24-h periods, AQLQ, AE
Lin J [23]	2014	double-blind, double-dummy, active-comparator, parallel-group, multicenter study	persistent asthma	China, South Korea, 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, Thailand	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-controlled study	persistent asthma	Germany, Poland, 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 measurements, 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.

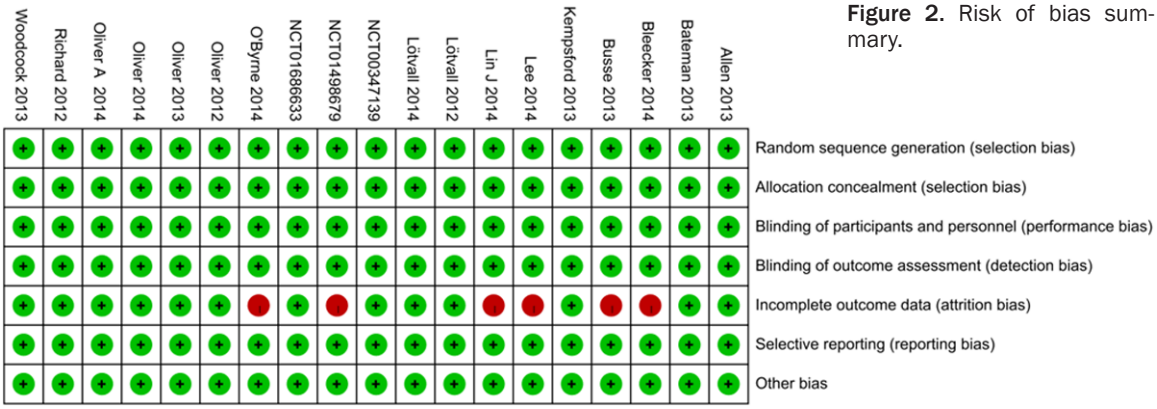

Figure 2. Risk of bias summary.

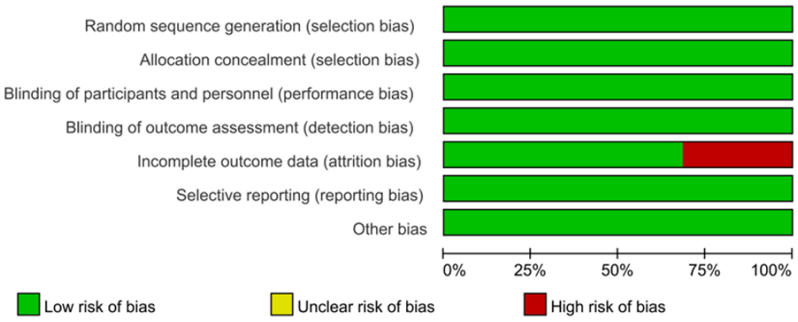

Figure 3. Risk of bias graph.

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**).

Meta-analysis results

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 increased trough FEV1 with an improvement of 140 ml (95% CI: 0.11-0.18, P<0.001) [9-11] and 170 ml (95% CI: 0.09-0.26, P<0.001) respectively [12] (**Figure 4**). FF/VI was more potent than FF (95% CI: 0.06-0.11, P<0.001) [12-16] and FP (95% CI: 0.13-0.29, P<0.001) [15] and had similar potency to fluticasone furoate/umeclidinium (FF/UMEC) (95% CI: 0.00-0.06, P=0.03) [13] and fluticasone propionate/salmeterol (FP/SAL) (95% CI: -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**).

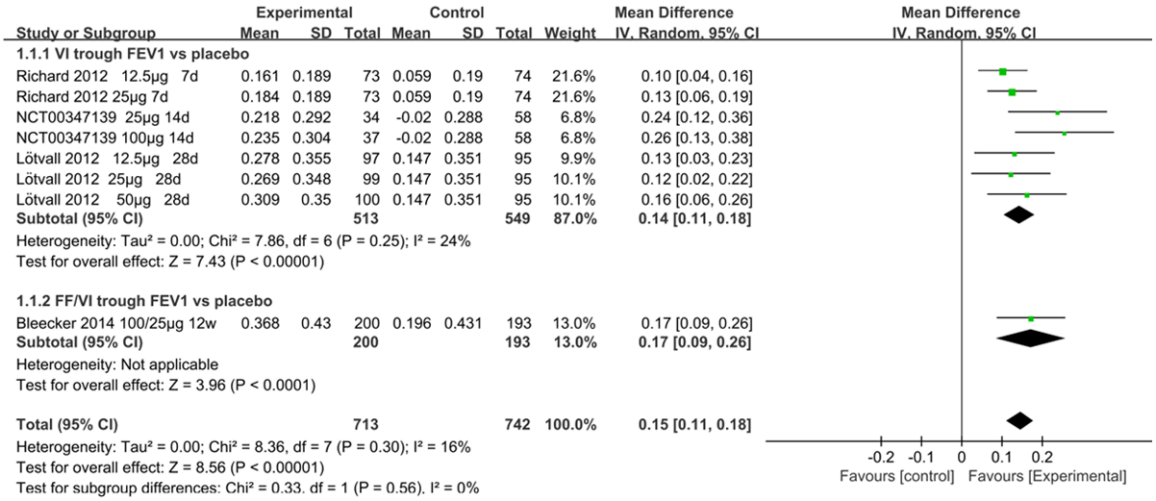

Figure 4. Monotherapy with VI and combined FF/VI treatment significantly increased trough FEV1 with an improvement of 140 ml (P<0.001) and 170 ml (P<0.001) respectively.

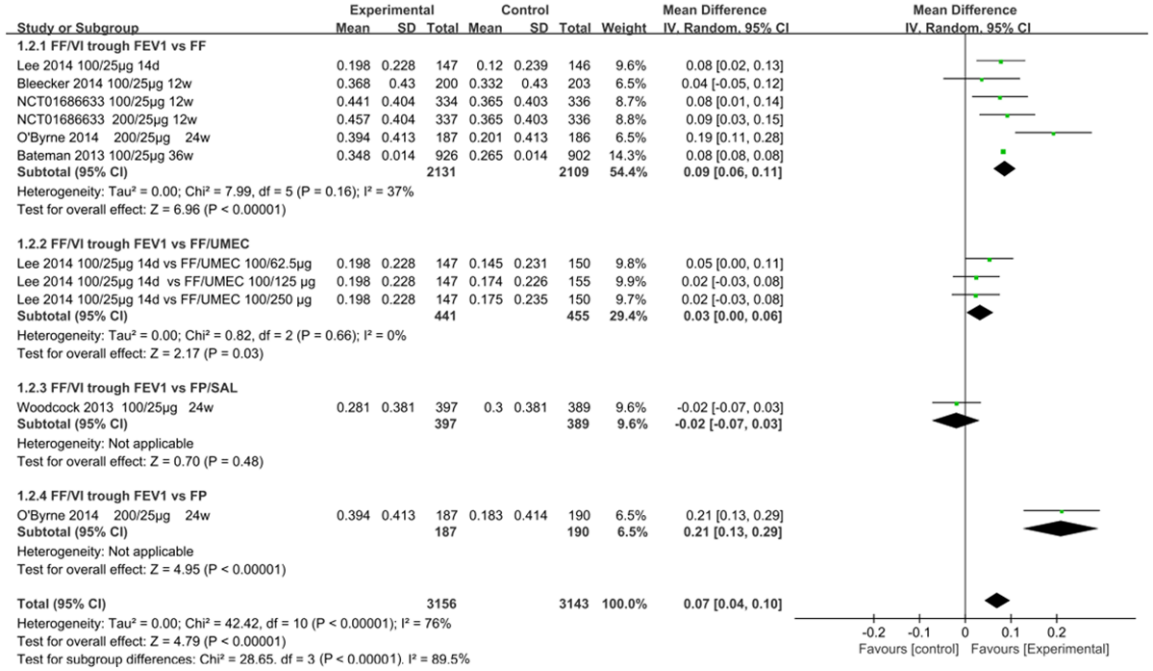

Figure 5. FF/VI was more potent than FF (P<0.001), FP (P<0.001) and FF/UMEC (P=0.03) and had similar potency to FP/SAL (P=0.48) in improving trough FEV1.

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-

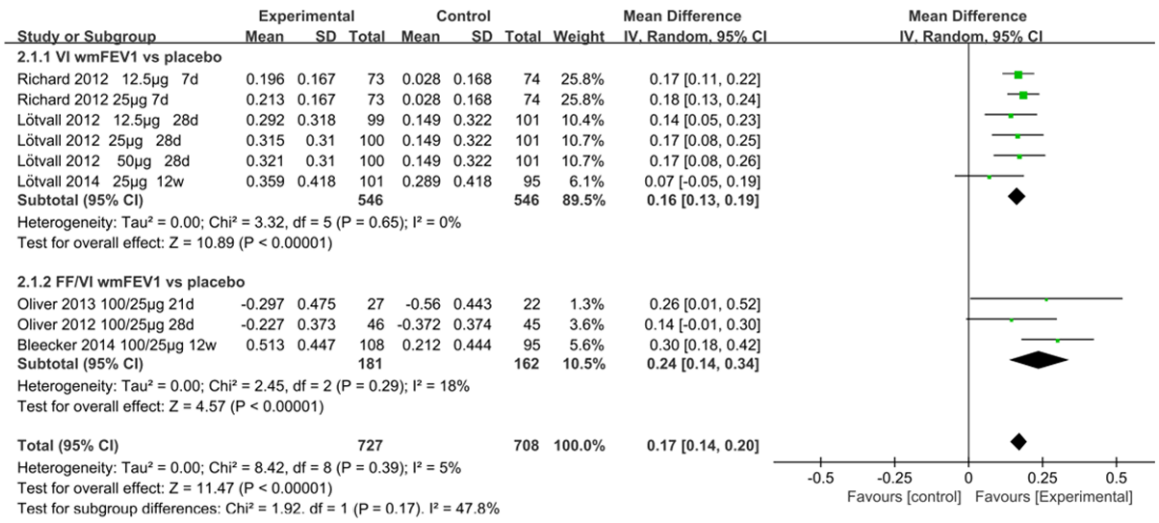

Figure 6. VI and FF/VI significantly improved wmFEV1 with an increase of 160 ml (P<0.001) and 240 ml (P<0.001) respectively compared to placebo.

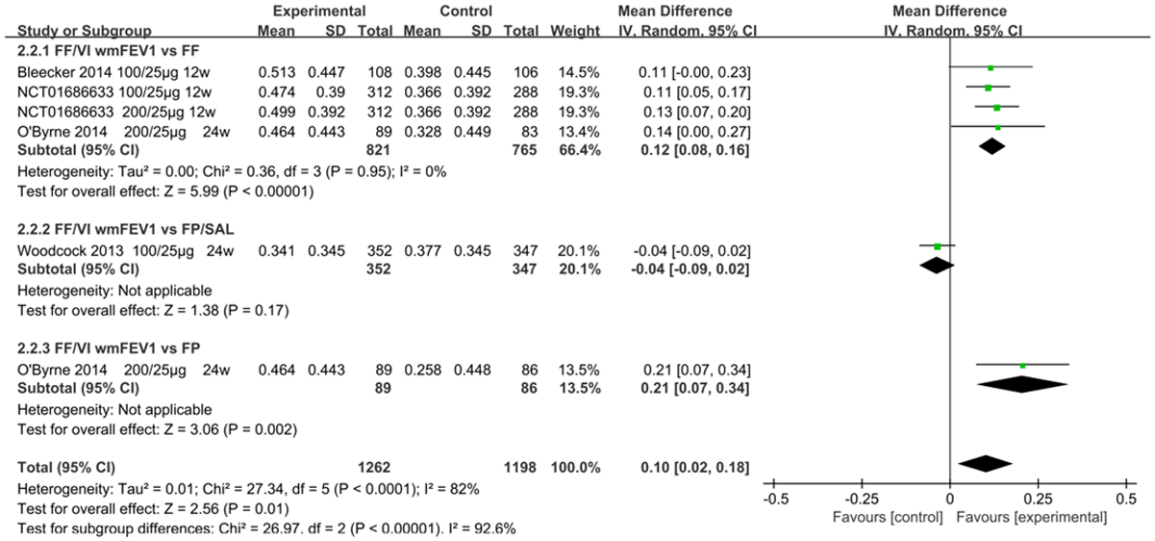

Figure 7. FF/VI was more potent than FF (P<0.001) and FP (P=0.002) and had similar potency to FP/SAL (P=0.17) in improving wmFEV1.

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 (I^2=9%, 95% CI: 12.21-

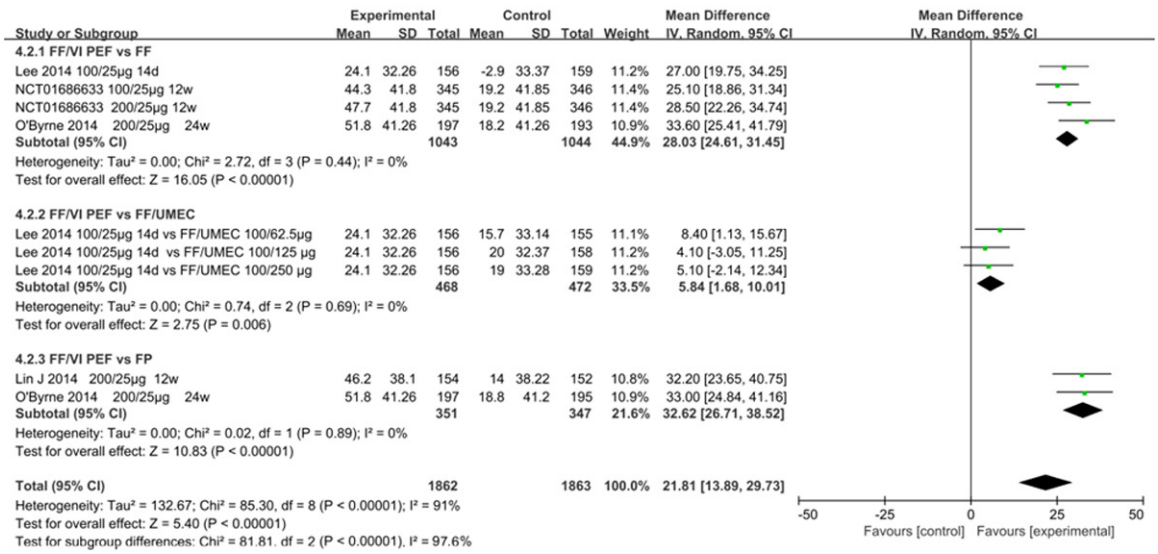

Figure 8. FF/VI was more potent than FF (P<0.001), FP (P<0.001) and FF/UMEC (P=0.006) in improving PEF.

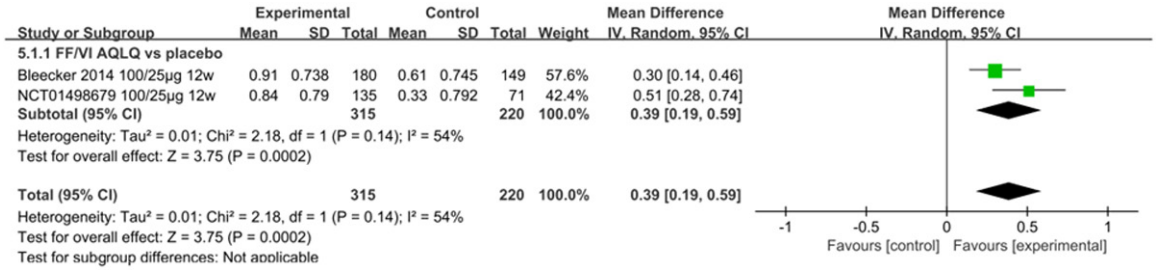

Figure 9. FF/VI administration could significantly improve the life quality relative to placebo (P<0.001).

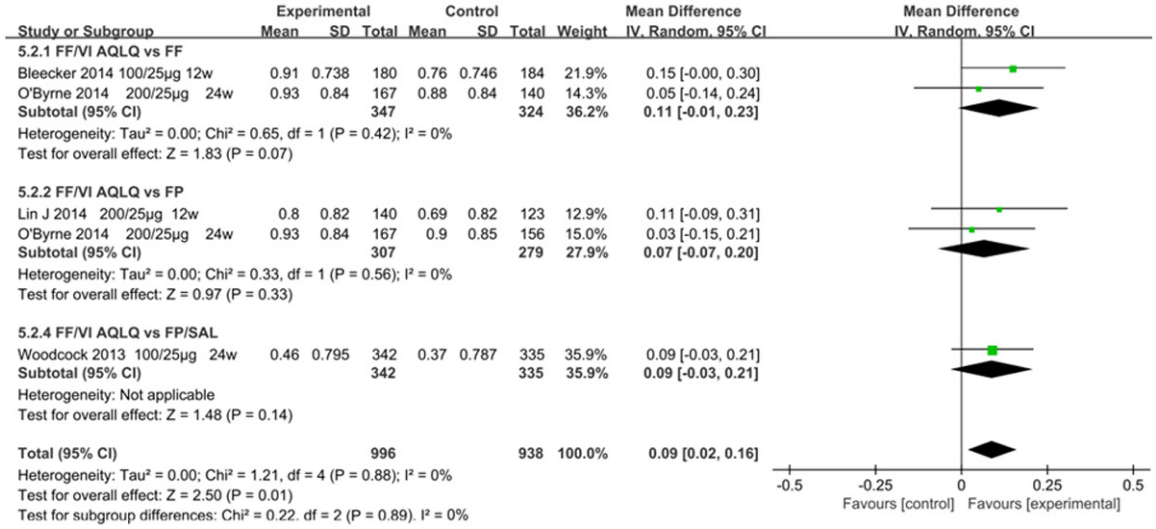

Figure 10. AQLQ scores were similar between FF/VI and FF (P=0.07), FP (P=0.33) and FP/SAL (P=0.14).

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

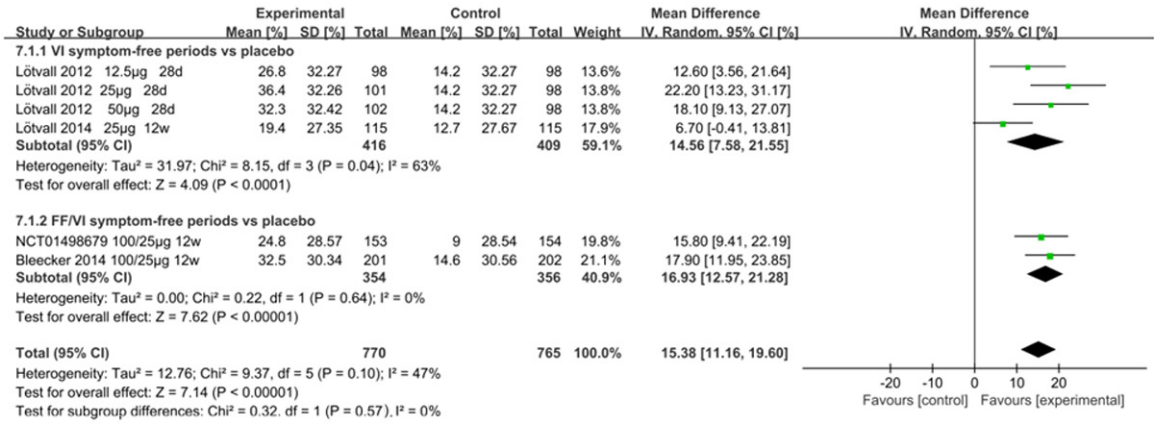

Figure 11. Compared with placebo, VI and FF/VI significantly reduced occurrence of affecting asthma symptoms (*P*<0.001). Subgroup analysis showed that a duration of 28 days of VI treatment markedly relieved the asthma symptoms (I^2=9%, 95% CI: 12.21-23.10, *P*<0.001).

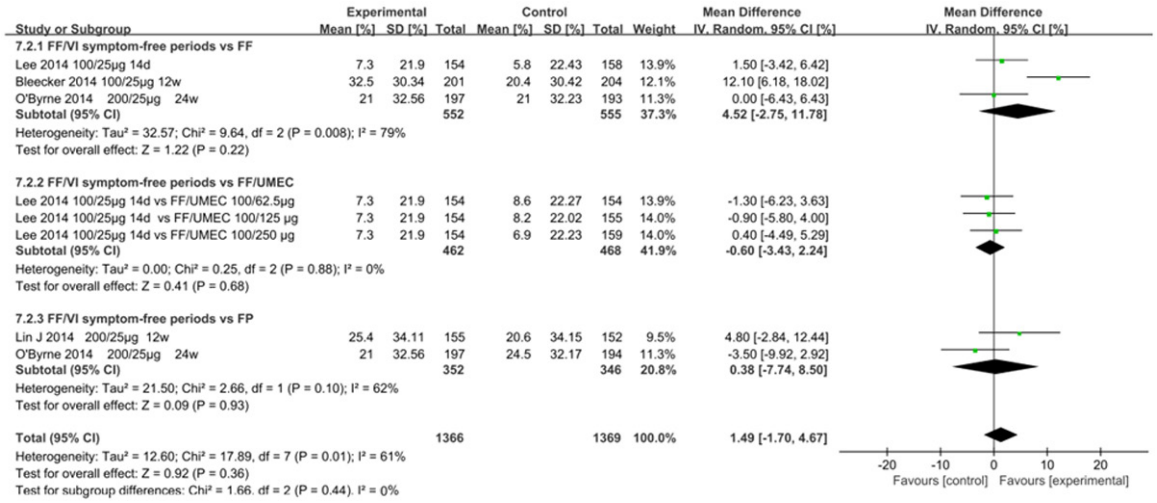

Figure 12. FF/VI was non-superior to FF (*P*=0.22), FP (*P*=0.93) or FF/UMEC (*P*=0.68) in relieving asthma symptoms. Due to different observation periods in the FF/VI group compared with FF, subgroup analysis was unavailable.

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 (I^2=56%, 95% CI: 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]

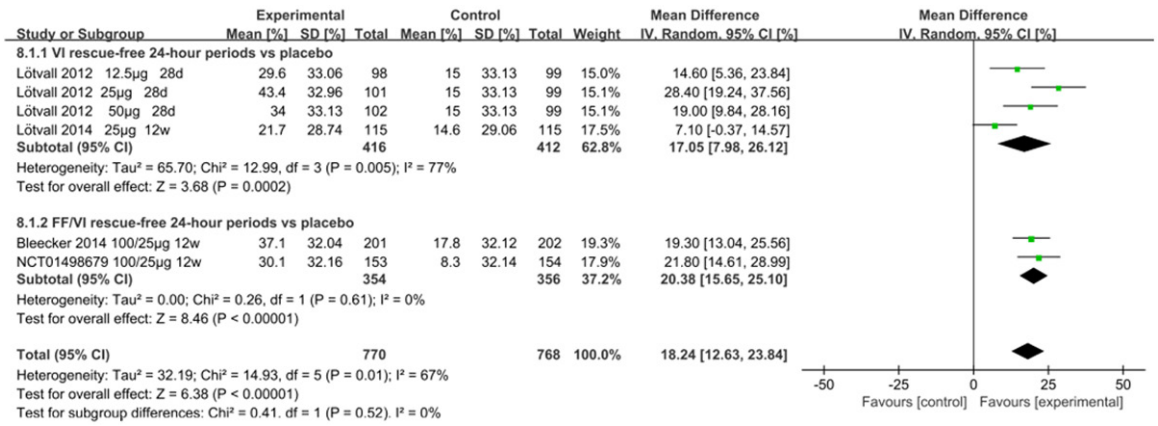

Figure 13. VI and FF/VI reduced the number of rescue drug use significantly compared with placebo (P<0.001). Subgroup analysis found that a duration of 28 days of VI treatment substantially reduced the rescue drug use (I^2=56%, 95% CI: 12.71-28.66, P<0.001).

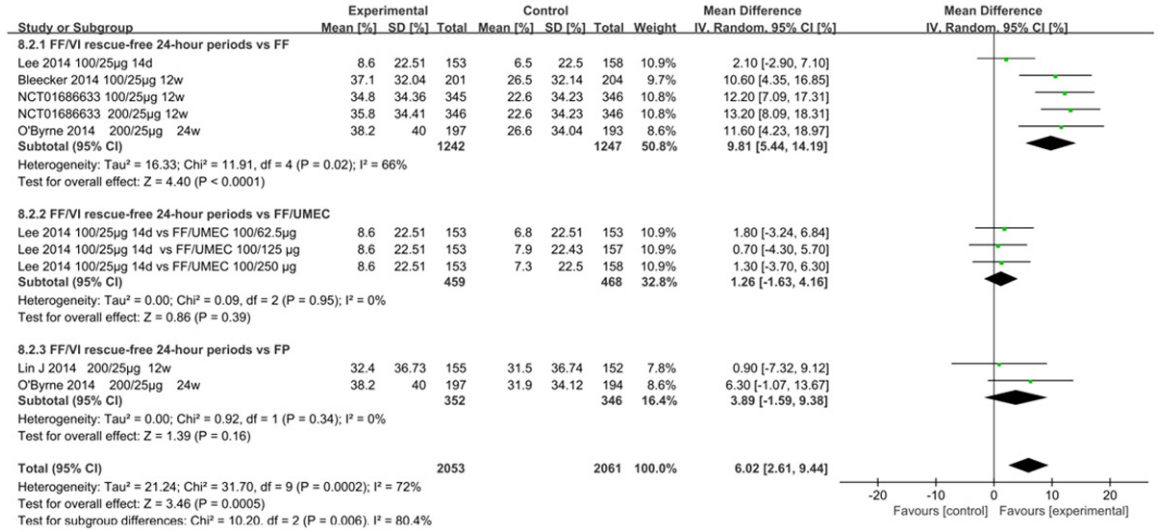

Figure 14. FF/VI was more effective than FF in reducing rescue drug use (P<0.001), with similar potency to FP (P=0.16) and FF/UMEC (P=0.39). Subgroup analysis showed that compared with FF, a duration of 12 weeks of FF/VI treatment remarkably reduced the rescue drug use (I^2=0%, 95% CI: 9.04-15.30, P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

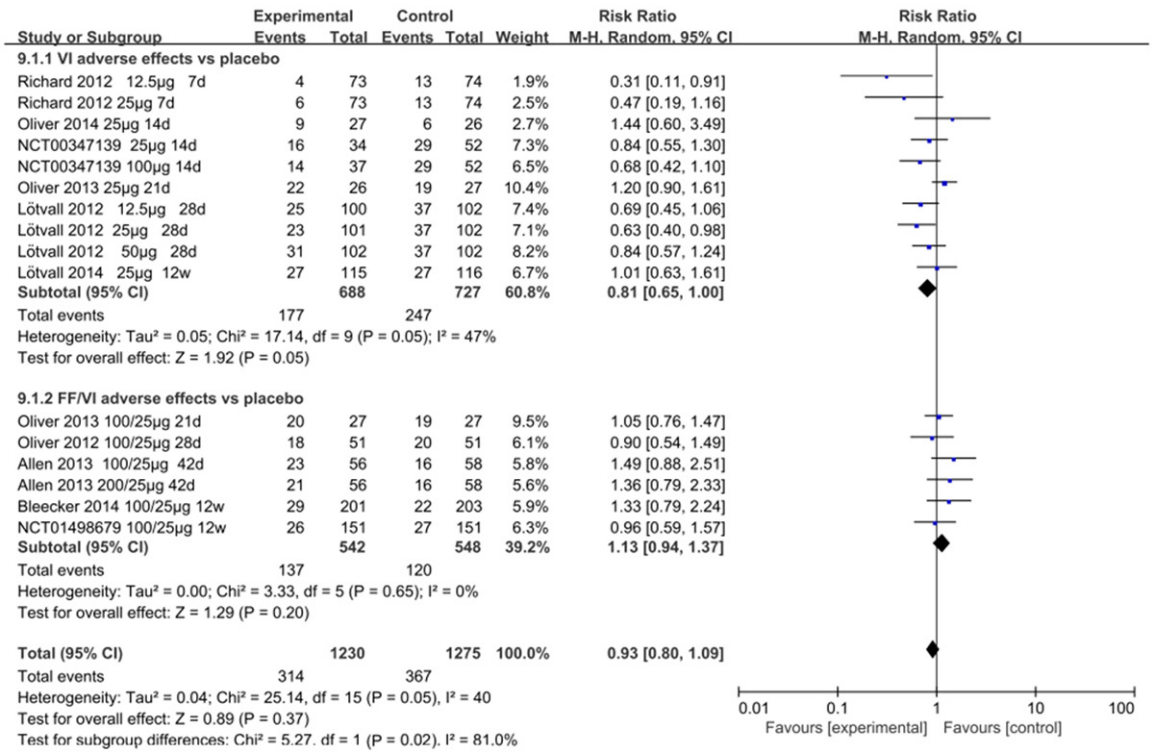

Figure 15. Adverse events occurred during VI and FF/VI treatment were similar compared with placebo.

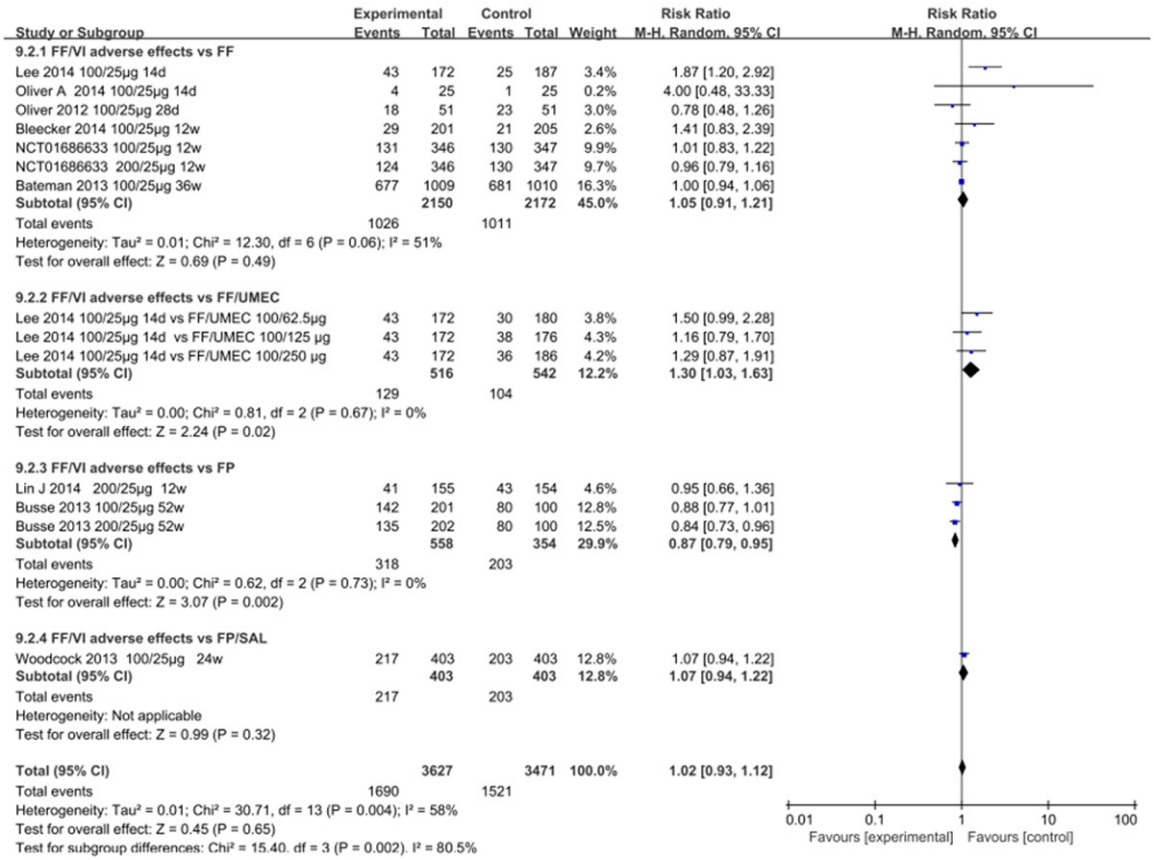

Figure 16. Once-daily FF/VI 100/25 μg produced similar adverse events compared with FF 100 μg once per day (*P*=0.49). FF/VI was superior to FP (*P*=0.002), non-superior to FP/SAL (*P*=0.32) and had relatively more adverse events than FF/UMEC (*P*=0.02).

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 long-acting 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 μg for 24-78 weeks delayed the time to first severe asthma exacerbation and reduced the rate of exacerbation, compared with once-daily FF 100 μg 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 μg was more effective than FP 500 μg 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 AQLQ 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 24-hour 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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References

[1] Löwhagen O. Diagnosis of asthma-a new approach. Allergy 2012; 67: 713-7.

[2] Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitzgerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008; 31: 143-78.

[3] Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. J Allergy ClinImmunol 2011; 127: 145-52.

[4] To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012; 12: 204.

[5] Schluger NW, Koppaka R. Lung disease in a global context. A call for public health action. Ann Am Thorac Soc 2014; 11: 407-16.

[6] Urbano FL. Review of the NAEPP 2007 Expert Panel Report (EPR-3) on Asthma Diagnosis and Treatment Guidelines. J Manag Care Pharm 2008; 14: 41-49.

[7] British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on themanagement of asthma. Thorax 2014; 69 Suppl 1: 1-192.

[8] European Medicines Agency. RelvarEllipta (fluticasone furoate/vilanterol): summary of product characteristics 2013. http://www.ema.europa.eu. Accessed on Sep 30, 2015.

[9] Sterling R, Lim J, Frith L, Snowise NG, Jacques L, Haumann B. Efficacy and optimal dosing interval of the long-acting beta2 agonist, vilanterol, in persistent asthma: a randomised trial. Respir Med 2012; 106: 1110-5.

[10] GSK Protocol ID B2C106093 (NCT00347139). http://www.gsk-clinicalstudyregister.com/study/B2C106093#ps. Assessed on Sep 30, 2015.

[11] Lötvall J, Bateman ED, Bleecker ER, Busse WW, Woodcock A, Follows R, Lim J, Stone S, Jacques L, Haumann B. 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. Eur Respir J 2012; 40: 570-9.

[12] Bleecker ER, Lötvall J, O'Byrne PM, Woodcock A, Busse WW, Kerwin EM, Forth R, Medley HV, Nunn C, Jacques L, Bateman ED. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. J Allergy ClinImmunol Pract 2014; 2: 553-61.

[13] Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. Respir Med 2015; 109: 54-62.

[14] GSK. Protocol ID 116863 (NCT01686633). http://www.gsk-clinicalstudyregister.com/study/116863#ps. Assessed on Sep 30, 2015.

[15] O'Byrne PM, Bleecker ER, Bateman ED, Busse WW, Woodcock A, Forth R, Toler WT, Jacques L, Lötvall J. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. Eur Respir J 2014; 43: 773-82.

[16] Bateman ED, O'Byrne PM, Busse WW, Lötvall J, Bleecker ER, Andersen L, Jacques L, Frith L, Lim J, Woodcock A. Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone. Thorax 2014; 69: 312-9.

[17] Woodcock A, Bleecker ER, Lötvall J, O'Byrne PM, Bateman ED, Medley H, Ellsworth A, Jacques L, Busse WW. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest 2013; 144: 1222-9.

[18] Lötvall J, Bateman ED, Busse WW, O'Byrne PM, Woodcock A, Toler WT, Jacques L, Goldfrad C, Bleecker ER. Comparison of vilanterol, a novel long-acting beta2 agonist, with placebo and a salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids. J Negat Results Biomed 2014; 13: 9.

[19] Oliver A, Bjermer L, Quinn D, Saggu P, Thomas P, Yarnall K, Lötvall J. Modulation of allergen-induced bronchoconstriction by fluticasone furoate and vilanterol alone or in combination. Allergy 2013; 68: 1136-42.

[20] Oliver A, Quinn D, Goldfrad C, van Hecke B, Ayer J, Boyce M. Combined fluticasone furoate/vilanterol reduces decline in lung function following inhaled allergen 23 h after dosing in adult asthma: a randomised, controlled trial. Clin Transl Allergy 2012; 2: 11.

[21] Kempsford RD, Oliver A, Bal J, Tombs L, Quinn D. The efficacy of once-daily fluticasone furoate/vilanterol in asthma is comparable with morning or evening dosing. Respir Med 2013; 107: 1873-80.

[22] GSK. Protocol ID 113719 (NCT01498679). http://www.gsk-clinicalstudyregister.com/study/113719#ps. Assessed on Sep 30, 2015.

[23] Lin J, Kang J, Lee SH, Wang C, Zhou X, Crawford J, Jacques L, Stone S. Fluticasone furoate/

vilanterol 200/25 mcg in Asian asthma patients: a randomized trial. Respir Med 2015; 109: 44-53.

[24] Busse WW, O'Byrne PM, Bleecker ER, Lötvall J, Woodcock A, Andersen L, Hicks W, Crawford J, Jacques L, Apoux L, Bateman ED. Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients≥12 years old with asthma: a randomised trial. Thorax 2013; 68: 513-20.

[25] Oliver A, VanBuren S, Allen A, Hamilton M, Tombs L, Kempsford R, Qaqundah P. Safety, tolerability, pharmacokinetics, and pharmacodynamics of vilanterol, a novel inhaled long-acting β-agonist, in children aged 5-11 years with persistent asthma: a randomized trial. Clin Pharmacol Drug Dev 2014; 3: 215-221.

[26] Allen A, Schenkenberger I, Trivedi R, Cole J, Hicks W, Gul N, Jacques L. Inhaled fluticasone furoate/vilanterol does not affect hypothalamic-pituitary-adrenal axis function in adolescent and adult asthma: randomised, double-blind, placebo-controlled study. Clin Respir J 2013; 7: 397-406.

[27] Oliver A, VanBuren S, Allen A, Hamilton M, Tombs L, Inamdar A, Kempsford R. Tolerability of fluticasone furoate/vilanterol combination therapy in children aged 5 to 11 years with persistent asthma. Clin Ther 2014; 36: 928-939. e1.

[28] Phan H, Brown MA. Fluticasone furoate for the treatment of childhood asthma. Expert Rev Respir Med 2015; 9: 391-404.

[29] Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006; 129: 15-26.

[30] Valotis A, Högger P. Human receptor kinetics and lung tissue retention of the enhanced-affinity glucocorticoid fluticasone furoate. Respir Res 2007; 8: 54.

[31] Rossios C, To Y, To M, Ito M, Barnes PJ, Adcock IM, Johnson M, Ito K. Long-acting fluticasone furoate has a superior pharmacological profile to fluticasone propionate in human respiratory cells. Eur J Pharmacol 2011; 670: 244-51.

[32] Cazzola M, Page CP, Rogliani P, Matera MG. β2-agonist therapy in lung disease. Am J Respir Crit Care Med 2013; 187: 690-6.