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Fluticasone/Formoterol compared with other ICS/LABAs in asthma: A systematic review

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Abstract

Background

An ICS-LABA combination has become the standard of care in asthma. Various ICS-LABAs are commercially available providing the clinician with many choices. A thorough understanding of the clinical efficacy and safety of various formulations will immensely benefit the prescribing doctor to decide the choice of agent. The present review compares the clinical efficacy and safety of formoterol fluticasone (FF) to other ICS/LABA combinations in asthmatics.

Methods

The review adhered to the general principles mentioned in the CRD guidance and the PRISMA statement. We searched Medline, Embase, and Cochrane Controlled Trials Register databases on the efficacy of FF in treating asthma compared with other ICS-LABAs. A total of 138 trials identified initially. Only trials comparing the efficacy and safety of FF in comparison with Salmeterol/fluticasone (SF) or Budesonide/Formoterol (BF) were selected. The outcomes compared were onset of bronchodilator action, improvement in lung function, asthma control, asthma related quality of life and risk of pneumonia.

Results

16 studies were included in the final analysis. FF therapy provided faster onset of bronchodilatation than SF. A better improvement in lung function was seen with FF inhaler use as compared with comparators in two studies. Patients using the FF inhaler had a non-inferior asthma control and asthma related quality of life. Pneumonia risk was least with FF usage.

Conclusion

FF provides faster onset of action, numerically superior improvement in lung function and comparable asthma control than other ICS-LABA formulations. FF has better safety evidenced by lower occurrence of pneumonia.

Keywords: Control/Management, Pharmacotherapy

Introduction

Asthma is a common health problem that affects most age groups and has prevalence ranging from 1% to 21% in adults¹. Up to 20% of children report severe wheezing episodes². Although some countries are reporting downward trends in asthma-related hospitalizations and deaths³, the morbidity due to exacerbations and daily symptoms has increased to the tune of 30% in the last two decades. ICS are the cornerstone of asthma treatment⁴ with a short-acting b2-agonist (SABA) often utilised for acute relief. However, many subjects treated with ICS and prn SABA have suboptimal asthma control⁵. In such patients, usage of ICS-LABA combination has proved to improve asthma control⁶ and hence this combination has become the standard of care in asthma guidelines^{5,7}. A fixed-dose combination (FDC) of ICS-LABA has beneficial impact on patient compliance to therapy. The combination inhaler minimises the risk of symptom guided isolated SABA overuse and ICS discontinuation. The additional health care costs associated with separate drug inhalers prescription is circumvented. Many different ICS/LABA combinations are being marketed across various countries, of FF is a promising option.

Both components of FF, fluticasone propionate (FP) and formoterol have peculiarities which places this inhaler in a substantially advantageous position in asthma therapy. FP has potent topical anti-inflammatory activity^{8,9}, and quick achievement of protective effect¹⁰. Its systemic availability occurs solely via absorption from lungs, whereas for the other ICS oral bioavailability also needs to be considered¹¹. FP has more potency than budesonide, beclomethasone and flunisolide in the airways¹². Differences in the pharmacological properties account for variabilities in clinical actions of inhaled beta 2 agonists^{13,14}. Formoterol is a complete agonist at the beta 2 receptors and has fast onset of action as compared to Salmeterol which is a partial agonist and causes bronchodilation with some degree of latency. Although both drugs have prolonged action, Formoterol has higher intrinsic activity than Salmeterol. Rapid action onset is due to reasonable water solubility and adequate lipophilicity of Formoterol which ensures faster diffusion to the smooth muscle.

A previous review¹⁵ on single inhaler FF has critically appraised some of the less examined aspects of FF and concluded that FF inhaler has favorable efficacy and safety profile in real world. Switch over of therapy from other ICS-LABA to FF was well tolerated and health care costs were reduced in the studies evaluated in this review. The impact of these attributes on inhaler compliance has not been formally evaluated. However, these properties are likely to encourage better compliance which in turn is a crucial factor associated with real-world improvements in asthma control^{16,17}. Prescribing clinicians would be eager to have an evidence based understanding of the comparative effects of FF versus other available ICS-LABA combinations on clinically relevant outcomes, which might have a bearing in their choice of agent. The present systematic review attempts to evaluate the efficacy and safety of FF in comparison to SF and Form-Bud.

Methods

The review adhered to the general principles mentioned in the Centre for Reviews and Dissemination (CRD)'s guidance for conducting systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement¹⁸. Selection and analysis of studies was based on PICOS (Population, Intervention, Comparators, Outcome and Study) design issues¹⁹. **The defined end points of the analysis were one or more of the following outcomes in FF treated asthmatics in comparison with other ICS-LABA combinations - lung function change (either PEF or FEV1), asthma symptom score, asthma related quality of life, occurrence of pneumonia in the study population or budget impact of therapy.**

Eligibility

This systematic review focused on published studies on asthmatics treated with FF inhaler fulfilling the following PRISMA-defined PICOS criteria: (1) Participants: Male/female adults, children or adolescents (5 years or older) diagnosed with asthma as per GINA guidelines; (2) Intervention: treatment with FF inhaler for at-least 8 weeks; (3) Comparators: Male/female adults, children or adolescents (5 years or older) diagnosed with asthma treated with ICS-LABA combinations other than FF; (4) Outcomes: one or more of the following outcomes - lung function change (either PEFr or FEV1), asthma symptom score, asthma related quality of life, occurrence of pneumonia in the study population or budget impact of therapy (5) Studies: randomized controlled trials or observational studies.

Search strategy, screening, and data extraction

An electronic literature search was carried out using Medline, Embase, and Cochrane Controlled Trials Register databases up to August 2020. In addition, relevant cross references from the retrieved articles were accessed to complete the search. The search terms employed were “fluticasone, formoterol” combined using the Boolean operator “AND”, applying the filter “clinical trial”.

Case reports, case series and purely descriptive studies without a comparator arm were excluded. Only original studies done on human population were considered. Abstract-only publications were not considered due to lack of precise data. Only studies published in English language were analysed. From articles that met the review criteria, basic information was extracted by study team members and tabulated in Microsoft excel summary tables. The following data were extracted: authors, study design, inclusion and exclusion criteria, treatment and comparison medications and baseline characteristics. Outcome measures were extracted, focusing on comparing time onset of bronchodilatation, lung functions, asthma control, asthma related quality of life, pneumonia occurrence and therapy related budget impact between the FF group and the group that received an alternate ICS-LABA. **In situations where lack of precision was perceived on reading the published studies, attempt to contact the respective authors and clarifications were obtained.** The studies screened, assessed for eligibility and included in the final analysis are further discussed in the results section.

Results

We identified a total of 109 articles initially using the search strategy. An additional 29 studies were identified via cross-references and other sources. From these 138 studies, 43 records were removed as they were found to be duplicate. Some of the full-text articles were excluded because of

- a. absence of an appropriate comparator arm,
- b. No background data on FF, SF therapy
- c. Inappropriate combination of drugs
- d. Presence of an additional unmatched drug in the active arm has an additional drug
- e. Endpoints not meeting the aim of the present review.

The number of articles finally included in the analysis was 16. Table 1 shows the details of the 16 studies finally selected for systematic review. Figure 1 depicts the flow-diagram elaborating on the methodological steps for identification and inclusion of articles till the final selection for analysis.

The individual treatment outcome measures and studies reporting them are discussed in detail under respective sub-headings.

Onset of Bronchodilatation

Two studies have attempted to compare the onset of bronchodilatation with FF to commercially available Sal-Flu. An open-label, parallel group, multicenter, RCT²² looked at 202 patients aged ≥ 18 years with persistent asthma. The study period spanned 12-weeks. Although the primary efficacy endpoint was mean pre-dose FEV1 at week 12, time of onset of action was also studied. FF was superior to Sal-Flu in the time to onset of bronchodilatation for the entire trial period.

A post hoc analysis of the previous study²³ examined the onset of bronchodilatation (the first point of time after drug administration at which the FEV1 was $\geq 12\%$ to the baseline), responder rates (the proportion of patients achieving significant bronchodilation), and changes in FEV1 at days 0 (baseline) and 84. A faster onset of bronchodilation was observed in patients taking FF than Sal-Flu and the effect was maintained over 12 weeks of treatment. Odds of achieving significant bronchodilatation within 5 minutes of dose were higher with FF group. On day 0 & day 84, FF was superior to Sal-Flu over the first 5 min & first 120 min post-therapy with respect to onset bronchodilation as given in Figure 1. On the basis of these two studies, it may be concluded that FF offers faster onset of bronchodilatation than Sal-Flu.

Lung function

7 studies have compared the influence of FF on lung function (PEFR or FEV1) in comparison with other ICS-LABAs. The details of the studies are summarized in table 2. Two studies showed similar improvement in lung function with FF in versus the corresponding ICS-LABA studied. Two trials showed a numerically better improvement in FEV1 with FF than the comparator, one of which showed a better gain in PEFR also. Four trials showed an improvement in PEFR with FF than corresponding combination used; FEV1 improvement was noninferior improvement in these trials. The improvements in PEFR and FEV1 in those studies that exhibited superiority are shown in Figures 2 and 3. Overall, FF when compared to Sal-Flu and Form-Bud showed superior results with regard to improving lung functions.

Asthma control

Nine studies have looked at the role of FF on asthma control with respect to that provided by other ICS-LABAs. The details of the studies are summarized in table 3. Five studies looked at exacerbation rates, three studies compared improvements in ACQ-7, two studies examined ACT and one study evaluated GINA defined asthma control. One study compared the impact of switch over to FF from Sal-Flu. Five studies showed similar improvement asthma control or exacerbation rates with FF versus others. Four studies revealed superior asthma control with FF in comparison to the alternate ICS-LABA studied. The improvements in ACQ-7 in three studies that exhibited superiority are shown in Figure 4. Overall, FF provides superior asthma control in almost half of the analysed studies, with remaining trials establishing non inferiority.

Asthma related Quality of life

Four studies evaluated the asthma related quality of life in FF treated patients. These studies are tabulated in table 4. Three studies revealed similar results irrespective of ICS LABA used. One study demonstrated better quality of life with FF when compared to Form-Bud. Notably, this study was done in India.

Real world safety

Short term safety and adverse events have been assessed in all the studies included in the review. However, RCTs conducted over 3-6 months may be too short to evaluate the real life pneumonia risk. The study spanning for the longest duration and examining the largest number of asthma patients using FF in a real-world scenario comes from the UK primary care database²⁹. This study has compiled data for upto 3 years after initiation of FF therapy. The primary index of safety was a composite measure of all adverse outcomes that occurred after initiation on an FDC ICS/LABA. The study retrospectively enrolled more than 45000 asthma patients receiving ICS LABA of which 5727 were treated with FF. Most AEs were mild. The rate of AEs observed with FF were lower than SF or FB combinations. Specifically, the pneumonia risk per 100 person years was lowest for FF as shown in figure 5.

Budget impact

Three studies have analysed the financial aspect of using FF inhaler in asthma. Dunlop et al³⁰ estimated the impact on yearly budget allocation in UK NHS with FF use as against SF. Expenses associated with drug procurement, administration and safety surveillance was ascertained for the two agents. Analysis of varying utilization rate, compliance, AE-related costs and resource use was made. Outcomes suggested that yearly drug purchase costs per person were lower with FF (£412) than with SF (£509). This impact on annual savings to the NHS was huge (£15,110,279). Results were replicated 3 year later in another British study³¹. Total yearly cost per person year was less with FF (£625) as compared to SF (£734). As FF-FP prescription volumes increased, the annual total costs to the NHS decreased.

Similar analysis was undertaken in a Spanish study³². FF was cheaper to procure than SF or FB (20% and 30% respectively). Cost per patient in the FF group was 9326€/year, which is 1.5% and 2.6% cheaper than SF and FB respectively. **However, it may be mentioned that the results of these economic analysis may not be generalisable to the rest of the world beyond these mentioned countries where the trials were done.** Extrapolation of these results may not be meaningful in India, as FB is marketed at a lower price than SF and FF inhalers. However, we do not have studies analyzing this aspect in Indian subcontinent till date.

Pediatric population

Two pediatric studies^{33,34} including 546 patients were evaluated, which compared FF with SF. The SF group revealed an enhanced improvement in pre-dose FEV1, asthma control, and sleep quality with regard to the FF group; however, the FF population had better improvement in PEFR. No significant differences existed between the two groups when post-dose FEV1 was analysed. Both agents were safe, and the incidence of adverse events were similar, except for the occurrence of nasopharyngitis.

Discussion

We report the second systematic review till date involving adult asthmatic population comparing FF with other ICS-LABA combinations. **A quick look summary of the clinical outcomes with FF versus Sal-Flu and Form-Bud is provided in table 5.** As previously mentioned, thorough understanding of the relative merits and demerits of various ICS-LABA combinations will aid practitioners in their choice of asthma therapy. **Although priority was given to randomised trials, we included a few observational studies also in our review to have real world data and long term safety of FF. The inclusion of observational studies was limited to analyse real work**

efficacy and safety. Our review looked at clinical outcomes of relevance in asthmatic patients with FF administration versus other ICS-LABA therapy. All the clinical outcomes were non inferior with FF treatment and FF usage resulted in superior outcomes in certain aspects.

One specific attribute which places FF in an advantageous position with respect to Sal-Flu is the rapidity in onset of action. This is a direct offshoot of the pharmacological properties of FF and has been consistent in all analysed studies. Patients prefer drugs with rapid onset of bronchodilatation and have sustained action; hence, while choosing ICS/LABA combination, the potency of the ICS and the rapidity of action onset of LABA are given importance by the clinicians.³⁶⁻⁴⁰. Hence a combination like FF containing components with the above-mentioned attributes has a definite edge.

ICS-LABA therapy improves asthma symptoms, lung function, asthma control and asthma related quality of life. Almost half the analysed studies demonstrate a superior efficacy for FF as compared to Sal-Flu and Form- Bud in these outcomes. The remaining studies tend to suggest non-inferiority of FF. Overall, it may be concluded that asthma control with FF is superior to or in par with other ICS-LABA formulations.

Studies analyzing the budget impact of FF conducted in Europe establish a lower cost of therapy associated with FF as opposed to the comparators. However, extrapolation of these data to Indian scenario may not hold true, considering the fact that Form-Bud is marketed at a lower price in India than FF.

Inhaled corticosteroids are associated with a small but substantial increased risk of pneumonia⁴¹. However, the benefits outweigh the risks in persistent asthma and an ICS finds its place in all asthma guidelines. Nevertheless, the steroid with least pneumonia risk has an obvious edge. RCTs are seldom representative of the patient populations who benefit most from the treatment. Further, quality of care seldom ensured in RCTs is not extrapolatable in the real world. Hence, we chose the largest and longest study from UK database to assess the pneumonia risk with various ICS-LABA formulations, which reveals that FF is associated with the least pneumonia risk.

One of the main drawbacks of this review is that we have not been able to identify and hence review any trial comparing newer ultra LABAs (like Indacaterol, vilanterol, olodaterol etc) and ICS with the FF combination. However, with such studies might be available in the future and next generation systematic reviews might come up with answers to this untouched aspect. Many of the studies reviewed have selected patient populations with moderate and reasonably controlled asthma; hence the superiority in severe asthmatics with frequent exacerbations is unclear. In spite of these shortcomings, the review provides valuable insights into the efficacy and safety of FF.

Conclusion

The present review critically and systematically analyses studies comparing the efficacy and safety of FF in asthma with other ICS-LABA formulations. FF consistently demonstrates a faster onset of action than Sal-Flu. The asthma control, improvement in lung function and asthma related quality of life with FF has been shown to be superior in some studies and non-inferior in others. Healthcare budget allocation was lowest for FF in studies conducted in Europe. Incidence of pneumonia was lowest with FF in a long term real world study. In the light of these results, it may be concluded that the single inhaler FF formulation provides a therapeutic option in asthmatics requiring an ICS/LABA, with clinical outcomes that may position it as the agent of choice in this patient subset.

Disclosures/conflicts of interest

Nil

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Nil

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Table 1 Summary of clinical studies included in the analysis

Study/Year	Country	Design	No. of Subjects	Study duration
Bodzenta-Lukaszyk and colleagues/2011 ²²	European Countries	Anphase 3 open-label, parallel group RCT, with active control	202	12 weeks
Cukier and colleagues/2013 ²¹	Brazil	A phase 3 open-label parallel-group, multicentre, RCT	196	12 weeks
Bodzenta-Lukaszyk and colleagues/2012 ²⁰	Poland, Bulgaria, Hungary, Romania, and India	A double-blind, double dummy, multicenter, Phase 3 RCT	279 patients	12 weeks
Aalbers and colleagues/2012 ²³	Germany, Hungary, Poland, Romania, and the UK	A post hoc analysis of an open-label RCT	202 patients	12 weeks
Usmani and colleagues/2017 ²⁴	England	An open label pragmatic, RCT	225 patients	24 weeks
Ghoshal and colleagues/2017 ²⁵	India	A prospective, open-label, observational real-world study	385 patients	24 weeks
Kaushal and colleagues/2016 ²⁶	India	Anopen label, active parallel group RCT	80 patients	12 weeks
Antilla M and colleagues/ 2014 ²⁷	Brazil	An open label multicenter, phase III RCT	243 patients	12 weeks
Ming and colleagues/2017 ²⁸	UK	Historical matched cohort study	2472 patients	2 years
David Price and colleagues /2020 ²⁹	UK	Retrospective, observational cohort study	241007 patients	36 months
Dunlop and colleagues/2013 ³⁰	UK	Non inferiority 1trial	202 patients	12 weeks
Farrington and colleagues/2016 ³¹	UK	Real-world evidence and budget Impact analysis		12 months
Moragon and colleagues/2016 ³²	Spain	Economic analysis of the database records		12 months
Płoszczuk and colleagues/2018 ³³	Ukraine, Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russian federation	Double-dummy, parallel group double-blind, RCT	512 patients	12 weeks
Emeryk and colleagues/2016 ³⁴	UK	A phase 3open-label, RCT with extension	210	12 weeks
Handa and colleagues/2019 ³⁵	Japan	Aprospective open-labelled clinical observational study	56	8 weeks

Table 2 Summary of studies comparing lung function

<u>Author / Year</u>	<u>Nature of study and number of subjects</u>	<u>Agents compared</u>	<u>Lung function parameter measured</u>	<u>Outcome</u>
Cukier and colleagues Year /2013 ²¹	A phase 3, open-label, parallel-group, RCT 196 patients	Fluticasone/formoterol versus Budesonide/Formoterol	Morning peak expiratory flow and FEV1	Non-inferiority of FF to Form-Bud in terms of morning PEF and the increase in the mean FEV1 of the asthma patients when compared from baseline to week 12, was statistically significant in the FF group as compared to Form-Bud.
Bodzenta-Lukaszyk and colleagues/2012 ²⁰	A phase 3 open-label, parallel group RCT with active control arm 202 patients	Fluticasone/formoterol versus Budesonide/Formoterol	Pre-dose FEV1 at week 12, and PEFr	FF showed similar improvement in the mean change of pre dose FEV1 at week 12 as compared to Sal-Flu.
Bodzenta-Lukaszyk and colleagues/2011 ²²	A phase 3 double-blind, double dummy, RCT 279 patients	Fluticasone/formoterol versus Salmeterol/fluticasone	Mean change in pre-dose FEV1 at baseline to 12 weeks Mean FEV1 increment from pre-dose at baseline to 2 hours post-dose at Week 12. Improvement in PEFr	The trial showed comparable efficacy of FF to Sal-Flu
Ghoshal and colleagues/2017 ²⁵	A prospective, open-label, observational real-world study 395 patients	Fluticasone/Formoterol Vs Various other ICS-LABAs	Morning and evening PEFr	Significant improvement in the PEFr from the baseline till 24 weeks
Kaushal and colleagues/2016 ²⁶	A prospective, open-label, randomized, parallel study/ 80 patients	Fluticasone/formoterol versus Budesonide/Formoterol	FEV1 and PEFr	FF provided more fast and significant improvement in the PEFr values. Both the combinations showed comparable results in terms of change in FEV1
Antilla M and colleagues/ 2014 ²⁷	A randomized, multicenter, open phase III trial/243 patient	Fluticasone/formoterol versus Budesonide/Formoterol versus Fluticasone	FEV1 and PEFr	FF non inferiority was established for the parameter FEV1. PEFR was significantly improvement in FF group than Form-Bud
Handa and colleagues/2019 ³⁵	A prospective open-labelled clinical observational study/56 patients	Fluticasone/formoterol versus Salmeterol/ fluticasone	FEV1 and PEF	FF group patients had numerically significant improvement in FEV1 and PF as compared to Sal-Flu

Table 3 Summary of studies comparing asthma control

<u>Author / Year</u>	<u>Nature of study and number of subjects</u>	<u>Agents compared</u>	<u>Asthma control parameter measured</u>	<u>Outcome</u>
Cukier and colleagues/2013 ²¹	A phase 3, open-label, parallel-group, RCT 196 patients	Fluticasone/formoterol versus Budesonide/Formoterol	Asthma control questionnaire (ACQ-7)	There was statistically significant improvement in ACQ for both groups; $p < 0.01$ for both group Numerically better improvement with FF
Bodzenta-Lukaszyk and colleagues/2012 ²⁰	A phase 3 open-label, parallel group RCT with active control arm 202 patients	Fluticasone/formoterol versus Salmeterol/Fluticasone	Asthma exacerbations	Similar efficacy was demonstrated by both the combination in terms reduction of asthma exacerbations ($p > 0.999$)
Bodzenta-Lukaszyk and colleagues/2011 ²²	A double-blind, double dummy, multicenter, Phase 3 RCT 279 patients	Fluticasone/formoterol versus Budesonide/Formoterol	Severe asthma exacerbations	Non-inferiority was demonstrated by the both the combination in terms of asthma control and exacerbations
Usmani and colleagues/2017 ²⁴	A randomized controlled, pragmatic, open label Trial/225 patients	Fluticasone/formoterol versus Salmeterol/Fluticasone	ACQ7 and asthma exacerbation	Both the combination had similar exacerbations rate and the same ACQ7 scores
Ghoshal and colleagues/2017 ²⁵	A prospective, open-label, observational real-world study 395 patients	-	Asthma control test and (ACT) exacerbations	A statistically significant improvement in the ACT scores of the asthmatic patients with switch over from other ICS-LABA to FF
Kaushal and colleagues/2016 ²⁶	A prospective, open-label, randomized, parallel study/ 80 patients	Fluticasone/formoterol versus Budesonide/Formoterol	Level of asthma control as per GINA definitions	FF combination improved the need for rescue medication ($p = 0.000$) and daytime asthma symptoms ($p = 0.006$)
Antilla M and colleagues/ 2014 ²⁷	A randomized, multicenter, open phase III trial/243 patient	Fluticasone/formoterol versus Budesonide/Formoterol	ACQ7 score	Asthma control was significantly better with fluticasone/formoterol as compared to budesonide/formoterol
Handa and colleagues/2019 ³⁵	A prospective open-labelled clinical observational study/56	Fluticasone/formoterol versus Salmeterol/Fluticasone	ACT and Asthma health questionnaire-33	There was an improvement in the ACT score from the patients were switched from salmeterol/fluticasone to fluticasone/formoterol.
Ming and colleagues/2017 ²⁸	Historical matched cohort/2472	Fluticasone/formoterol versus Salmeterol/Fluticasone	Exacerbation rate	Fluticasone/formoterol had comparable efficacy to salmeterol/fluticasone in terms of patients with no severe exacerbation episode.

Table 4 Studies comparing asthma related QoL

<u>Author / Year</u>	<u>Nature of study and number of subjects</u>	<u>Agents compared</u>	<u>QoL parameter measured</u>	<u>Outcome</u>
Usmani and colleagues/2017 ²⁴	An open label pragmatic, RCT Trial 225 patients	Fluticasone/formoterol versus Salmeterol/Fluticasone	Mini-asthma quality of life (AQLQ)	No significant difference was observed between both the groups in terms of AQLQ score
Bodzenta-Lukaszyk and colleagues/2012 ²⁰	A phase 3 open-label, parallel group RCT with active control arm 202 patients	Fluticasone/formoterol versus Budesonide/Formoterol	AQLQ score	Analysis of AQLQ score at 12 weeks showed similar values for both groups.
Bodzenta-Lukaszyk and colleagues/2011 ²²	A double-blind, double dummy, multicenter, Phase 3 RCT 279 patients	Fluticasone/formoterol versus Salmeterol/Fluticasone	AQLQ score	The AQLQ score was same for both the treatment groups at week 12
Kaushal and colleagues/2016 ²⁶	A prospective, open-label, randomized, parallel study/ 80 patients	Fluticasone/formoterol versus Budesonide/Formoterol	AQLQ score	The trial showed a significant improvement in the AQLQ score at 6 weeks (p=0.006) with fluticasone/formoterol as compared to budesonide/formoterol

Table 5 Summary of clinical outcomes with FF versus other ICS-LABA

Clinical Outcome	Number of studies	Agents Compared	Results
Onset of action	2	FF Vs Sal-Flu	FF provides faster onset of action
Improvement in lung function	7	FF Vs Sal-Flu or Form-Bud	Better improvement in lung function with FF (5 studies); similar outcomes in 2 studies
Asthma control	9	FF Vs Sal-Flu or Form-Bud	Superior asthma control with FF (4 studies); similar control in 5 studies
Asthma related QoL	4	FF Vs Sal-Flu or Form-Bud	Better QoL with FF in one study; similar QoL in 3 studies
Long term risk of pneumonia	1	FF Vs Sal-Flu or Form-Bud	Least with FF

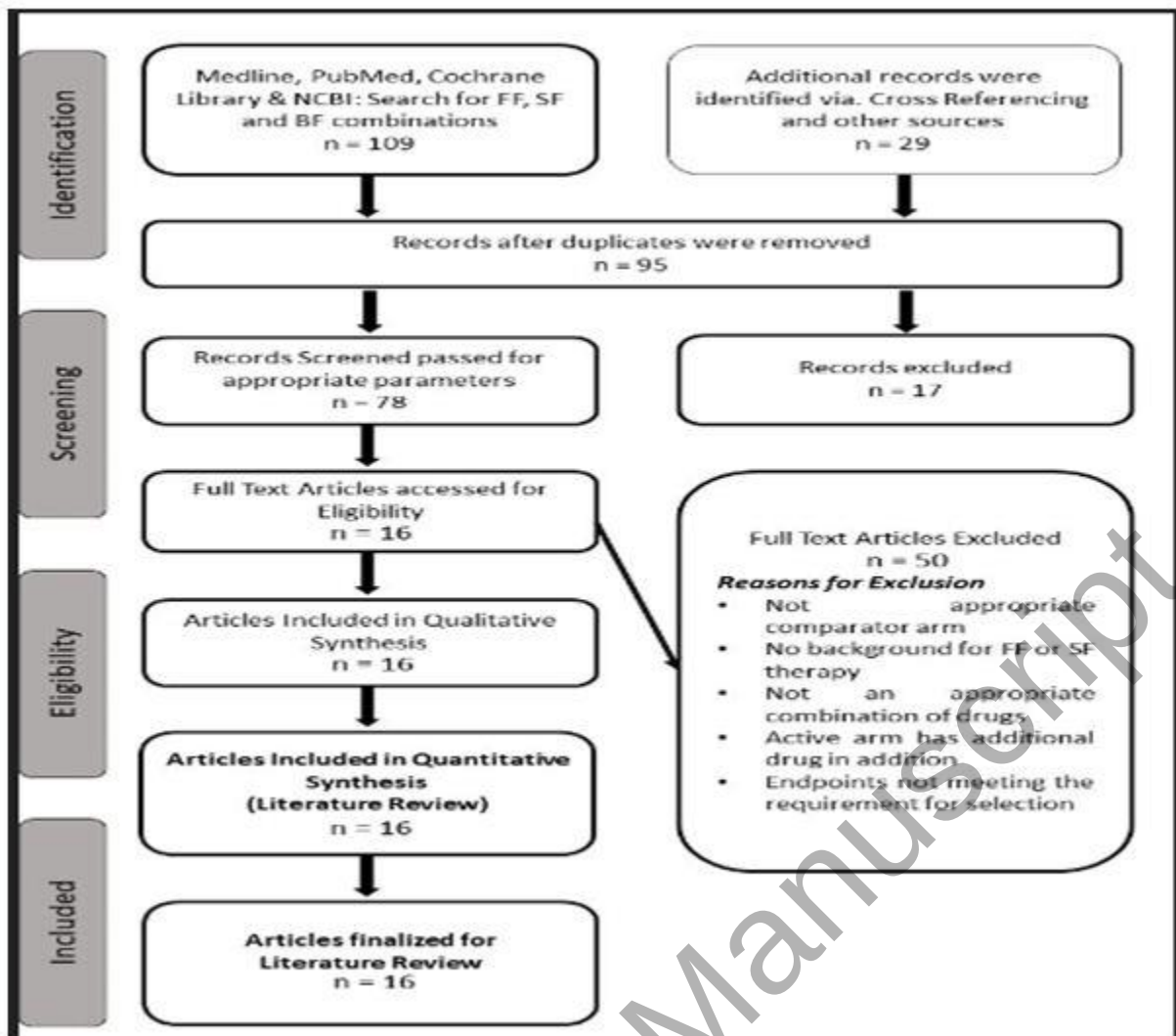


Figure 1: Flow-diagram elaborating on the methodological steps

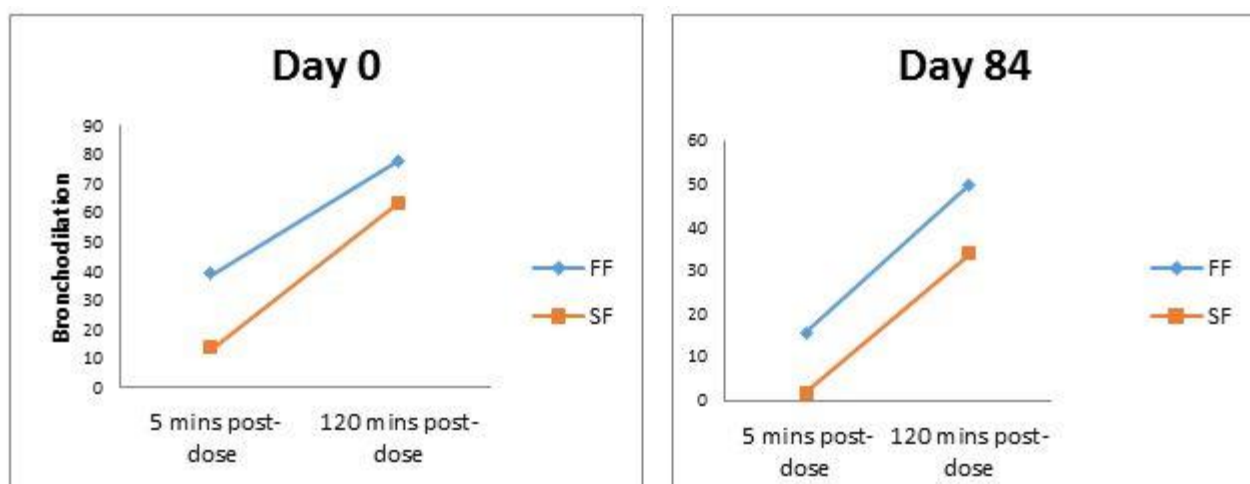


Figure 2 onset of bronchodilatation with FF compared to SF

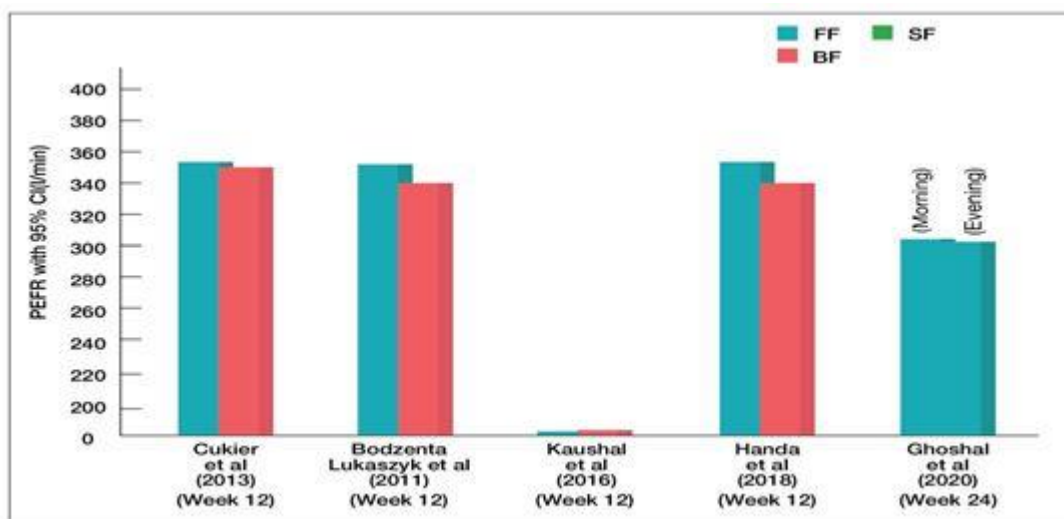


Figure 3 Improvement in PEFR with FF Vs other ICS-LABAs

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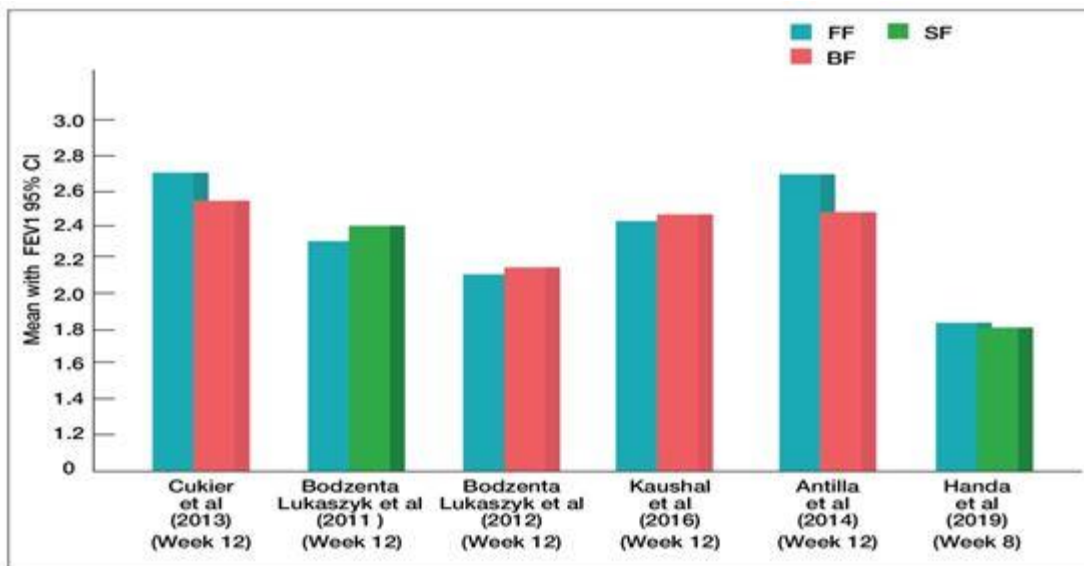


Figure 4 improvement in FEV1 with FF compared to other ICS-LABAs

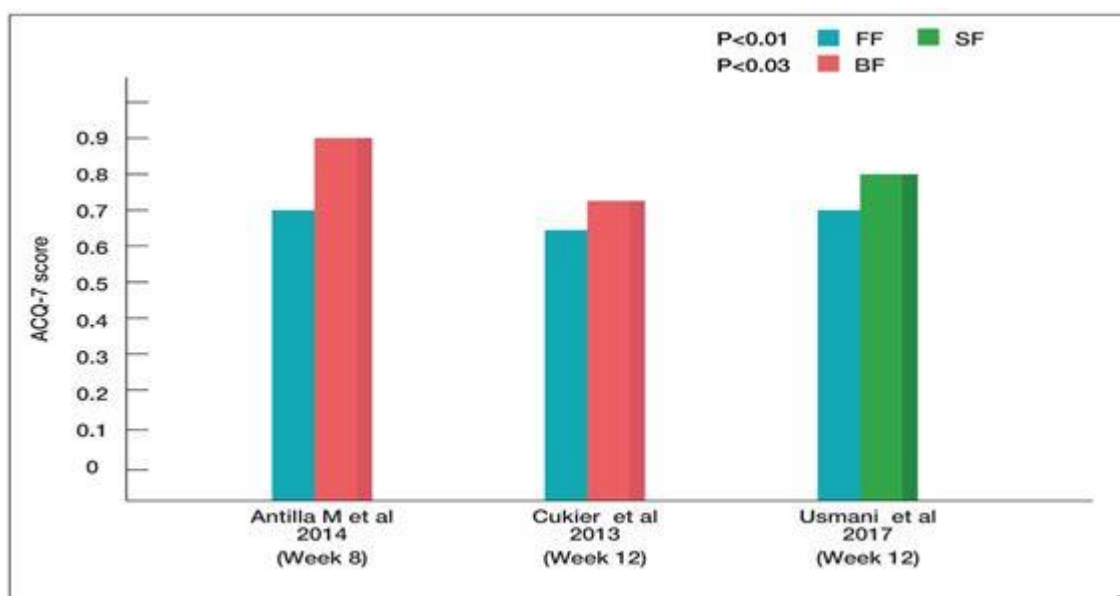


Figure 5 Asthma control with FF compared to SF and BF

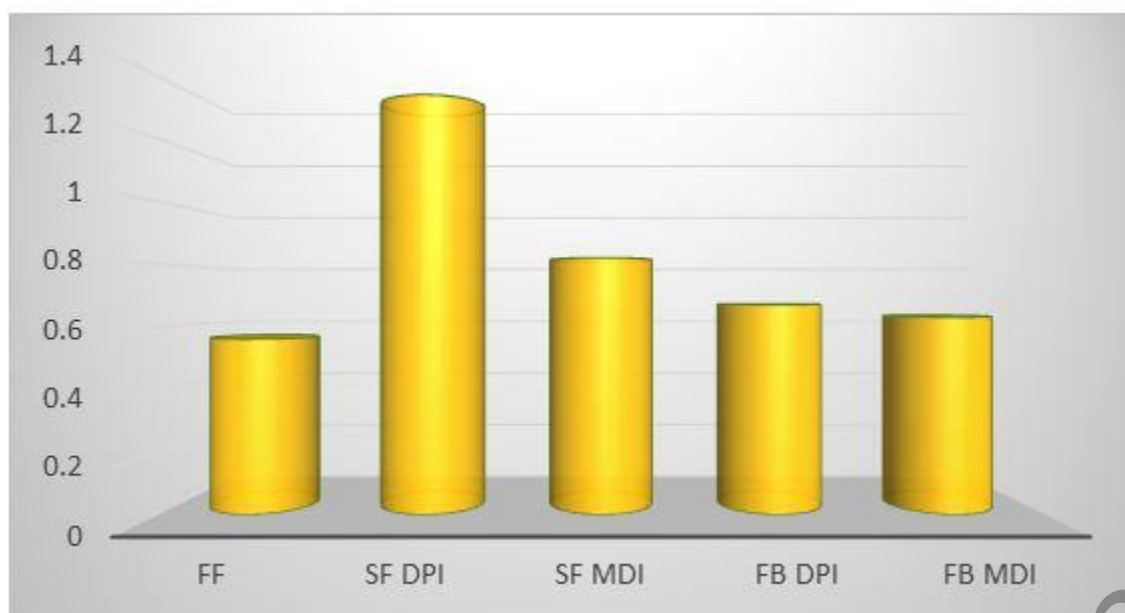


Figure 6 pneumonia risk with various ICS-LABA formulations