Journal of Applied Pharmaceutical Science Vol. 10(10), pp 036-049, October, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.10104
ISSN 2231-3354

Three-drug therapy versus two-drug therapy for management of patient-reported manifestations and quality of life in chronic obstructive pulmonary disease patients: A meta-analysis

Ganesh Narayan Sharma[1], Syed Aamir Ali[1*], Birendra Shrivastav[1], Aleemuddin Naveed Mohd[2]

[1]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India.
[2]Department of Pulmonology, Princess Esra Hospital, Shah ali banda, Hyderabad, India.

ARTICLE INFO

Received on: 17/03/2020
Accepted on: 30/08/2020
Available online: 05/10/2020

Key words:
COPD assessment test (CAT), adverse events, St George Respiratory Questionnaire (SGRQ), meta-analysis, rescue medication use.

ABSTRACT

Patient-reported manifestations and quality of life (QoL) data for chronic obstructive pulmonary disease (COPD) drugs are sparse. This study compared three-drug therapy comprising inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA), and long-acting muscarinic antagonists (LAMA) with two-drug therapy (ICS/LABA or LABA/LAMA) in terms of patient-reported manifestations and QoL. Randomized controlled trials (RCTs) comparing three-drug therapy with two-drug therapy in COPD patients were searched through Pubmed and meta-analyzed. Efficacy endpoints included St George Respiratory Questionnaire (SGRQ) score, SGRQ responders, COPD assessment test (CAT) score, rescue drug use, rescue drug-free days, and adverse events resulting in drug cessation. Three-drug therapy showed improvement in SGRQ scores [mean difference (MD), −1.66; 95% confidence interval (CI), −2.09 to −1.23] and SGRQ responders [Odds Ratio (OR), 1.30; 95% CI, 1.18–1.44] compared to ICS/LABA dual therapy; and SGRQ scores (MD, −1.65; 95%CI, −2.31 to −0.99) and SGRQ responders (OR, 1.20; 95%CI, 1.08–1.34) compared to LABA/LAMA dual therapy. Similarly, results with CAT scores, rescue medication use, percentage of rescue medication-free days, and adverse events resulting in drug cessation favored the three-drug therapy compared to the two-drug therapy. Three-drug therapy had improved SGRQ scores, CAT scores, reduced rescue medication use, and better QoL.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a significant contributor to morbidity and mortality worldwide (Decramer *et al*., 2012; GBD 2016 Risk Factors Collaborators, 2017). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advocate a stepwise advancement from monotherapy to three-drug therapy comprising long-acting beta2 agonists (LABA), inhaled corticosteroids (ICS), and long-acting muscarinic antagonists (LAMA), as the management for severe symptoms and exacerbations (Global Initiative for Chronic Obstructive Lung Disease(GOLD), 2017). The supreme objective of COPD treatment is improving pulmonary health, quality of life (QoL), and eliminating exacerbations (Hutchinson *et al*., 2010). Weakened physical and mental health, dyspnea, and increased hospitalizations have been shown to be predictors of poor health-related quality of life (HRQoL) (Balcells *et al*., 2010; Carrasco *et al*., 2006; Cully *et al*., 2006; Hu and Meek, 2005). HRQoL can thus be viewed as an important marker for treatment efficacy providing a finishing touch to the existing efficacy parameters (Cazzola *et al*., 2008).

Recently, many multicenter randomized clinical trials have been performed to study three-drug therapy with two-drug therapy for pulmonary function, QoL, and exacerbations. All these trials proved three-drug therapy to be safer and efficacious than two-drug therapy in medium to serious COPD patients (Aaron *et al*., 2007; Ferguson *et al*., 2018; Lipson *et al*., 2018; Papi *et al*., 2018). Nevertheless, there are inconsistent results for patient-reported outcomes, like QoL, rescue drug use, and drug discontinuation, due to adverse events. Moreover, the previous meta-analysis did not document the effectiveness of three-drug therapy versus two-

*Corresponding Author
Syed Aamir Ali, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India. E-mail: syed.aamir12 @ gmail.com

drug therapy in context to the above-mentioned patient-reported outcomes (Calzetta *et al*., 2019; Zayed *et al*., 2019; Zheng *et al*., 2018).

In view of the increasing generalization of three-drug therapy in clinical application, this meta-analysis was conducted in order to study three-drug therapy (ICS/LABA/LAMA) with two-drug therapy (LABA/LAMA or LABA/ICS) for patient-reported outcomes and QoL, and to find out the effect of potential modifiers that may alter the effects of treatment regimens.

METHODS

Search strategy

Medline and Cochrane databases were manually explored to find the relevant randomized controlled trials (RCTs) contrasting three-drug therapy (ICS/LABA/LAMA) with two-drug therapy [(ICS/LABA) or (LABA/LAMA)]. The following search strategies were used to find the relevant RCTs in the Pubmed database.

#1 (COPD OR "Chronic obstructive pulmonary disease")
#2 (Beta agonist OR LABA OR salmeterol OR indacaterol OR formoterol OR vilanterol OR olodaterol)
#3 (muscarinic OR LAMA OR tiotropium OR glycopyrronium OR umeclidinium OR aclidinium OR ipratropium)
#4 (ICS OR fluticasone OR budesonide OR beclomethasone OR ciclesonide OR flunisolid OR mometasone OR triamcinolone)
#5 #1 AND #2 AND (#3 OR #4)

The filters used were clinical study, clinical trial, and comparative study. The search was conducted for the period of January 2006 to July 2019.

Inclusion criteria

1) RCTs with duration no less than 12 weeks.
2) Studies contrasting three-drug therapy (ICS/LABA/LAMA) with two-drug therapy [(ICS/LABA) or (LABA/LAMA)].
3) Patients with medium to serious COPD.
4) Outcomes included were rescue drug use, St George Respiratory Questionnaire (SGRQ) score, COPD assessment test (CAT) score, and adverse events resulting in drug cessation.

Quality assessment

The present study confirms the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher *et al*., 2015). The data were drawn out by two reviewers and the differences were settled by a third reviewer. The extricated data are shown in Table 1 and 2. Cochrane manual of systematic review was used to examine the likelihood of bias of included studies. The following items were taken into consideration: random sequence generation, allotment concealment, blinding of patients and trial staff, blinding of result evaluation, incomplete result reporting, selective reporting, and other bias (Higgins *et al*., 2011). The Consolidated Standards of Reporting Trials (CONSORT) guidelines were used for checking the completeness of clinical trials (Moher, 1998). Only those trials which matched the completeness criteria of CONSORT guidelines were incorporated in the meta-analysis. The grading of recommendations assessment, development, and evaluation (GRADE) approach was utilized for categorizing the standard of evidence and produced absolute effect estimates for the outcomes (Guyatt *et al*., 2011).

Statistical analysis

For dichotomous outcomes, an effect measure was presented as odds ratio (OR) accompanied by their related 95% confidence interval employing the Mantel–Haenszel method. Similarly, parametric data effect measures were presented as average differences, with their corresponding 95% confidence intervals employing the inverse variance method. Heterogeneity between trials was examined employing chi-square tests and I^2 statistics and I^2 values more than 50% representing significant heterogeneity. The fixed-effects model was employed where heterogeneity was less than 50%; in all other cases, the random-effects model was utilized. Publication bias was examined employing funnel plots in the case where 10 or more trials were involved in meta-analysis. Meta-regression analysis assessed the possible causes of heterogeneity. Data were analyzed employing RevMan v5.3 software as well as Comprehensive Meta-analysis v3 software.

RESULTS

An exhaustive literature search yielded 584 research articles contrasting three-drug therapy with two-drug therapy in COPD patients. After careful evaluation by the reviewers, 12 publications (14 RCTs), published between 2007 and 2018, were found to be eligible as per the inclusion/exclusion criteria and incorporated in this meta-analysis (Aaron *et al*., 2007; Cazzola *et al*., 2007; Ferguson *et al*., 2018; Frith *et al*., 2015; Hoshino *et al*., 2011; Lipson *et al*., 2017; Lipson *et al*., 2018; Papi *et al*., 2018; Siler *et al*., 2015, 2016; Singh *et al*., 2016; Sousa *et al*., 2016), A summary of study sorting process is shown in Figure 1. The study baseline characteristics are presented in Table 1 and 2. The duration of study varied between 12 and 52 weeks. Five trials (Ferguson *et al*., 2018; Lipson *et al*., 2017; Lipson *et al*., 2018; Papi *et al*., 2018; Singh *et al*., 2016) used single inhaler triple therapy, while the remaining included trials used separate inhalers for triple therapy. Two publications (Siler *et al*., 2015, 2016) presented a pair of RCTs as a joint result. The possibility of bias in incorporated studies was categorized into low, high, and unclear based on Cochrane's risk of bias instrument (Figs. 2 and 3).

Triple therapy versus ICS/LABA dual therapy

Ten publications (Cazzola *et al*., 2007; Ferguson *et al*., 2018; Frith *et al*., 2015; Hoshino *et al*., 2011; Lipson *et al*., 2017; Lipson *et al*., 2018; Siler *et al*., 2015, 2016; Singh *et al*., 2016; Sousa *et al*., 2016) used three-drug therapy versus ICS/LABA therapy in comparison with moderate to severe COPD patients. Three-drug therapy showed improvement in terms of

Table 1. Characteristics of incorporated trials (three-drug therapy *vs.* ICS/LABA and LABA/LAMA).

Study	Intervention	Total patients	Average age (years)	Male (%)	SGRQ score (Average difference from baseline)	CAT score (Average difference from baseline)	Rescue medication use(puffs/day)	Follow up (weeks)
Cazzola, 2007	FCP/STL/TTM	29	66.9	86.7	NA	NA	5.20	12
	FCP/STL	26	64.4	86.7	NA	NA	5.13	
Frith, 2015 (GLISTEN)	FCP/STL/GPM	257	68.2	63.4	−2.81	NA	2.19	12
	FCP/STL/TTM	258	68.0	62.0	−3.90	NA	2.09	
	FCP/STL	257	67.8	67.7	−0.65	NA	2.91	
Lipson, 2017 (FULFILL)	FTF/ULM/VTL	911	64.2	74	−6.6	−2.5	−1.8	24
	BSD/FOR	899	63.7	74	−4.3	−1.6	−1.8	
Lipson, 2018 (IMPACT)	FTF/ULM/VTL	4151	65.3	67	−5.5	NA	NA	52
	FTF/VTL	4134	65.3	66	−3.7	NA	NA	
Siler, 2016 A	FCP/STL/ULM	205	63.2	69	−2.77	−0.92	NA	12
	FCP/STL/ULM	204	62.7	65	−3.57	−0.81	NA	
	FCP/STL	205	63.4	64	−2.26	−0.77	NA	
Siler, 2016 B	FCP/STL/ULM	202	65.5	59	−4.54	−1.42	NA	12
	FCP/STL/ULM	203	64.5	69	−3.50	−1.31	NA	
	FCP/STL	201	65.7	61	−1.50	0.41	NA	
Siler, 2015 C	FTF/VTL/ULM	207	63.8	61	−1.77	−0.1	−0.6	12
	FTF/VTL/ULM	206	64.9	67	−3.05	−1.1	−0.7	
	FTF/VTL	206	64.7	68	−2.23	0.3	−0.3	
Siler, 2015 D	FTF/VTL/ULM	207	63.6	63	−1.04	−0.5	−0.3	12
	FTF/VTL/ULM	206	62.6	66	−1.56	−0.6	−0.4	
	FTF/VTL	206	62.6	61	0.1	0.59	0.1	
Singh, 2016 (TRILOGY)	BCD/FTF/GPM	687	63.3	74	−5.13	NA	NA	52
	BCD/FTF	680	63.8	77	−3.45	NA	NA	
Sousa, 2016	ICS/LABA/ULM	119	65.2	83	−2.26	−0.37	− 0.53	12
	ICS/LABA	117	63.1	75	−0.00	0.94	− 0.15	
Ferguson, 2018 (KRONOS)	BSD/FOR/GPM	639	64.9	72.0	−7.5	NA	−1.3	24
	BSD/FOR	314	65.2	71.3	−7.1	NA	−1.1	
	BSD/FOR (open label)	318	65.9	74.2	−6.3	NA	−1.6	
Hoshino 2013	FCP/STL/TTM	15	73	86.7	−11.77	NA	NA	16
	FCP/STL	16	67	81.3	−4.73	NA	NA	

SGRQ = St Georges respiratory questionnaire; CAT = COPD assessment test; LAMA = long acting muscarinic receptor antagonist; LABA = long acting β2 adrenoreceptor agonist; FCP = fluticasone propionate; STL = salmeterol; TTM = tiotropium; BCD = beclometasone dipropionate; FTF = formoterol fumarate; GPM = glycopyrronium; ULM = umeclidinium; VTL = vilanterol; BSD = budesonide; FOR = formoterol; IDL = indacaterol; NA = not available.

Table 2. Characteristics of included studies (Triple therapy *vs.* LAMA/LABA).

Study	Intervention	Total patients	Average age (years)	Male (%)	SGRQ(Average differencefrom baseline)	CAT(Average difference from baseline)	Rescue medication use (puffs/day)	Follow up (weeks)
Lipson, 2018	FTF/ULM/VTL	4151	65.3	67	−5.5	NA	NA	52
	ULM/VTL	2070	65.2	66	−3.7	NA	NA	
Ferguson, 2018 (KRONOS)	BSD/FOR/GPM	639	64.9	72.0	−7.5	NA	−1.3	24
	FOR/GPM	625	65.1	68.8	−6.3	NA	−1.1	
Papi, 2018 (TRIBUTE)	BCD/FTF/GPM	764	64.4	72	−3.51	-0.8	NA	52
	IDL/GPM	768	64.5	72	−1.86	-0.6	NA	
Aaron 2007	FCP/STL/TTM	145	67.5	57.9	−8.6	NA	NA	52
	STL/TTM	148	67.6	57.4	−6.3	NA	NA	

SGRQ = St Georges respiratory questionnaire; CAT = COPD assessment test; LAMA = long acting muscarinic receptor antagonist; LABA = long acting β2 adrenoreceptor agonist; FCP = fluticasone propionate; STL = salmeterol; TTM = tiotropium; BCD = beclometasone dipropionate; FTF = formoterol fumarate; GPM = glycopyrronium; ULM = umeclidinium; VTL = vilanterol; BSD = budesonide; FOR = formoterol; IDL = indacaterol; NA = not available.

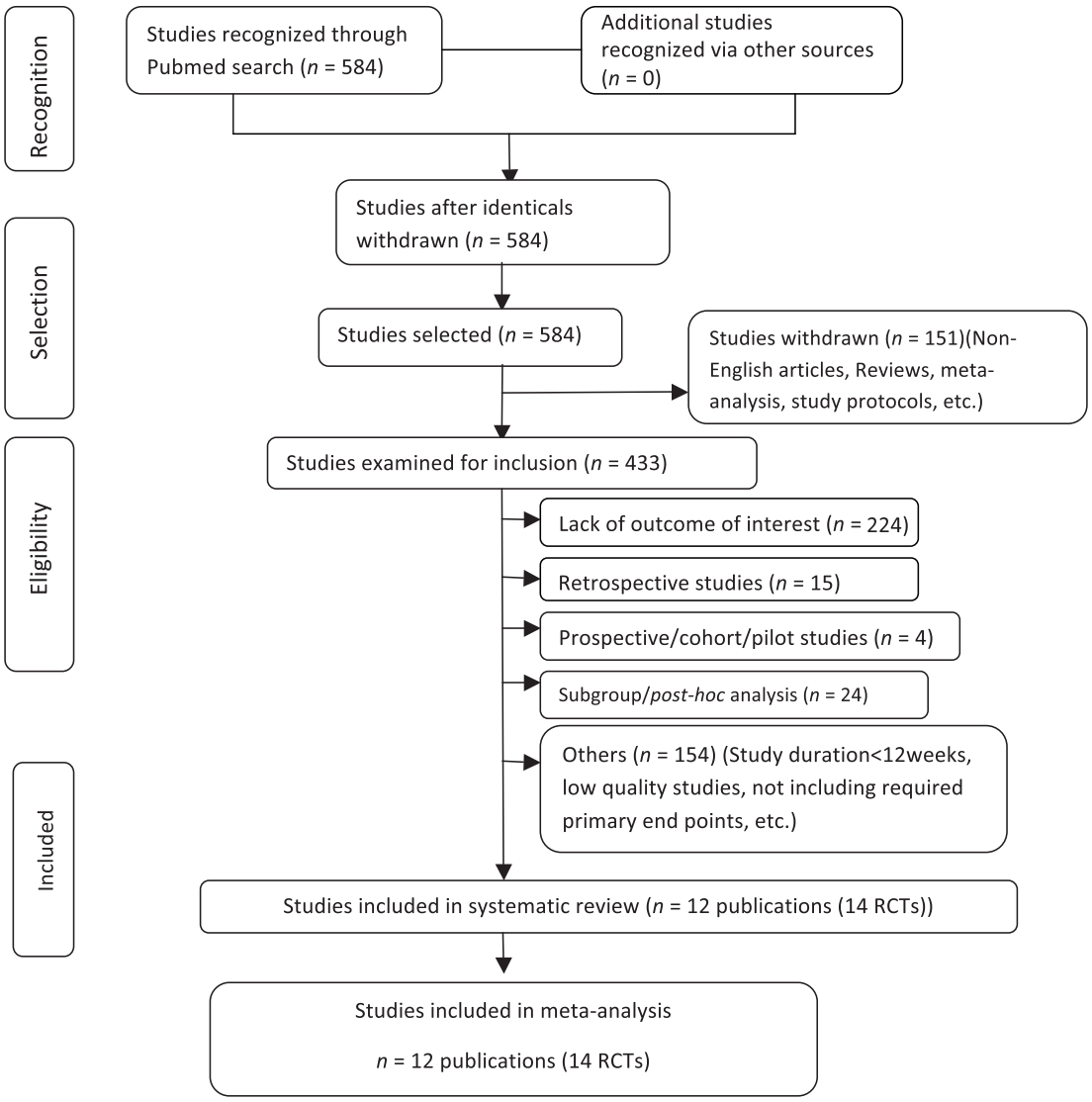

Figure 1. Algorithm for study search and selection.

SGRQ scores [MD, −1.66; 95% Confidence interval (CI), −2.09 to −1.23] (Fig. 4) and SGRQ responders [OR, 1.30; 95% CI, 1.18–1.44] (Fig. 5) compared to ICS/LABA therapy. Similarly, triple therapy showed improvements in CAT scores (MD, −0.86; 95% CI, −1.29 to −0.43) (Fig. 6) compared to ICS/LABA therapy. Three-drug therapy resulted in reduced use of rescue medication use (MD, −0.30; 95% CI, −0.40 to −0.20) (Fig. 7), puffs/day and enhancement in percentage of rescue medication-free days (MD, 6.42; 95% CI, 3.51–9.33) (Fig. 8). Three-drug therapy resulted in reduced adverse events relating to medication discontinuation (OR, 0.96; 95%CI, 0.74–1.25) (Fig. 9), albeit this association was far from statistical significance.

Triple therapy versus LABA/LAMA dual therapy

Four trials (Aaron *et al*., 2007; Ferguson *et al*., 2018; Lipson *et al*., 2018; Papi *et al*., 2018) used three-drug therapy versus LABA/LAMA therapy in comparison with moderate to severe COPD patients. Three-drug therapy showed improvement in SGRQ scores (MD, −1.65; 95% CI, −2.31 to −0.99) (Fig. 10) as well as SGRQ responders (OR, 1.00; 95% CI, 1.08–1.34) (Fig. 11) compared to LABA/LAMA therapy. Triple therapy showed a statistically insignificant reduction in adverse events (OD, 0.89; 95% CI, 0.65–1.23) (Fig. 12)

Bias, quality of evidence, and meta-regression analysis

The use of funnel plots demonstrated the largely symmetrical distribution of studies for the outcome SGRQ scores' average difference from baseline (Fig. 13). Nevertheless, the chance of evident publication bias has to be ruled in for other outcomes like SGRQ responders, CAT scores, rescue drug use, and adverse events, leading to drug discontinuation due to a lesser amount of available trials included in the meta-analysis.

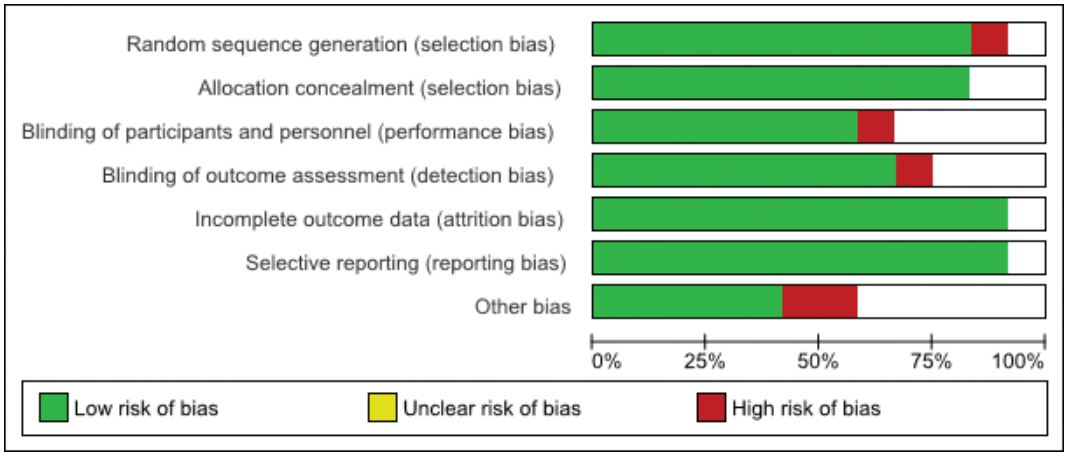

Figure 2. Graph of bias across studies.

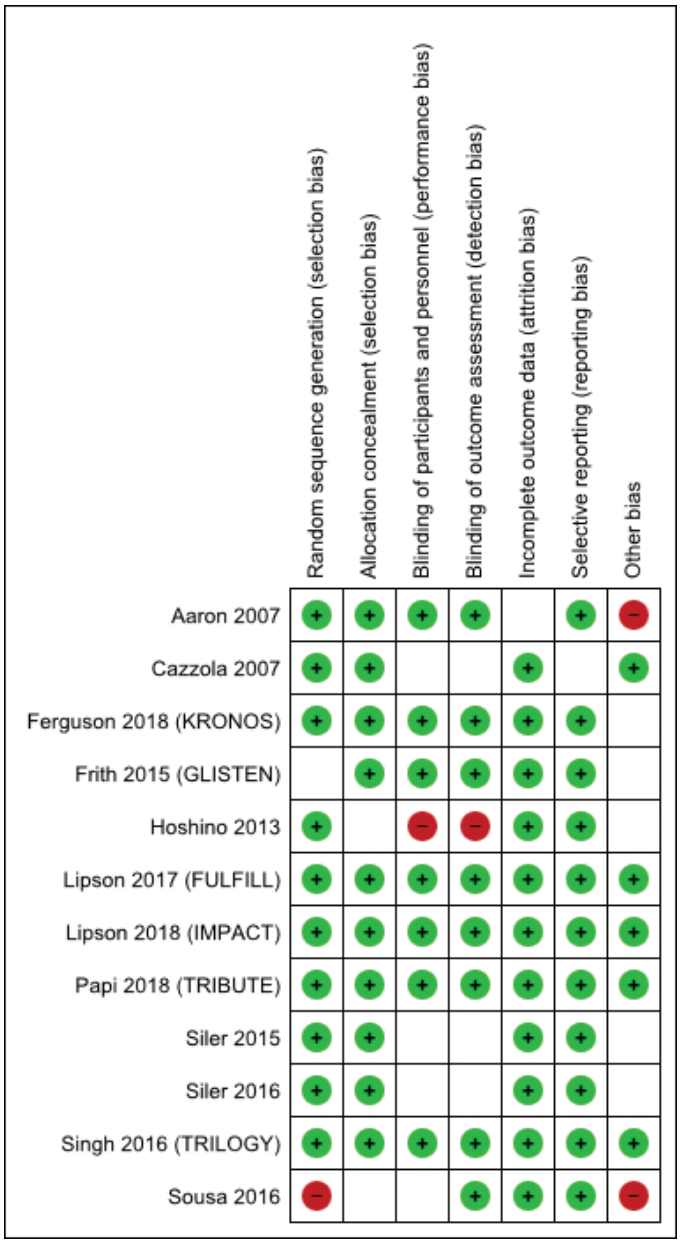

Figure 3. Graph of bias in included studies.

The GRADE approach revealed a medium quality of evidence for efficacy of three-drug therapy versus ICS/LABA and LABA/LAMA therapy on the SGRQ scores average difference from baseline and SGRQ responders, with no less than a 4-unit drop in the SGRQ score. Likewise, the medium standard of evidence was found for three-drug therapy versus LABA/LAMA therapy in terms of adverse events resulting in drug cessation. On the other hand, a very low quality of evidence was available for CAT scores' average difference from baseline and rescue medication use when three-drug therapy was compared with ICS/LABA therapy. Similarly, adverse events resulting in drug cessation produced low quality of evidence when three-drug therapy was compared with ICS/LABA therapy (Table 3).

Meta-regression analysis revealed the impact of several variables that may act as potential effect modifiers for the effect of three-drug therapy compared to ICS/LABA and LABA/LAMA therapy. These variables included age, percentage of men, fixed combination (single inhaler) versus open combination (separate inhaler), consistent versus inconsistent drug combination, study duration, and FEV1 (%pred). An inconsistent drug combination compared ICS/LABA/LAMA therapy with a non-identical ICS/LABA or LABA/LAMA drug therapy that was different from the three-drug therapy. None of the variables was found to significantly affect the SGRQ scores (Table 4). The graphical representation of the impact of different variables on SGRQ scores is shown in Figures 14–19. The condensed results table along with the standard of evidence is given in Table 5.

DISCUSSION

The findings of our meta-analysis demonstrated superior benefits of three-drug therapy in contrast to both ICS/LABA and LABA/LAMA combinations in various efficacy parameters. These efficacy parameters included improvement in SGRQ scores, more number of SGRQ responders (patients who gained a 4 or more units decrease in SGRQ scores), improvement in CAT scores, rescue drug use decrease, increase in rescue drug use free days, and decrease in drug discontinuation due to adverse events. Thus, the ICS/LABA/LAMA based three-drug therapy was able to improve HRQoL and dyspnea with the adverse events profile that was not significantly distinct from the two-drug therapy.

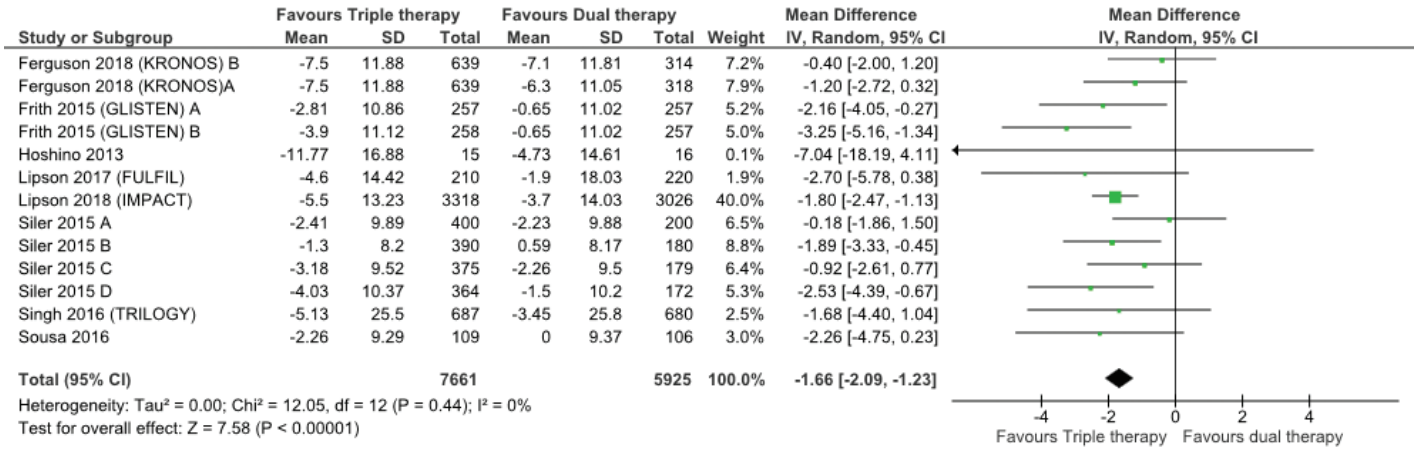

Figure 4. Average difference from baseline in SGRQ scores for triple therapy versus LABA/ICS dual therapy.

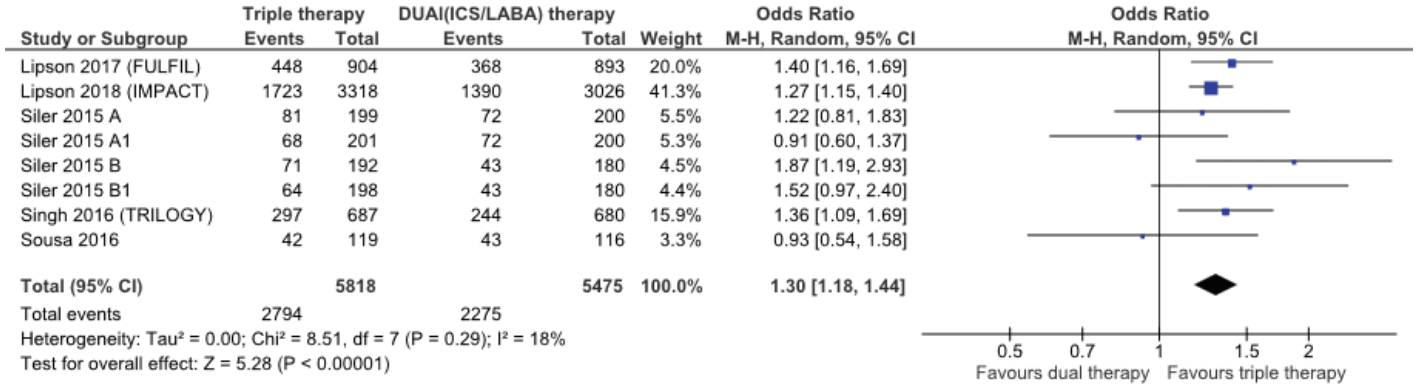

Figure 5. SGRQ responders with a minimum 4-unit decrease in SGRQ scores for triple therapy versus LABA/ICS dual therapy.

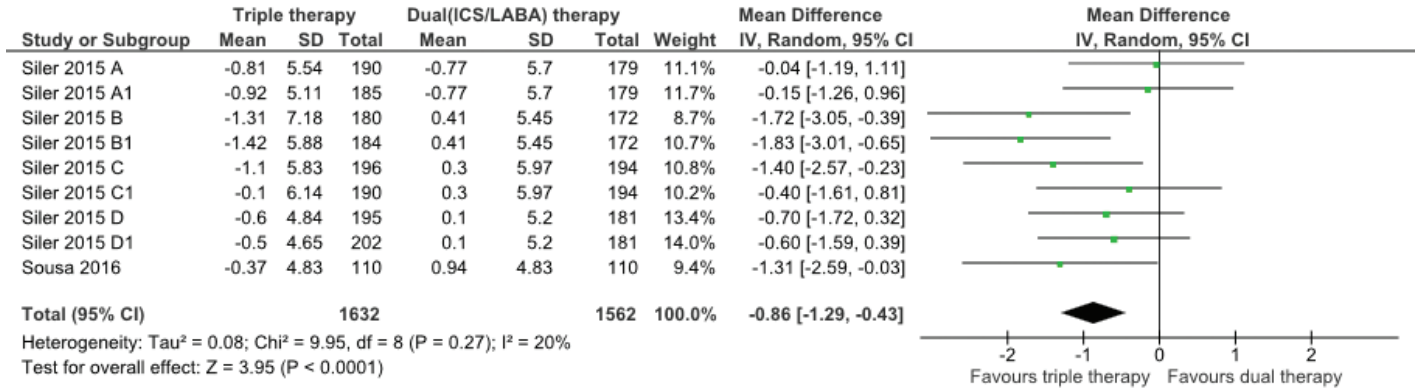

Figure 6. Average difference from baseline in CAT scores for triple therapy versus LABA/ICS dual therapy.

Our results are similar with the most recent meta-analysis that demonstrated the dominance of three-drug therapy over two-drug therapy in improving SGRQ scores and reduction in drug discontinuation attrition rates due to adverse events (Calzetta *et al*., 2019; Zayed *et al*., 2019; Zheng *et al*., 2018). Many of the patient-oriented efficacy parameters, like CAT scores and rescue drug use, which were neglected in the above-mentioned meta-analysis were the center of interest of our meta-analysis. Patient-oriented perspectives capture additional insights into efficacy parameters that are of particular interest for the practicing pulmonologist in the choice and monitoring of therapies at the individual patient level (Tabberer *et al*., 2018).

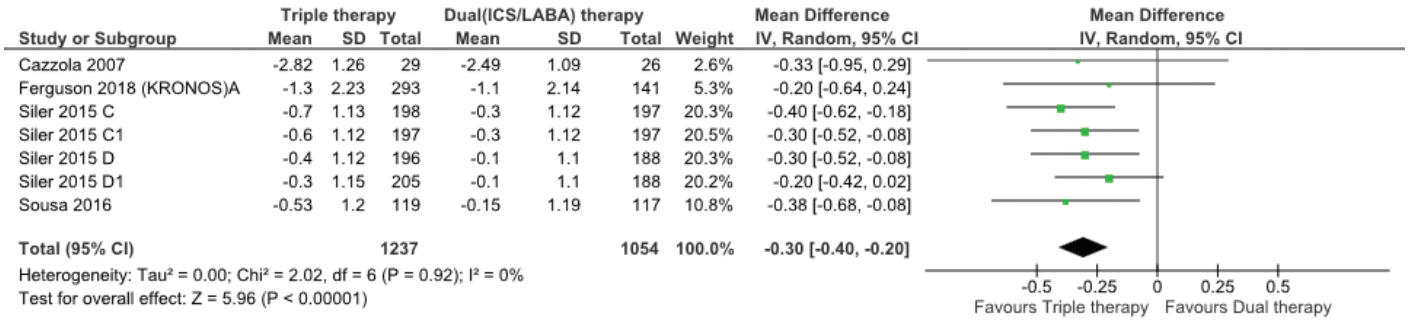

Figure 7. Average difference from baseline in rescue drug use (puffs/day) for triple therapy versus LABA/ICS dual therapy.

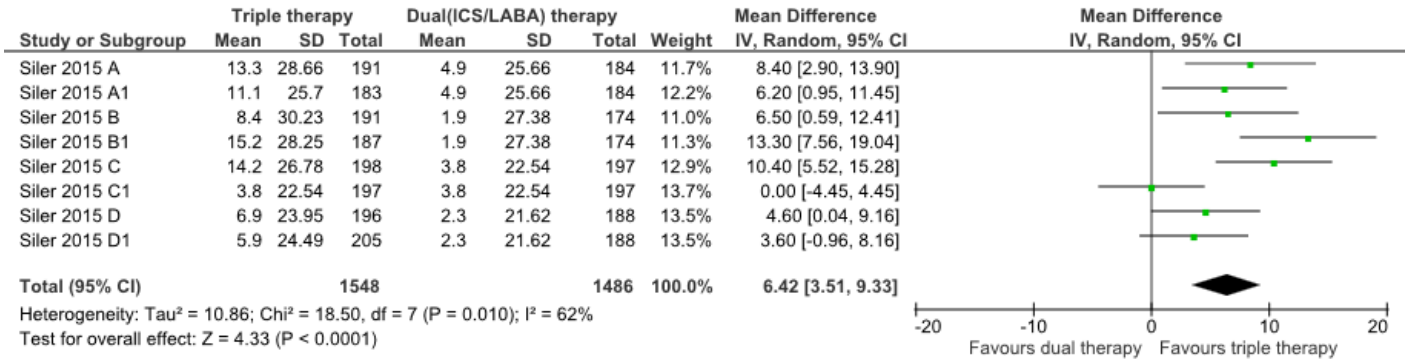

Figure 8. Average difference from baseline in percentage of rescue drug-free days for triple therapy versus LABA/ICS dual therapy.

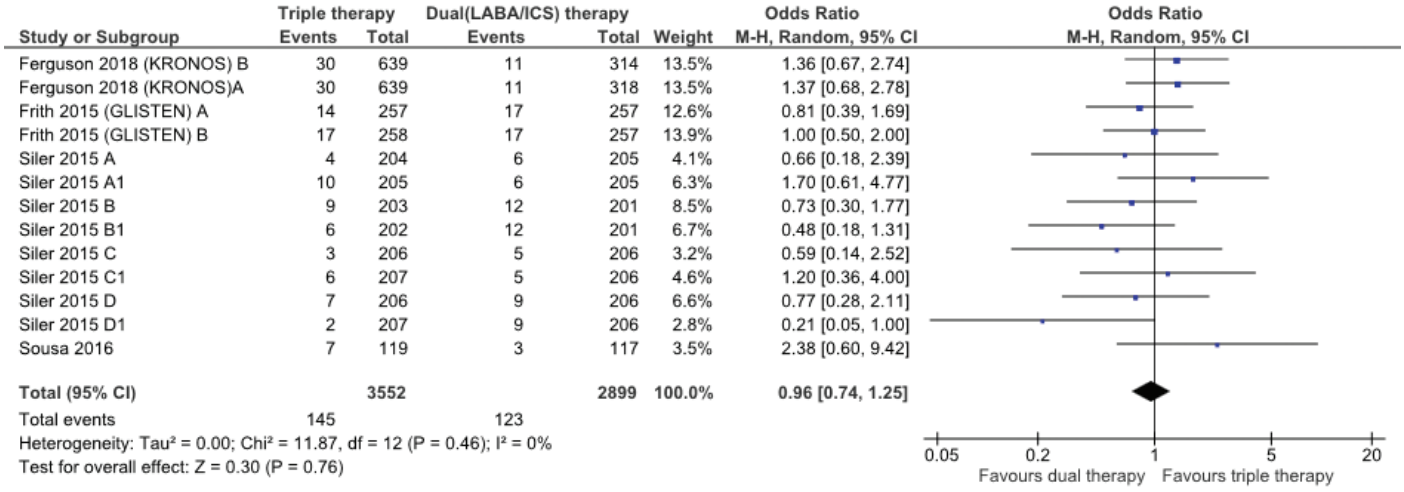

Figure 9. Adverse events resulting in drug cessation for triple therapy versus LABA/ICS dual therapy.

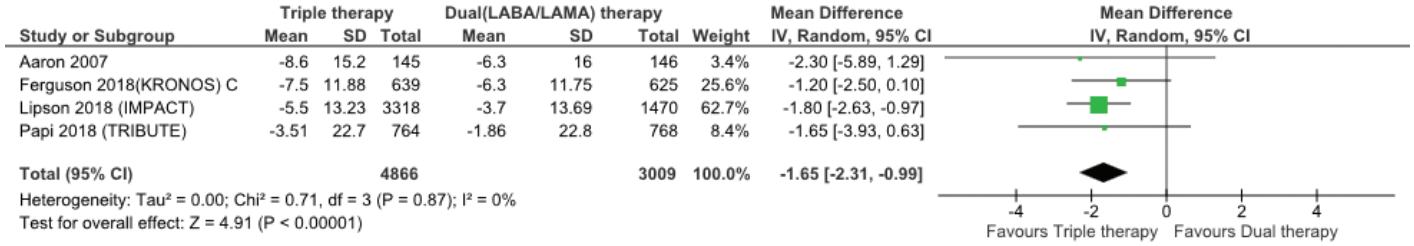

Figure 10. Average difference from baseline in SGRQ scores for triple therapy versus LABA/LAMA dual therapy.

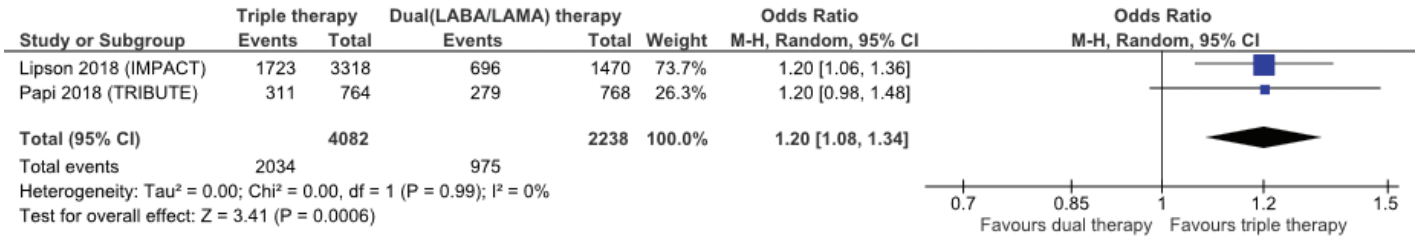

Figure 11. SGRQ responders with a minimum 4-unit drop in SGRQ score for triple therapy versus LABA/LAMA dual therapy.

Figure 12. Adverse events resulting in drug cessation for triple therapy versus LABA/LAMA dual therapy.

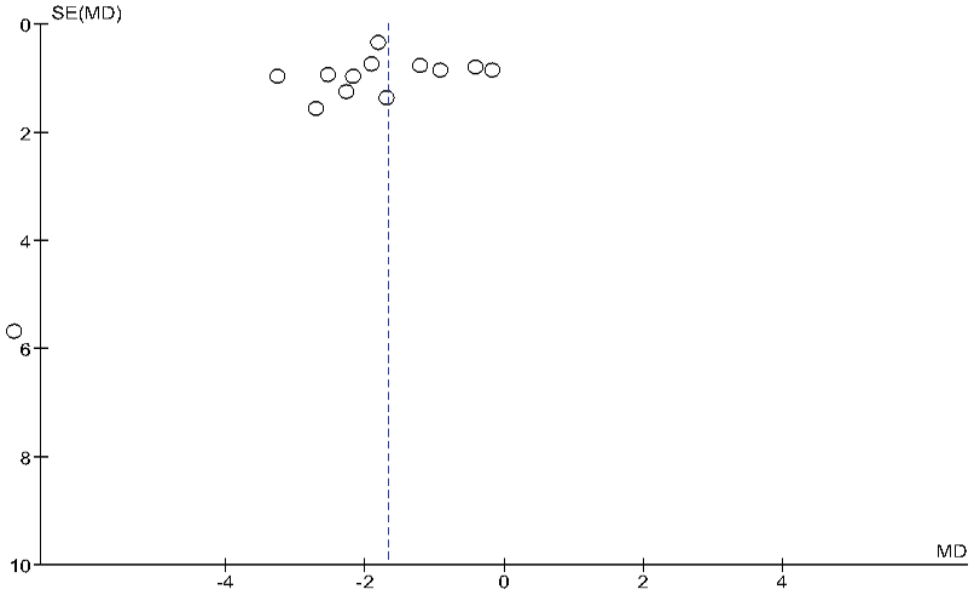

Figure 13. Funnel plot of publication bias for MD in SGRQ scores (Three-drug therapy *vs.* ICS/LABA therapy).

Moreover, this study analyzed the modifier impact of various variables on the SGRQ score which was not done in the previous meta-analysis.

Meta-regression analysis failed to show any significant confounding effect of the variables on the SGRQ average difference of three-drug therapy versus two-drug therapy. SGRQ scores have been shown to predict exacerbations, hospitalizations, and death due to COPD making SGRQ scores a valid tool to evaluate drug efficacy (Mullerova *et al*., 2017). Thus, factors affecting SGRQ scores will add additional insights into drug efficacy. Previous studies have shown significant correlations of SGRQ scores with age, frequency of exacerbations per year, comorbidities, and modified Medical Council Research Dyspnea scale (Farag *et al*., 2018; Lee *et al*., 2017). In the present study, covariates, consistent versus inconsistent drug combination, and fixed versus open combination were found to have the maximum influence on the SGRQ mean difference (MD), although this influence was ruled out due to statistically insignificant results. Unfortunately, the lesser number of available RCTs included can be one of the reasons behind the statistical insignificant covariates in the meta-regression analysis.

Table 3. Condensed results.

Certainty assessment						No of patients /Study events		Effect	Certainty of evidence	Absolute Benefit with Triple therapy over dual therapy
No of patients/ study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Triple therapy**	**Dual therapy**	**Absolute (95% CI)**		
Mean change from baseline in SGRQ scores (Triple therapy vs. ICS/LABA dual therapy)										
13,586 (9 RCTs)	Not serious	Not serious	Not serious	Serious[a]	None	7,661	5,925	MD 1.66 lower (2.09 lower to 1.23 lower)	⊕⊕⊕○ MODERATE	
Mean change from baseline in SGRQ scores (Triple therapy vs. LABA/LAMA dual therapy)										
7,875 (4 RCTs)	Serious[b]	Not serious	Not serious	Not serious	None	4,866	3,009	MD 1.65 lower (2.31 lower to 0.99 lower)	⊕⊕⊕○ MODERATE	
SGRQ responders with at least 4 unit decrease in SGRQ score(Triple vs. ICS/LABA dual therapy)										
11,293 (6 RCTs)	Not serious	Not serious	Not serious	Serious[c]	None	2,794/5,818 (48.0%)	2,275/5,475 (41.6%)	OR 1.30 (1.18–1.44)	⊕⊕⊕○ MODERATE	65 more per 1,000 (from 41 more to 90 more)
SGRQ responders with at least 4 unit decrease in SGRQ score (Triple vs. LABA/LAMA dual therapy)										
6,320 (2 RCTs)	Serious[d]	Not serious	Not serious	Not serious	None	2,034/4,082 (49.8%)	975/2,238 (43.6%)	OR 1.20 (1.08–1.34)	⊕⊕⊕○ MODERATE	45 more per 1,000 (from 19 more to 73 more)
Mean change from baseline in CAT scores (Triple vs. ICS/LABA dual therapy)										
3,194 (3RCTs)	Very serious[e]	Not serious	Serious [f]	Serious[g]	None	1,632	1,562	MD 0.86 lower (1.29 lower to 0.43 lower)	⊕○○○ VERY LOW	
Mean change from baseline in rescue medication use (Triple therapy vs. ICS/LABA dual therapy)										
2,291 (5RCTs)	Serious[e]	Serious[h]	Serious[f,g]	Serious[g]	None	1,237	1,054	MD 0.3 lower (0.4 lower to 0.2 lower)	⊕○○○ VERY LOW	
Adverse events leading to medication discontinuation (Triple therapy vs. ICS/LABA dual therapy)										
6,451 (5 RCTs)	Serious[e]	Serious[h]	Not serious	Not serious	None	145/3,552 (4.1%)	123/2,899 (4.2%)	OR 0.96 (0.74–1.25)	⊕⊕○○ LOW	2 fewer per 1,000 (from 11 fewer to 10 more)
Adverse events leading to medication discontinuation (Triple therapy vs. LABA/LAMA dual therapy)										
3,089 (3 RCTs)	Not serious	Not serious	Serious[f]	Not serious	None	75/1,548 (4.8%)	83/1,541 (5.4%)	OR 0.89 (0.65–1.23)	⊕⊕⊕○ MODERATE	6 fewer per 1,000 (from 18 fewer to 12 more)

[a]Two studies had insufficient sample size to produce precise results.

[b]Incomplete outcome data from one study.

[c]One study had sample size less than 300.

[d]Results obtained by meta-analysing only two studies.

[e]Allocation concealment not done. Blinding of result examination not done. Blinding of patients and trial staff not done.

[f]Smaller sample size makes generalizability difficult.

[g]Smaller sample size and wider confidence intervals.

[h]Wider confidence intervals. Results inconsistent across studies.

Table 4. Meta-regression analysis for variables influencing SGRQ scores.

Covariates	Coefficient	Std Error	95% CI lower	95% CI higher	Z-value	2 sided P-value
Intercept	7.6238	19.592	−30.7759	46.0234	0.39	0.6972
Age	−0.0558	0.3637	−0.7687	0.6571	−0.15	0.8781
% Men	−0.0111	0.1099	−0.2264	0.2042	−0.1	0.9194
Fixed versus open combination	−0.7616	1.316	−3.3409	1.8177	−0.58	0.5628
Inconsistent versus consistent combination	−0.7783	1.2345	−3.1978	1.6413	−0.63	0.5284
Study duration	−0.0285	0.0419	−0.1106	0.0535	−0.68	0.4957
FEV1 %predicted	−0.0795	0.1316	−0.3373	0.1784	−0.6	0.5464

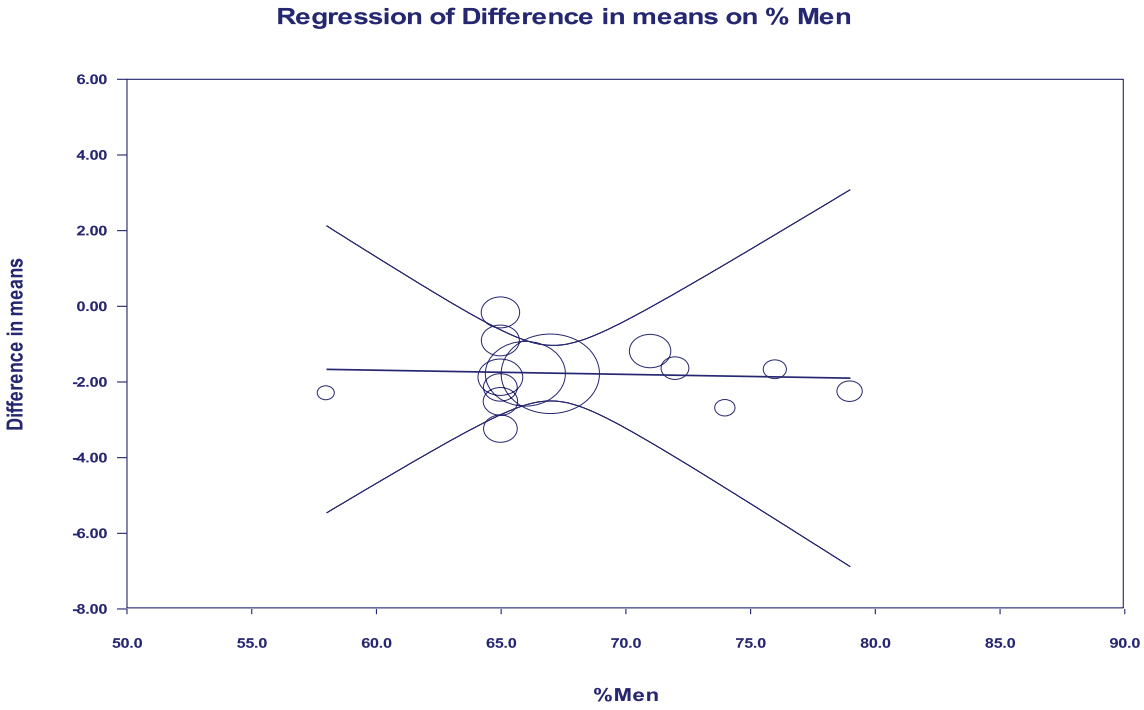

Figure 14. Variation in SGRQ MD scores based on percentage of men.

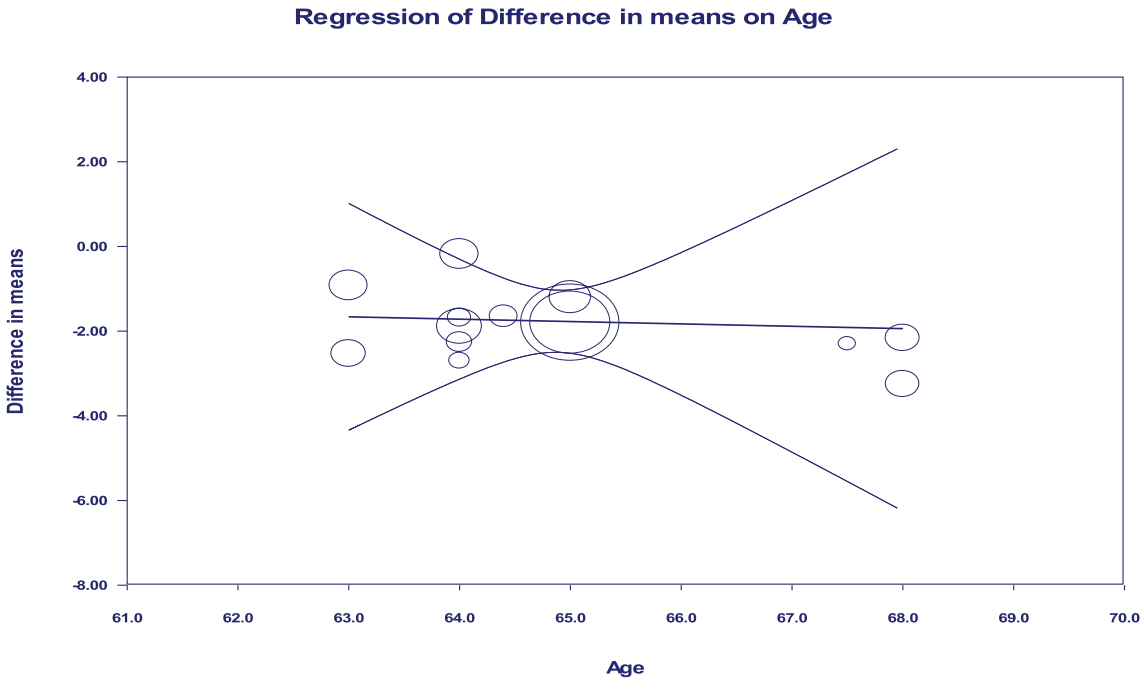

Figure 15. Variation in SGRQ MD scores based on age.

Triple therapy excelled in terms of SGRQ scores, indicating better patient QoL and additional number of patients gaining a 4 or more units improvement in SGRQ score compared to both ICS/LABA and LABA/LAMA therapies. Surprisingly, the advantage of triple therapy over both the dual therapies was almost similar when the SGRQ score and the number of SGRQ responders were taken into account. Nevertheless, two of the included studies (Siler *et al*., 2015; Sousa *et al*., 2016) did not show significant improvement in the SGRQ scores.

The patient's viewpoint is an inseparable part of clinical studies when it comes to the clinical application of drugs. Patient perspectives can be easily measured using CAT scores,

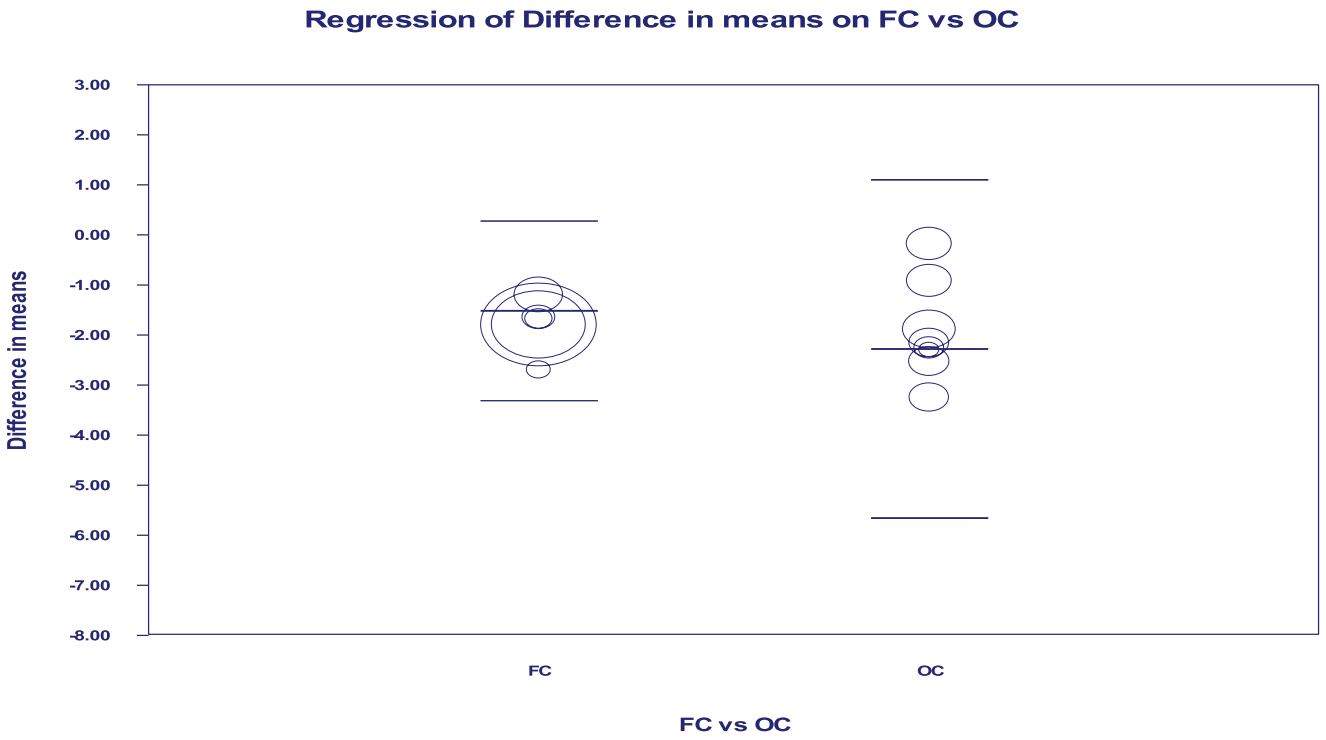

Figure 16. Variation in SGRQ MD scores based on fixed combination (single inhaler) versus open combination(dual inhaler).

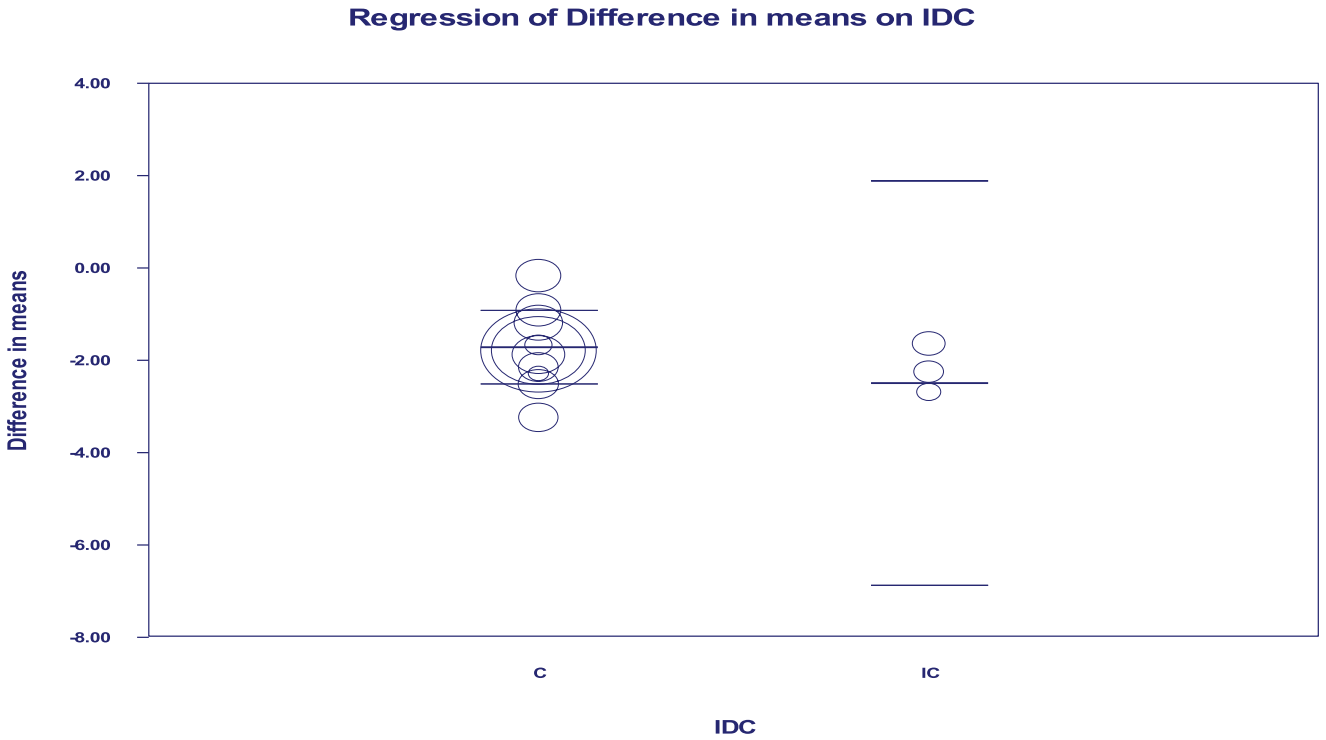

Figure 17. Variation in SGRQ MD scores based on drug combination [consistent(C) *vs.* inconsistent(IC)].

rescue medication use, and safety parameters like medication discontinuation due to adverse events (Lipson *et al.*, 2017; Perfetto *et al.*, 2015). This study reported moderate improvements in CAT scores for triple therapy versus ICS/LABA dual therapy, indicating moderate patient satisfaction as CAT scores are a reflection of patients' health status from the patient's perspective. Dismally, CAT scores did not reach minimally, clinically important differences (MCID) of ≥2-unit change, which is the minimum

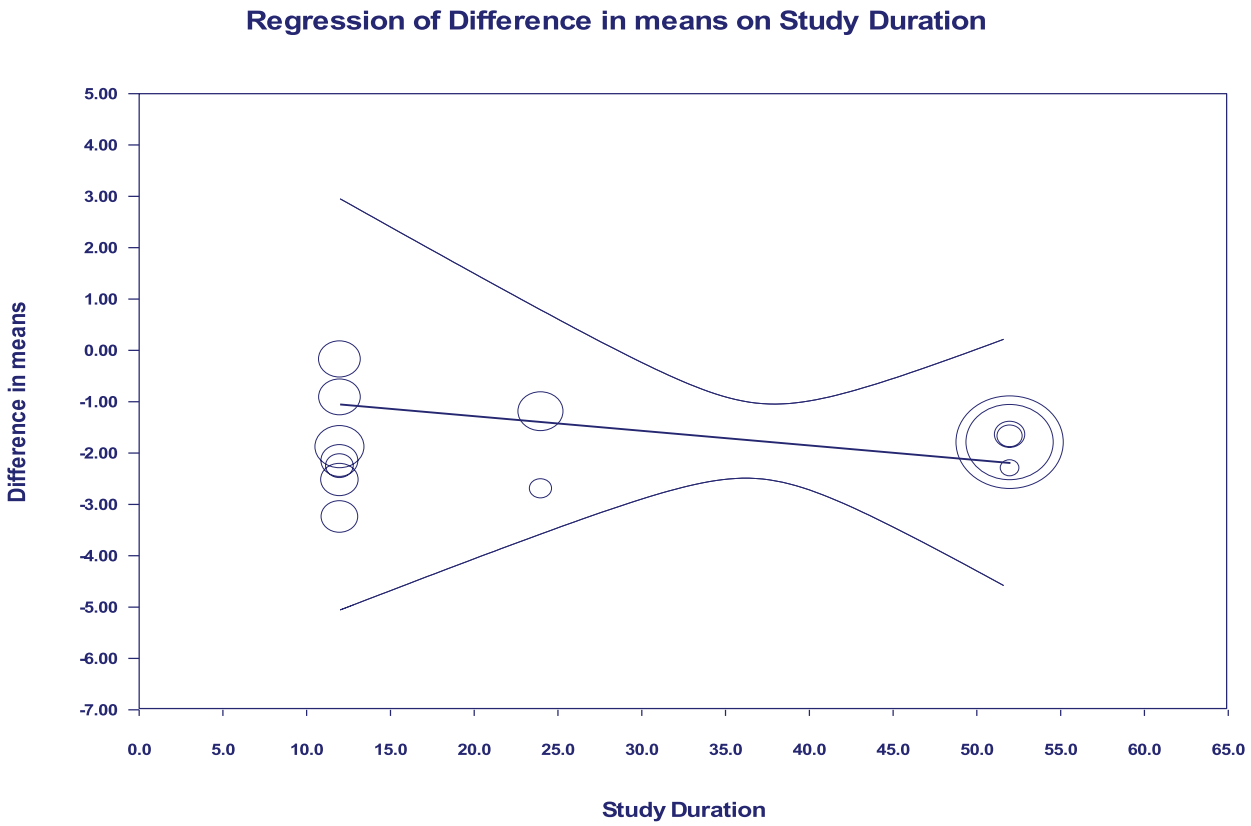

Figure 18. Variation in SGRQ MD scores based on study duration.

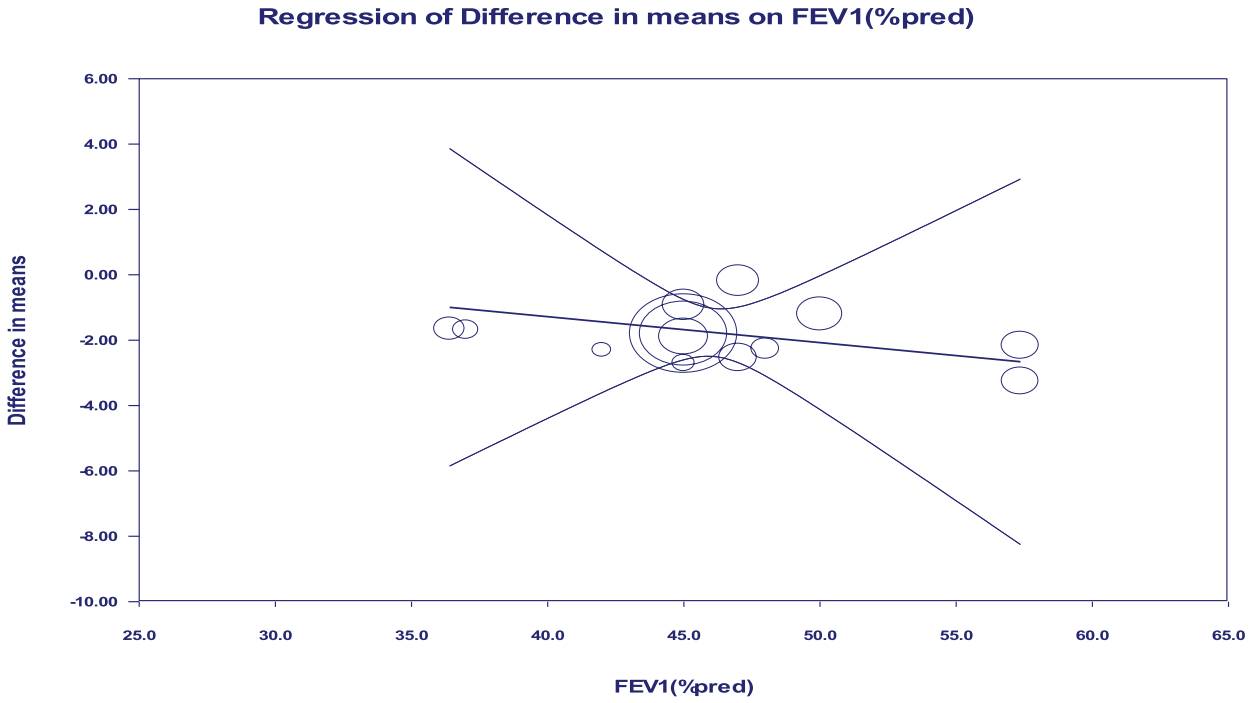

Figure 19. Variation in SGRQ MD scores based on FEV1 (%pred).

difference in score that patients confirm as advantageous or harmful and is helpful in clinical interpretation of results (Jones *et al*., 2012; Kon *et al*., 2014). On similar lines, none of the included studies (Siler *et al*., 2015, 2016; Sousa *et al*., 2016) reached MCID, indicating the inability of triple therapy toward complete patient satisfaction against ICS/LABA dual therapy.

Table 5. Standard of evidence.

Outcomes	No of trials	Effect size(95% CI)	I^2	*p*-value	GRADE evidence
Triple therapy versus LABA and LAMA (4 trials)					
Average difference from baseline in SGRQ scores	4	−1.65 (−2.31 to −0.99)	0	0.87	Moderate
SGRQ responders	2	1.20 (1.08 to 1.34)	0	0.99	Moderate
Adverse events resulting in drug cessation	3	0.89 (0.65 to 1.23)	0	0.58	Moderate
Triple therapy versus LABA and ICS (12 trials)					
Average difference from baseline in SGRQ scores	9	−1.66 (−1.09 to −1.23)	0	0.44	Moderate
SGRQ responders	6	1.30 (1.18–1.44)	18	0.29	Moderate
Average difference from baseline in CAT scores	3	−0.86 (−1.29 to −0.43)	20	0.27	Very low
Average difference from baseline in rescue medication use	5	−0.30 (−0.40 to −0.20)	0	0.92	Very low
Average difference from baseline in percentage of rescue drug free days	2	6.42 (3.51 to 9.33)	62	0.010	Very low
Adverse events resulting in drug cessation	5	0.96(0.74 to 1.25)	0	0.46	Low

LIMITATIONS

Several limitations can be attributed in this meta-analysis. Most of the trials did not include a run-in period and patients were given triple or dual therapies at baseline, making it difficult to judge whether the efficacy outcomes were due to baseline therapy or previous therapies. Head-to-head analysis was not performed in any of the trials and comparison was made between different medications with distinct devices and frequency schedules. Trials lacked real-world data and all the studies were designed as RCTs. Cost-effectiveness was not performed in any of the trials which could change the overall results. This meta-analysis was focused on patient-reported outcomes and QoL. Hence, other efficacy parameters, like FEV1 change, exacerbations, and incidence of adverse events, were not taken into consideration.

CONCLUSION

Triple therapy improved the QoL and patient-described outcomes compared to ICS/LABA and LAMA/LABA dual therapies in medium to serious COPD patients. Future trials should focus on other efficacy parameters like cost-effectiveness, cost–utility analysis, and stratification of results based on eosinophil levels, phenotypes, age, exacerbation history, etc.

ACKNOWLEDGMENTS

We express our profound gratitude to Dr. Syed Abdul Azeez Basha, the Honorable Principal of Deccan School of Pharmacy, Hyderabad, and Dr. Birendra Shrivastav, Honorable Director of School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, for providing necessary facilities, valuable guidance, and continuous encouragement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

None.

AUTHOR'S CONTRIBUTION

Syed Aamir Ali: concept, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. Dr. Ganesh Narayan Sharma: concept, design, and definition of intellectual content. Dr. Birendra Shrivastav and Dr. Mohd Aleemuddin Naveed: literature search, data acquisition, and data analysis.

REFERENCES

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, Balter M, O'Donnell D, McIvor A, Sharma S, Bishop G, Anthony J, Cowie R, Field S, Hirsch A, Hernandez P, Rivington R, Road J, Hoffstein V, Hodder R, Marciniuk D, McCormack D, Fox G, Cox G, Prins HB, Ford G, Bleskie D, Doucette S, Mayers I, Chapman K, Zamel N, FitzGerald M, Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med, 2007; 146:545–55.

Balcells E, Gea J, Ferrer J, Serra I, Orozco-Levi M, de Batlle J, Rodriguez E, Benet M, Donaire-González D, Antó JM, Garcia-Aymerich J, PAC-COPD Study Group. Factors affecting the relationship between psychological status and quality of life in COPD patients. Health Qual Life Outcomes, 2010; 8:108.

Calzetta L, Cazzola M, Matera MG, Rogliani P. Adding a LAMA to ICS/LABA therapy: a meta-analysis of triple combination therapy in COPD. Chest, 2019; 155:758–70.

Carrasco GP, de Miguel Díez J, Rejas GJ, Centeno AM, Vázquez EG, de Miguel ÁG, Carballo MG, and García RJ. Negative impact of chronic obstructive pulmonary disease on the health-related quality of life of patients. Results of the EPIDEPOC study. Health Qual Life Outcomes, 2006; 4:31.

Cazzola M, Andò F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, D'Amato M. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther, 2007; 20:556–61.

Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PMA, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palange P, Parr D, Pistolesi M, Rennard SI, Rutten-van Mölken MP, Stockley R, Sullivan SD, Wedzicha JA, Wouters EF. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J, 2008; 31:416–69.

Cully JA, Graham DP, Stanley MA, Ferguson CJ, Sharafkhaneh A, Souchek J, Kunik ME. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. Psychosomatics, 2006; 47:312–9.

Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet, 2012; 379(9823):1341–51.

Farag TS, Sobh ES, Elsawy SB, Fahmy BM. Evaluation of health-related quality of life in patients with chronic obstructive pulmonary disease. Egypt J Bronchol, 2018; 12:288–94.

Ferguson GT, Rabe KF, Martinez FJ, Fabbri LM, Wang C, Ichinose M, Bourne E, Ballal S, Darken P, DeAngelis K, Aurivillius M, Dorinsky P, Reisner C. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. Lancet Respir Med, 2018; 6:747–58.

Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, Frenzel C, Kurstjens N, Glisten Study Group. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study – a randomised controlled trial. Thorax, 2015; 70:519–27.

GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet, 2017; 390:1345–422.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD, 2017. Available via https://goldcopd.org. (Accessed 12 April 19)

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction to GRADE evidence profiles and summary of findings tables. J Clin Epidemiol, 2011; 64:383–94.

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC, Cochrane Bias Methods Group, Cochrane Statistical Methods Group, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ, 2011; 343:d5928.

Hoshino M, Ohtawa J. Effects of adding salmeterol/fluticasone propionate to tiotropium on airway dimensions in patients with chronic obstructive pulmonary disease. Respirology, 2011; 16:95–101.

Hu J, Meek P. Health-related quality of life in individuals with chronic obstructive pulmonary disease. Heart Lung, 2005; 34:415–22.

Hutchinson A, Brand C, Irving L, Roberts C, Thompson P, Campbell D. Acute care costs of patients admitted for management of chronic obstructive pulmonary disease exacerbations: contribution of disease severity, infection and chronic heart failure. Intern Med J, 2010; 40(5):364–71.

Jones PW, Harding G, Wiklund I, Berry P, Tabberer M, Yu R, Leidy NK. Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. Chest, 2012; 142:134–40.

Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, Haselden BM, Polkey MI, Man WDC. Minimum clinically important difference for the COPD assessment test: a prospective analysis. Lancet Respir Med, 2014; 2:195–203.

Lee H, Jhun BW, Cho J, Yoo KH, Lee JH, Kim DK, Lee JD, Jung KS, Lee JY, Park HY. Different impacts of respiratory symptoms and comorbidities on COPD-specific health-related quality of life by COPD severity. Int J Chron Obstruct Pulmon Dis, 2017; 12:3301–10.

Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ. FULFIL trial: once daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2017; 196:438–46.

Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ, IMPACT Investigators. Once daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med, 2018; 378:1671–80.

Moher D. CONSORT: an evolving tool to help improve the quality of reports of randomized controlled trials. Consolidated Standards of Reporting Trials. JAMA, 1998; 279:1489–91.

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev, 2015; 4:1.

Mullerova H, Gelhorn H, Wilson H, Benson VS, Karlsson N, Menjoge S, SI Rennard, Tabberer M, Tal-Singer R, Merrill D, Jones PW. St George's respiratory questionnaire score predicts outcomes in patients with COPD: analysis of individual patient data in the COPD biomarkers qualification consortium database. Chronic Obstr Pulm Dis, 2017; 4:141–9.

Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet, 2018; 391:1076–84.

Perfetto EM, Burke L, Oehrlein EM, Epstein RS. Patient focused drug development: a new direction for collaboration. Med Care, 2015; 53:9–17.

Siler TM, Kerwin E, Singletary K, Brooks J, Church A. Efficacy and safety of umeclidinium added to fluticasone propionate/salmeterol in patients with COPD: results of two randomized, double- blind studies. COPD, 2016; 13:1–10.

Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. Respir Med, 2015; 109:1155–63.

Singh D, Papi A, Corradi M, Pavlisova I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet, 2016; 388:963–73.

Sousa AR, Riley JH, Church A, Zhu CQ, Punekar YS, Fahy WA. The effect of umeclidinium added to inhaled corticosteroid/long-acting β2-agonist in patients with symptomatic COPD: a randomised, double-blind, parallel-group study. NPJ Prim Care Respir Med, 2016; 26:16031.

Tabberer M, Lomas DA, Birk R, Brealey N, Zhu CQ, Pascoe S, Locantore N, Lipson DA. Once daily triple therapy in patients with COPD: patient-reported symptoms and quality of life. Adv Ther, 2018; 35:56–71.

Zayed Y, Barbarawi M, Kheiri B, Haykal T, Chahine A, Rashdan L, Hamid K, Sundus S, Banifadel M, Aburahma A, Bachuwa G, Chandran A. Triple versus dual inhaler therapy in moderate-to-severe COPD: a systematic review and meta-analysis of randomized controlled trials. Clin Respir J, 2019; 13(7):413–28.

Zheng Y, Zhu J, Liu Y, Lai W, Lin C, Qiu K, Wu J, Yao W. Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. BMJ, 2018; 363:k4388.

How to cite this article:
Sharma GN, Ali SA, Shrivastav B, Mohd AN. Three-drug therapy versus two-drug therapy for management of patient-reported manifestations and quality of life in chronic obstructive pulmonary disease patients: A meta-analysis. J Appl Pharm Sci, 2020; 10(10):036–049.