



Meta-analysis of cost-effectiveness of three-drug therapy versus two-drug therapy in chronic obstructive pulmonary disease patients

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ABSTRACT

Healthcare expenditures on chronic obstructive pulmonary disease (COPD) have increased substantially globally. Thus, there is a need to find a cost-effective approach for the treatment of COPD. This meta-analysis aimed to evaluate the cost-effectiveness of triple therapy [long acting beta2 agonists (LABA)/long-acting muscarinic antagonist (LAMA)/inhaled corticosteroids (ICS)] versus dual therapy (LABA/LAMA and LABA/ICS) in moderate to severe COPD patients. Studies evaluating the cost-effectiveness of triple therapy versus dual therapy were identified through PubMed and Scopus from 2011 (January) to 2021 (January) and meta-analyzed using a random-effects model. Results were presented as standardized mean differences (SMD) of quality-adjusted life years (QALY), life years (LY) gained, Costs, incremental cost-effectiveness ratios (ICER), incremental net monetary benefits (INMB), and incremental net health benefits (INHB). Of the 125 studies identified, four model analyses were included and meta-analyzed. QALY [SMD: 0.22; 95% confidence interval (CI): 0.16, 0.28], LY gained (SMD: 0.14; 95% CI: 0.10, 0.19), ICER (SMD: 0.96; 95% CI: 0.55, 1.38), INMB (SMD: 0.14; 95% CI: 0.12, 0.16), and INHB (SMD: 0.17; 95% CI: 0.13, 0.21) favored triple therapy. The results indicate that triple therapy is cost-effective than dual therapy in moderate to severe COPD patients as it provides more QALY and LY but at an additional cost.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an advancing pulmonary disorder distinguished by diminished airflow and enhanced chronic inflammatory reaction in the airways. The goal of COPD drug therapy is to diminish symptoms, boost exercise resistance and health condition, and reduce exacerbation recurrence. Long acting beta2 agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) remain the extensively used therapeutic options for COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2020). Inhaled triple therapy containing (ICS/LAMA/LABA) can improve pulmonary function, symptoms, and health status, and can reduce exacerbations compared with dual therapy (LAMA/LABA or ICS/LABA) (Ferguson *et al.*, 2018; Lipson *et al.*, 2017, 2018).

COPD costs colossal expenditures through drugs, clinician visits, hospitalizations, and emergency room visits and adversely affects the patient's quality of life (Ehteshami-Afshar *et al.*, 2016; Lopez-Campos *et al.*, 2016). Various factors may affect the healthcare costs in COPD including but not limited to symptom severity and frequency and nature of exacerbations (Blasi *et al.*, 2014; Iheanacho *et al.*, 2020; Rutten-van Mülken and Lee, 2006; Toy *et al.*, 2010). Apart from its economic strain, COPD decreases patient's overall health status and negatively impacts the quality of life owing to high levels of anxiety and depression (Soler-Cataluna *et al.*, 2016).

Cost-effectiveness analysis (CEA) is a kind of monetary evaluation that differentiates relative costs and outcomes (effects) of different therapeutic approaches. CEA is presented as a ratio where the numerator is the cost associated with the therapeutic approach and the denominator is health gain associated with the therapeutic approach. The most commonly used outcome measure of CEA is quality-adjusted life year (QALY). Frequently, CEA guides treatment decisions on the choice of therapeutic approaches for COPD patients. CEA aids stakeholders discover the way how

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clinical benefit observed in research translates into the quality of life and whether the additional costs justify the additional benefits as opposed to emphasizing costs alone (Drummond and Jefferson, 1996).

Numerous studies have been performed across the globe to evaluate the cost-effectiveness of triple therapy (ICS/LAMA/LABA) versus dual therapy (LAMA/LABA or ICS/LABA) (Driessen *et al.*, 2018; Ismaila *et al.*, 2019; Schroeder *et al.*, 2019, 2020). To the authors' knowledge, no previous meta-analysis has been performed evaluating the cost-effectiveness of triple therapy (ICS/LAMA/LABA) versus dual therapy (LAMA/LABA or ICS/LABA). Thus, the aim of the present study was to meta-analyze the cost-effectiveness of triple therapy (ICS/LAMA/LABA) versus dual therapy (LAMA/LABA or ICS/LABA) from the United States (US) National Healthcare System (NHS) perspective.

MATERIALS AND METHODS

Search strategy

Medline and Scopus databases were hand checked to locate relevant economic studies evaluating triple therapy (ICS/LAMA/LABA) versus dual therapy (LAMA/LABA or ICS/LABA). The search was conducted to include all relevant papers from 2011 (January) to 2021 (January). Search strategy used to find the relevant articles in the PubMed database is as follows:

#1 (COPD[Title]) OR (“chronic obstructive pulmonary disease”[Title])
 #2 (“cost-effectiveness”[Title]) OR (“cost-utility”[Title]) OR (“economic evaluation”[Title])
 #3 #1 AND #2

The data were extracted individually by two reviewers based on the following inclusion criteria:

Inclusion criteria

1. Economic studies evaluating triple therapy (ICS/LAMA/LABA) versus dual therapy (LAMA/LABA or ICS/LABA).
2. Economic studies which are designed as cost-effectiveness or cost-utility analysis.
3. Patients with moderate to severe COPD.
4. English Language publications.
5. Only original research papers.
6. Full text available.

The discrepancies between the two reviewers were resolved by the third reviewer. Titles and abstracts were first reviewed followed by a full-text review of papers comparing triple therapy versus dual therapy. All the studies included in this meta-analysis were model-analysis of already published randomized clinical trials. Costs, QALYs, Life years (LY's), net monetary benefit (NMB), and net health benefit (NHB) were used as evaluation parameters. The present study was done in agreement with the preferred reporting items for systematic reviews and meta-analyses guidelines (Moher *et al.*, 2015).

Data extraction

Data collection was done taking into consideration Consolidated Health Economic Evaluation Reporting Standard checklist (Husereau *et al.*, 2013). Extracted data included

baseline characteristics of the study population, intervention and comparator drug, target population, country, modeling approach, time horizon, discounting, perspective of study, sensitivity analysis, most sensitive parameter, funding, costs, effectiveness (QALY/LY), incremental cost-effectiveness ratio (ICER), and Exacerbations.

Data analysis

To standardize costing data, all costs were converted and presented as annual costs in the year 2020 US dollars (\$). As none of the included studies reported standard deviation (SD) of the costs and utility values, we made use of sample size, 95% confidence interval (CI), and standard error to derive the SD. Alternatively, Revman software calculators were also used for calculating the SD (Higgins *et al.*, 2021).

Comparative efficiency research provides a way for meta-analyzing cost-effectiveness studies by pooling incremental net benefits (INB) (Crespo *et al.*, 2014). Net Benefit Calculations combine cost, effectiveness, and willingness to pay (WTP) into a single value. $INMB = (E2 - E1) * WTP - (C2 - C1)$

$$INHB = (E2 - E1) - (C2 - C1) / WTP$$

Where E2 and E1 are the effectiveness of the two strategies

and C2 and C1 are the costs of the two strategies. The optimal strategy will have the highest Net Benefit value. The new treatment is said to be cost-effective if the INB is positive (Stinnett, 1998; Willan, 2004).

Costs per QALY, costs per LY, and ICER were used to evaluate cost-effectiveness. If the new treatment is more costly and less effective than the standard treatment, it is said to be dominated. If it is less costly and more effective, it is said to be dominant. However, if the new treatment is more costly and more effective, it is said to be cost-effective if ICER is less than the WTP for that particular country. Error Propagation methods were applied to costs and utility values to obtain the SD of cost-effectiveness (Taylor, 1997). The ICER was calculated by the formula given below:

$$ICER = (C2 - C1) / (E2 - E1)$$

Where E2 and E1 are the effectiveness of the two strategies and C2 and C1 are the costs of the two strategies. ICER represents the average incremental cost associated with one additional unit of the measure of effect. Costs are estimated in monetary units whereas effectiveness is measured in health status values (McFarlane and Bayoumi, 2004) in this study the QALY and LY gained.

Statistical analysis

As all the outcomes in this study were continuous, standardized mean differences (SMD) with its 95% CI were used to present the comparison between triple therapy and dual therapy. The random-effects model was used because the incorporated studies had variations in geographical location and population characteristics. Statistical heterogeneity between trials was assessed using the I^2 statistic, with I^2 values greater than 50% indicating significant heterogeneity between studies. Variation in the studies was evaluated using Meta-regression analysis. Data were analyzed using RevMan v5.3 software and Comprehensive Meta-analysis v3 software.

RESULTS AND DISCUSSION

A comprehensive literature search resulted in 125 research articles considering cost-effectiveness in COPD patients. Following meticulous assessment by the reviewers, four model analyses published between 2011 and 2021 were included in this meta-analysis based on the inclusion criteria. A summary of the study selection procedure is presented in Figure 1. Study baseline characteristics used as model inputs in the model analysis are given in Table 1.

In the current meta-analysis, four new articles presented the cost-effectiveness of triple therapy (LABA/LAMA/ICS) versus dual therapy (LABA/LAMA or ICS/LABA) (Tables 2–5). Two studies were conducted from the UK National Health service perspective while the remaining two were conducted from the Spain National Healthcare system and Canadian public healthcare perspective. In general, all the studies were performed from the National healthcare system perspective.

The ICS evaluated were Fluticasone furoate, Budesonide and Fluticasone propionate, LAMA was Umeclidinium, and LABA were Vilanterol, Salmeterol, and formoterol. All the studies were model analyses of previously published clinical trial data, were sponsored by the pharmaceutical company, and used QALY/LY as an outcome measure for effectiveness analysis. One study (Ismaila *et al.*, 2019) used IMPACT trial data (Lipson *et al.*, 2018), the other two (Schroeder *et al.*, 2019, 2020) used FULFILL trial data (Lipson *et al.*, 2017), and the fourth study (Driessen *et al.*,

2018) used data from three different trials (Siler *et al.*, 2015, 2016; Sousa *et al.*, 2016). In all the four studies, triple therapy (ICS/LABA/LAMA) was found to be cost-effective than dual therapy (LABA/LAMA and ICS/LABA) as the ICER remained below the WTP threshold of that particular country.

Triple therapy demonstrated higher costs compared with dual therapy (SMD: 0.27; 95% CI: 0.18, 0.36) which was statistically significant (Fig. 2). Meta-analysis of QALY revealed greater utility associated with triple therapy compared to dual therapy (SMD: 0.22; 95% CI: 0.16, 0.28) (Fig. 3). Triple therapy resulted in greater LY gained compared to dual therapy (SMD: 0.14; 95% CI: 0.10, 0.19) (Fig. 4). The cost-effectiveness of triple therapy was better than dual therapy as the ICER was well below the WTP (SMD: 0.96; 95% CI: 0.55, 1.38) (Fig. 5). INMB revealed NMB associated with triple therapy was higher than dual therapy (SMD: 0.14; 95% CI: 0.12, 0.16) (Fig. 6). Similarly, triple therapy resulted in more NHB than dual therapy as evidenced from positive INHB (SMD: 0.17; 95% CI: 0.13, 0.21) (Fig. 7). Meta-regression analysis was performed to evaluate the effect of baseline variables that may act as potential effect modifiers for additional QALY gain from triple therapy versus dual therapy. These variables included previous exacerbations in 1 year, baseline St. George Respiratory Questionnaire (SGRQ), and 6-minute walk test (6MWT). Among all the included variables, only exacerbations in the previous year significantly negatively impacted QALY ($p < 0.01$) (Fig. 8 and Table 6). The summary of findings is presented in Table 7.

This study is the first to meta-analyze the cost-effectiveness of triple therapy versus dual therapy from the US National healthcare system perspective. This meta-analysis revealed higher gains in QALY, LY, NMB, and NHB with triple therapy compared to dual therapy. Although cost was more with triple therapy, this was offset by the benefits in QALY and LY than dual therapy. This was evidenced by the fact that ICER was cost-effective well below the WTP in favor of triple therapy when both QALY and LY were taken into account. However, the subtleness of QALY and LY gain from triple therapy should make stakeholders think about the higher costs associated with triple therapy especially when adverse events decrease the QALY and increase the costs of triple therapy (Lopez-Campos *et al.*, 2018; Suissa and Drazen, 2018).

Costs of triple therapy were higher compared to both ICS/LABA and LABA/LAMA dual therapies because of the inclusion of an extra third drug in the triple therapy. This was balanced by lower non-drug costs associated with triple therapy owing to a lesser number of exacerbations and hospital days compared to LABA/LAMA dual therapy. When triple therapy is compared to ICS/LABA dual therapy, non-drug costs were higher for triple therapy not only because the exacerbation benefit is shared by both ICS/LABA dual therapy and triple therapy but also because triple therapy resulted in higher forced expiratory volume in 1 second (FEV1) benefit, prolonged survival, and the resultant increase in the utilization of healthcare resources (Ismaila *et al.*, 2019).

In the included studies, cost-effectiveness was sensitive to treatment effects, utility scores, healthcare costs, and SGRQ scores. Various reasons may be attributed to the heterogeneous nature of these parameters. The frequency and severity of exacerbations and resultant hospitalizations are greatly affected

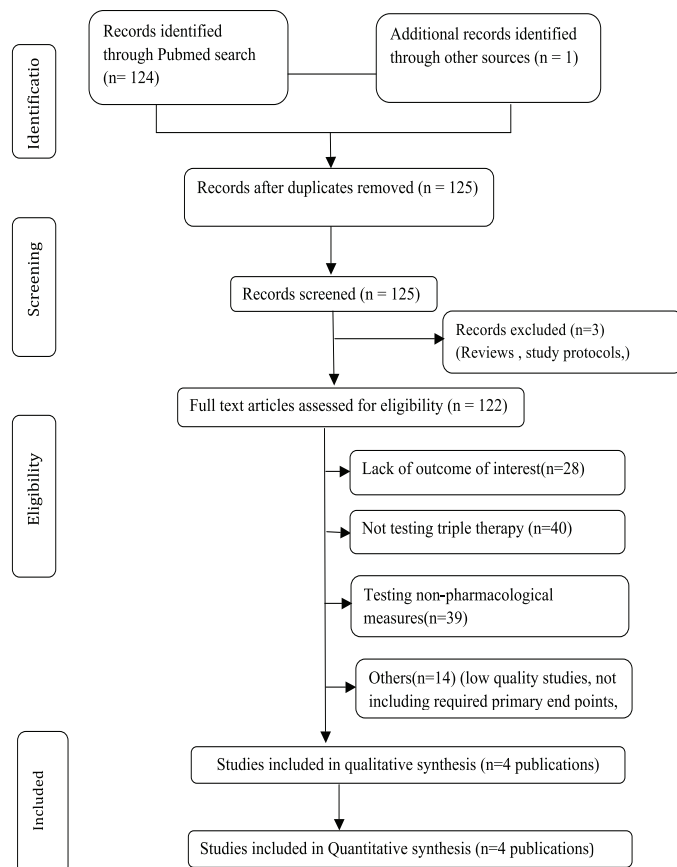


Figure 1. Flow Diagram of Literature search and study selection.

Table 1. Baseline characteristics used as model inputs used in studies.

Parameters Authors, country (Year) ↓	Female %	Age (years)	Prior exacerbation (mean)	mMRC score ≥2, %	Current smokers, %	Baseline SGRQ, mean (SE)	6MWT, mean	Baseline FEV1% predicted, mean	Any CVD comorbidity %	Any other comorbidity %
Ismaila <i>et al.</i> Canada, 2019	34	65.3	1.71	37	35	50.7	365.8	45.5	44	57
Schroeder <i>et al.</i> Spain, 2020	19.2	68.2	1.1	43	23.1	42.7	369.4	45.3	40	58
Schroeder <i>et al.</i> UK, 2019	26	63.9	1.1	43	44	51.3	370.7	45.3	40	58
Driessen <i>et al.</i> UK, 2018 (FF/ UMEC/VI vs. FF/VI)	34	63.7	0.21	100	50	43.8	359.5	46.0	69	89
Driessen <i>et al.</i> UK, 2018 (FP/UMEC/SAL vs. FP/SAL)	35	64.1	0.34	100	45	45.4	353.2	45.7	67	87
Driessen <i>et al.</i> UK, 2018 (UMEC/ICS/ LABA vs. ICS/ LABA)	35	63.9	0.28	100	48	44.5	356.5	46.1	68	88

SGRQ = St. George Respiratory questionnaire, UK = United Kingdom, UMEC = Umeclidinium, FF = Fluticasone furoate, VI = vilanterol, FP = fluticasone propionate, SAL = Salmeterol, ICS = Inhaled corticosteroids, LABA = Long acting beta2 agonists, mMRC score = Modified Medical Research council Dyspnea score, SE = standard error, 6MWT = 6 minute walk test, FEV1 = Forced expiratory volume in 1 second, CVD = cardiovascular disease.

Table 2. Baseline characteristics of economic evaluations in studies.

Parameter Study	Intervention	Comparator	Target Population	Modeling Approach	Time Horizon	Discount rate	Perspective	Sensitivity analysis	Most sensitive parameter	Funding
Ismaila <i>et al.</i> Canada, 2019	FF/UMEC/VI	FF/VI, UMEC/VI	Moderate to severe COPD	GALAXY- COPD disease progression model	Lifetime horizon	1.5% annually	Canadian public health care perspective	Scenario and probabilistic sensitivity analysis	Utility value, Treatment effect, and exacerbation rate	GlaxoSmithKline
Schroeder <i>et al.</i> Spain, 2020	FF/UMEC/VI	BUD/FOR	Moderate to severe COPD	GALAXY- COPD disease progression model	3-year time horizon	3% discount rate	Spanish NHS perspective	One-way sensitivity, scenario analyses, probabilistic sensitivity analysis	Treatment effect, variations in exacerbations, healthcare resource utilization costs	GlaxoSmithKline
Schroeder <i>et al.</i> UK, 2019	FF/UMEC/VI	BUD/FOR	Moderate to severe COPD	GALAXY- COPD disease progression model	Lifetime horizon	3.5% discount rate	UK NHS perspective	Deterministic and probabilistic sensitivity analyses	SGRQ and exacerbation treatment effects	GlaxoSmithKline
Driessen <i>et al.</i> UK, 2018	FF/UMEC/ VI, UMEC/ FP/SAL, UMEC/ICS/ LABA	FF/VI, FP/ SAL, ICS/ LABA	Moderate to severe COPD	GALAXY- COPD disease progression model	Lifetime horizon	3.5% discount rate	UK NHS perspective	One-way sensitivity, scenario analyses, probabilistic sensitivity analysis	Results were robust to sensitivity analysis	GlaxoSmithKline

UMEC = Umeclidinium; FF = Fluticasone furoate; VI = vilanterol; FP = fluticasone propionate; ICS = Inhaled corticosteroids; LABA = Long acting beta2 agonists; SAL = Salmeterol; BUD = Budesonide.

Table 3. Triple therapy versus dual therapy cost-effectiveness.

Authors	Incremental costs (95% CI) (valuation year)	Difference in outcomes (95% CI)	ICER threshold	ICER	Conclusion
Ismaila <i>et al.</i> Canada, 2019 (FF/UMEC/VI vs. UMEC/VI)	C\$1766 (C\$1167, C\$2336) (2017)	0.1177 (0.048, 0.186) LY's; 0.1282 (0.081, 0.177) QALY's	C\$50,000/QALY	C\$13,776 (C\$9787, C\$19,448)	FF/UMEC/VI is cost-effective.
Ismaila <i>et al.</i> Canada, 2019 (FF/UMEC/VI vs. FF/VI)	C\$2604 (C\$1980, C\$3285) (2017)	0.1388 (0.068, 0.207) LY's; 0.1371 (0.092, 0.182) QALY's	C\$50,000/QALY	C\$18,989 (C\$14,665, C\$25,753)	FF/UMEC/VI is cost-effective
Schroeder <i>et al.</i> Spain, 2020 (FF/UMEC/VI vs. BUD/FOR)	€69 (2019)	0.017 LY's, 0.107 QALY's	€30,000/QALY	€642	FF/UMEC/VI is cost-effective
Schroeder <i>et al.</i> UK, 2019 (FF/UMEC/VI vs. BUD/FOR)	£1,652 (£723, £2,462) (2017)	0.764 (0.33, 1.17) LY's, 0.492 (0.29, 0.69) QALY's	£20,000/QALY	£3,357 (£1,816, £5,194)	FF/UMEC/VI is cost-effective
Driessen <i>et al.</i> UK, 2018 (FF/UMEC/VI vs. FF/VI)	£783 (£465, £1,050) (2015)	0.232 (0.086, 0.361) LY's, 0.194 (0.123, 0.260) QALY's	£20,000/QALY	£4,050 (£2,720, £5,440)	FF/UMEC/VI is cost-effective
Driessen <i>et al.</i> UK, 2018 (FP/UMEC/SAL vs. FP/SAL)	£1,590 (£1,300, £1,890) (2015)	0.263 (0.099, 0.412) LY's, 0.220 (0.145, 0.297) QALY's	£20,000/QALY	£7210 (£5950, £9,570)	UMEC/FP/SAL is cost-effective
Driessen <i>et al.</i> UK, 2018 (UMEC/ICS/LABA vs. ICS/LABA)	£1,210 (£954, £1,470) (2015)	0.246 (0.095, 0.391) LY's, 0.210 (0.140, 0.282) QALY's	£20,000/QALY	£5,780 (£4,730, £7,380)	UMEC/ICS/LABA is cost effective

UMEC = Umeclidinium; FF = Fluticasone furoate; VI = vilanterol; FP = fluticasone propionate; BUD = Budesonide; SAL = Salmeterol; ICS = Inhaled corticosteroids; LABA = Long acting beta2 agonists; SAL = Salmeterol; ICER = Incremental cost-effectiveness ratio; UK = United Kingdom; QALY = Quality adjusted life year; LY = Life year; CI = Confidence interval.

Table 4. Costs and effectiveness of triple therapy.

Authors/therapy/year	Costs (95% CI)	Costs in USD	QALY gained	LY's gained	Exacerbations PPPY
Ismaila <i>et al.</i> Canada, 2019 (FF/UMEC/VI vs. FF/VI)	C\$67,137	53,394.39	5.0431	9.0524	1.5611
Ismaila <i>et al.</i> Canada, 2019 (FF/UMEC/VI vs. UMEC/VI)	C\$66,411	52817	5.0352	9.0258	1.4957
Schroeder <i>et al.</i> Spain, 2020 (FF/UMEC/VI vs. BUD/FOR)	€6660	7,870.47	2.130	2.841	0.856
Schroeder <i>et al.</i> UK, 2019 (FF/UMEC/VI vs. BUD/FOR)	£20,842	28,530.51	5.150	10.107	0.830
Driessen <i>et al.</i> UK, 2018 (FF/UMEC/VI vs. FF/VI)	£13,300	18,206.30	5.217	8.962	0.663
Driessen <i>et al.</i> UK, 2018 (FP/UMEC/SAL vs. FP/SAL)	£15,300	20,944.09	5.043	8.826	0.730
Driessen <i>et al.</i> UK, 2018 (UMEC/ICS/LABA vs. ICS/LABA)	£14,400	19,712.09	5.148	8.907	0.695

UMEC = Umeclidinium, FF = Fluticasone furoate, VI = vilanterol, FP = fluticasone propionate, BUD = Budesonide, SAL = Salmeterol, ICS = Inhaled corticosteroids, LABA = Long acting beta2 agonists, SAL = Salmeterol, UK = United Kingdom, QALY = Quality adjusted life year, LY = Life year, CI = Confidence interval, USD = United States Dollar, PPPY = per patient per year, C\$ = Canadian dollar, £ = British Pound, € = Spanish Euro.

Table 5. Costs and effectiveness of dual therapy [ICS/LABA OR LABA/LAMA].

Authors/therapy/year	Costs (95% CI)	Costs in USD	QALY gained	LY's gained	Exacerbations PPPY
Ismaila <i>et al.</i> , Canada, 2019 (FF/UMEC/VI vs. FF/VI)	C\$64,533	51,326.64	4.9060	8.9136	1.6661
Ismaila <i>et al.</i> , Canada, 2019 (FF/UMEC/VI vs. UMEC/VI)	C\$64,644	51,414.93	4.9070	8.9081	1.6671
Schroeder <i>et al.</i> , Spain, 2020 (FF/UMEC/VI vs. BUD/FOR)	€6591	7,790.50	2.023	2.823	1.106
Schroeder <i>et al.</i> , UK, 2019 (FF/UMEC/VI vs. BUD/FOR)	£19,190	26,274.66	4.657	9.343	1.119
Driessen <i>et al.</i> UK, 2018 (FF/UMEC/VI vs. FF/VI)	£12,500	17,114.81	5.023	8.730	0.690
Driessen <i>et al.</i> UK, 2018 (FP/UMEC/SAL vs. FP/SAL)	£13,700	18,757.83	4.823	8.563	0.765
Driessen <i>et al.</i> UK, 2018 (UMEC/ICS/LABA vs. ICS/LABA)	£13,100	17,936.32	4.938	8.661	0.726

UMEC = Umeclidinium; FF = Fluticasone furoate; VI = vilanterol; FP = fluticasone propionate; BUD = Budesonide; SAL = Salmeterol; ICS = Inhaled corticosteroids; LABA = Long acting beta2 agonists; SAL = Salmeterol; UK = United Kingdom; QALY = Quality adjusted life year; LY = Life year; CI = Confidence interval; USD = United States Dollar; PPPY = per patient per year; C\$ = Canadian dollar; £ = British Pound; € = Spanish Euro.

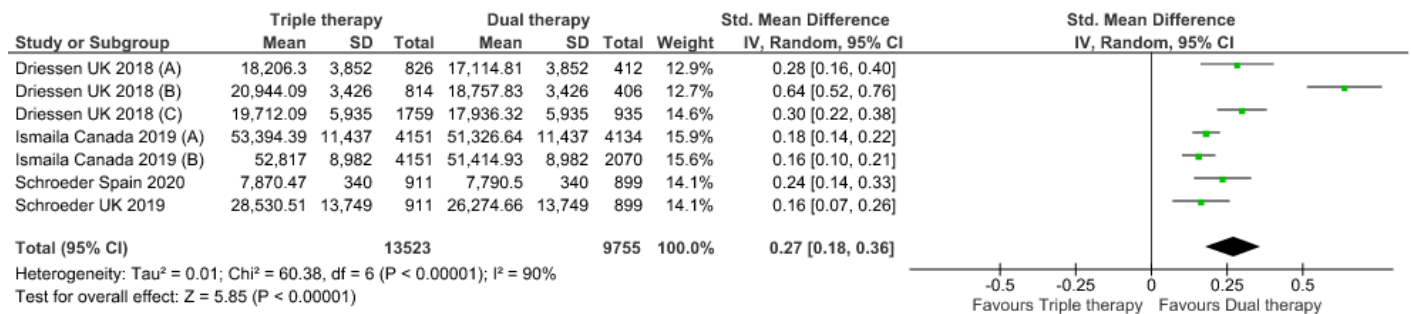


Figure 2. Comparison of cost between triple therapy and dual therapy in COPD patients.

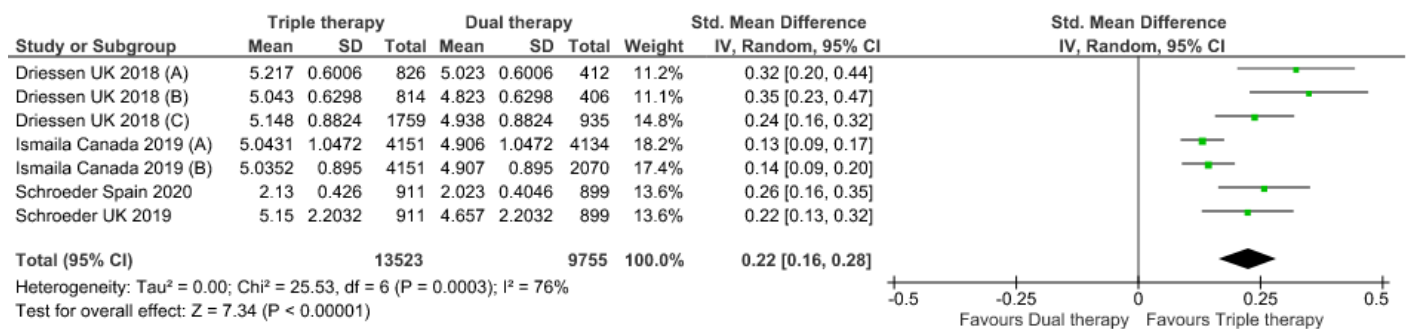


Figure 3. Comparison of QALY between triple therapy and dual therapy in COPD patients.

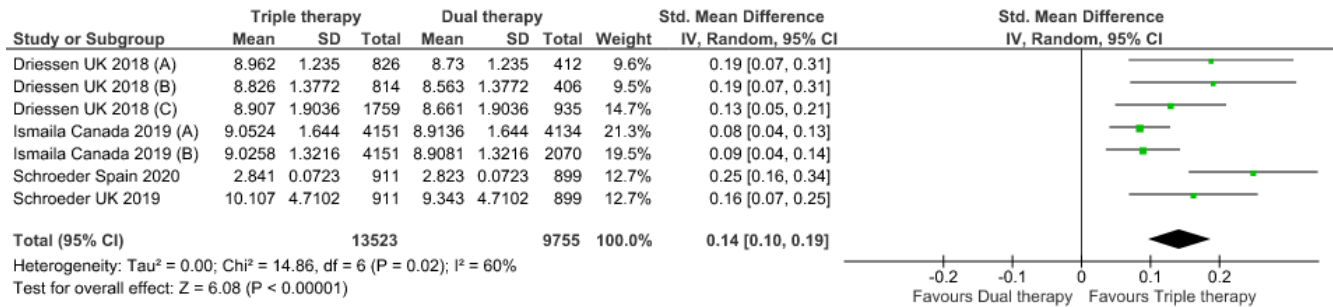


Figure 4. Comparison of LY between triple therapy and dual therapy in COPD patients.

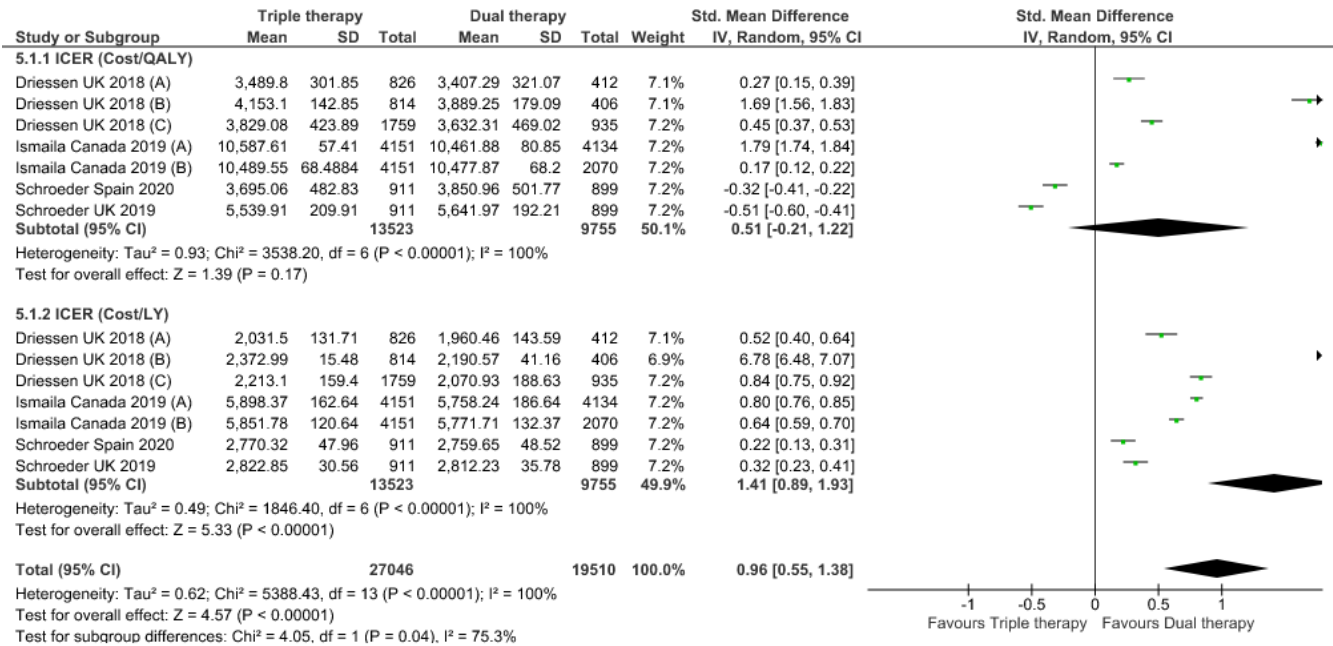


Figure 5. Incremental cost-effectiveness ratio of triple versus dual therapy in COPD patients.

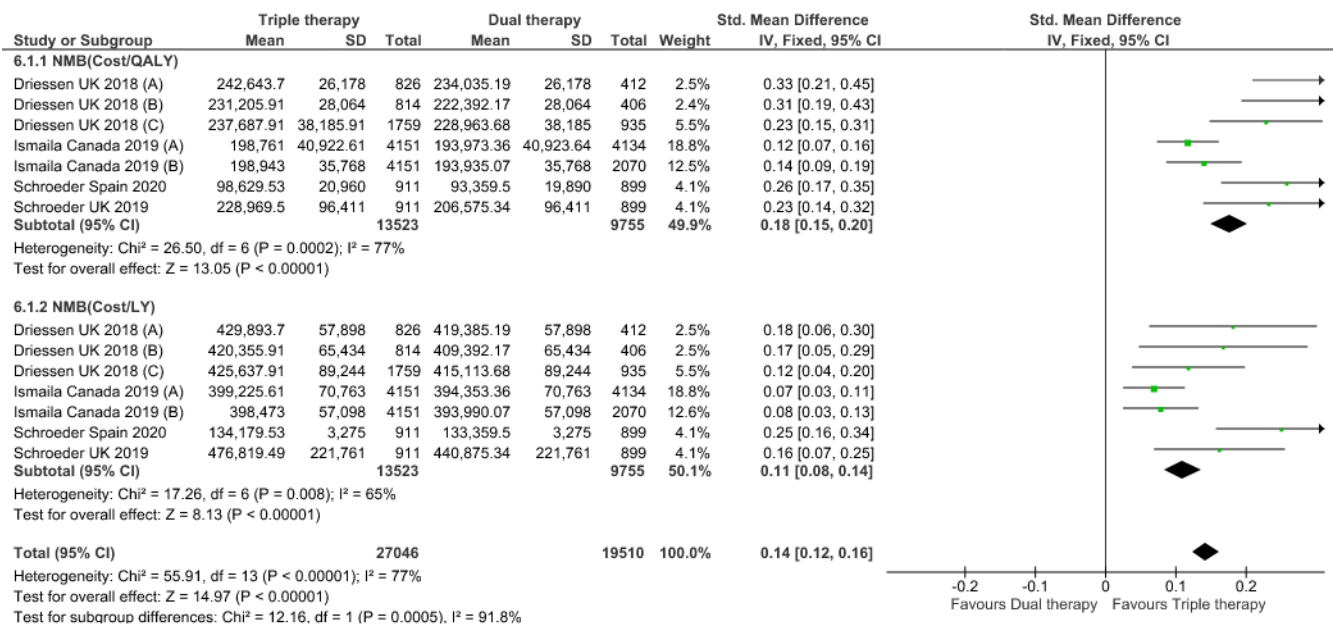


Figure 6. INMB of triple versus dual therapy in COPD patients.

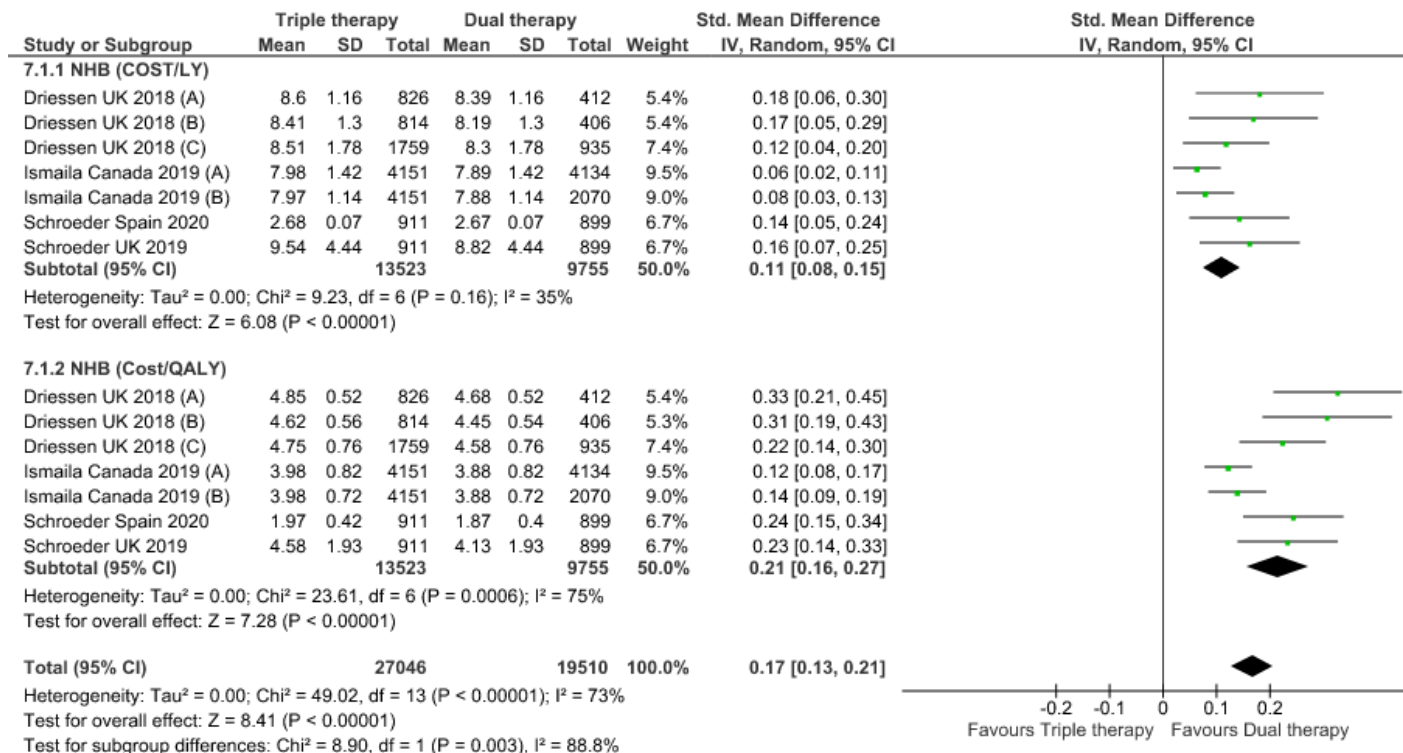


Figure 7. Incremental Net Health Benefit (INHB) of triple versus dual therapy in COPD patients.

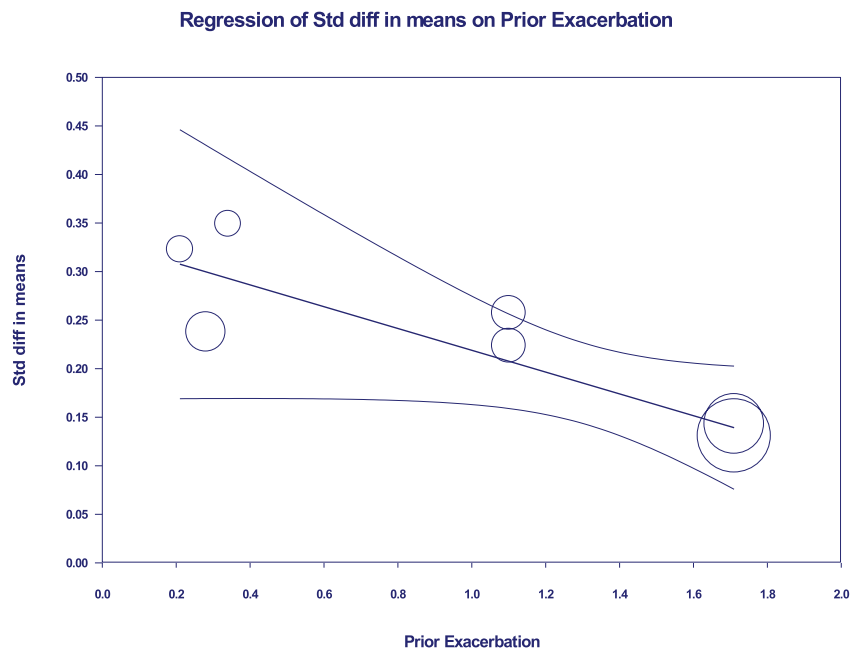


Figure 8. Meta-regression of QALY SMD based on previous exacerbations.

by patient characteristics and disease conditions between countries (McGarvey *et al.*, 2015). All the included studies were manufacturer funded and applied economic modeling approach to existing clinical trial data to generate results which may be a source of uncertainty in the sensitivity analysis. The cost of treating exacerbations has wide variations in different countries

depending upon the gross domestic product and per capita income of the country. Nevertheless, as the ICER of the present study falls under the Willingness to pay of US\$50,000/QALY, which is generally described as cost-effectiveness threshold in the US (Dubois, 2016), results of this study justify the excess costs of triple therapy as they are balanced by the added utility benefits

Table 6. Meta-regression of variables affecting QALY.

Covariate	Coefficient	Std error	95% CI lower	95% CI higher	Z-value	2 sided p-value
Intercept	-0.0866	1.9107	-3.8315	3.6583	-0.05	0.9639
Exacerbation in previous year, (mean)	-0.1121	0.0403	-0.1911	-0.0332	-2.78	0.0054
Baseline SGRQ, (Mean)	0.0001	0.0002	-0.0002	0.0005	0.78	0.438
6MWT, (Mean)	0.0011	0.0054	-0.0094	0.0117	0.21	0.8352

SGRQ = St. George respiratory questionnaire; 6MWT = 6 minute walk test; CI = Confidence interval.

Table 7. Summary of findings table.

Outcomes	No of trials	Mean difference (95% CI)	Standardized Mean difference (95% CI)	P	p-value
Triple therapy versus dual therapy					
Incremental costs	4	1,522.86 [614.47, 2,431.24]	0.27 [0.18, 0.36]	90%	<i>p</i> < 0.01
Incremental QALY's	4	0.18 [0.13, 0.22]	0.22 [0.16, 0.28]	76%	<i>p</i> < 0.01
Incremental LY's	4	0.18 [0.08, 0.27]	0.14 [0.10, 0.19]	60%	<i>p</i> < 0.01
Incremental cost-effectiveness ratio	4	76.50 [36.01, 117.00]	0.96 [0.55, 1.38]	75%	<i>p</i> < 0.01
INMB	4	1,451.30 [1,168.01, 1,734.58]	0.14 [0.12, 0.16]	77%	<i>p</i> < 0.01
Incremental net health benefit	4	0.15 [0.10, 0.20]	0.21 [0.16, 0.27]	73%	<i>p</i> < 0.01

QALY = Quality-adjusted life years, LY = Life years, CI = Confidence interval.

with triple therapy in moderate to severe symptomatic COPD patients.

As all the included studies were model analyses of clinical trial data, they did not include real-world effectiveness data. Treatment effect, discontinuation rates, and medication adherence were assumed to remain consistent over the lifetime horizon period. Sensitivity analysis and publication bias were not assessed due to the low number of available studies for meta-analysis. The majority of the values of baseline variables in the included studies were not available directly from clinical trial data and were derived from the risk equations of the Galaxy COPD disease progression model which may make the results of this meta-analysis uncertain. Taking into account the drawbacks of modeling approaches, future research on cost-effectiveness should put more emphasis on actual data from practical life effectiveness studies.

CONCLUSION

Triple therapy (ICS/LABA/LAMA) is cost-effective than dual therapy (LABA/LAMA and ICS/LABA) from the US National healthcare system perspective. This is confirmed by the results of this meta-analysis as NMB, NHB, QALY, and LY gained all favor triple therapy and ICER is less than the willingness to pay threshold of US\$50,000/QALY.

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ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

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