Single-inhaler Triple vs Single-inhaler Dual Therapy in Patients with Chronic Obstructive Pulmonary Disease: A Meta-analysis of Randomized Control Trials

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Abstract

BACKGROUND: A meta-analysis was performed to compare the efficacy and safety of single-inhaler triple therapy combining long-acting beta2-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroids (ICS) versus single-inhaler dual therapy (ICS/LABA and LABA/LAMA) in patients with chronic obstructive pulmonary disease (COPD).

METHODS: We used the following search terms in PubMed, MEDLINE (OvidSP), EMBASE and Cochrane Library databases to investigate the effect of single-inhaler triple therapy in COPD. The primary end points were the effect of single-inhaler triple therapy on all-cause mortality, risk of acute exacerbation of COPD (AECOPD), and some safety endpoints, compared with single-inhaler dual therapy. Cochrane Collaboration's tool was used to assess quality of each randomized trial and risk of bias.

RESULTS: A total of 25,171 patients suffering from COPD were recruited for the 6 studies. This meta-analysis indicated that single-inhaler triple therapy resulted in a significantly lower rate of all-cause mortality than single-inhaler dual therapy (risk ratio, 0.83; 95% CI 0.71-0.98). Single-inhaler triple therapy reduced the risk of exacerbation (rate ratio, 0.78; 95% CI 0.73-0.83), prolonged time to first exacerbation (hazard ratio, 0.86; 95% CI 0.84-0.89), improved trough FEV1 (mean difference, 81.35 ml; 95% CI 45.6–117.06) and St George Respiratory Questionnaire (SGRQ) Score (mean difference, -1.48; 95% CI -1.75–-1.22) vs. single-inhaler dual therapy. Risk of pneumonia was however significantly higher with ICS/LAMA/LABA than with LABA/LAMA (risk ratio, 1.25; 95% CI 1.04-1.50).

CONCLUSIONS: This meta-analysis suggests that single-inhaler triple therapy is effective in reducing the risk of moderate or severe exacerbations and death of any causes in COPD patients, compared with single-inhaler dual therapy. However, risk of pneumonia is higher with ICS/LAMA/LABA combination than with dual therapy of LABA/LAMA.

TRIAL REGISTRY: ClinicalTrials.gov; No.: CRD42020186726; URL: www.clinicaltrials.gov.

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide public health challenge with a high prevalence, morbidity, and mortality [1] [2]. Regular administration of inhaled drugs including long-acting beta2-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS) is widely acknowledged as a major component of treatment of COPD [3].

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that combining LABA, LAMA and ICS (triple therapy) be considered for the most severe COPD patients. [3] Triple therapy may be delivered via multiple separate inhalers (in open combination) [4] [5] [6] or within a single inhaler (in fixed-dose combination).[7] [8] [9] [10] In the real-world, triple therapy is still frequently administered via multiple devices,[11] which may lead to an incorrect inhalation technique in a significant proportion of patients. [12] Single-inhaler therapy may be of benefit in patients with COPD, by decreasing inhaler errors, improving adherence rates, and decreasing healthcare costs.[13] [14] [15] Single-inhaler triple therapy is expected to be soon widely available. We therefore performed this systematic review to determine the effect of single-inhaler triple therapy on the risk of exacerbation, mortality, and other relevant outcomes in patients with COPD.

Methods

Search strategy

This meta-analysis followed the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. [16] This study was prospectively registered in Prospero (CRD42020186726).

We used the following search terms in PubMed, MEDLINE (OvidSP), EMBASE and Cochrane Library databases to identify studies published up to August 1, 2020: “chronic obstructive pulmonary disease”, “triple”, “long acting antimuscarinics”, “long-acting beta-2 agonists” or “inhaled corticosteroids”. The “Patients, Intervention, Control, and Outcome” (PICO) framework was utilized to improve the relevance of search results, as previously described.[17] Patients included were “Stable COPD”; the intervention was “single-inhaler triple therapy (LABA/LAMA/ICS)”, control arm was “single-inhaler dual therapy (ICS/LABA or LABA/LAMA)”, and outcomes were “death, risk of moderate or severe exacerbations, time to exacerbation, lung function, health related quality of life and safety profile”.

Study selection and data extraction

Data were independently extracted by two reviewers, and any difference in opinion about eligibility was resolved through consensus. We collected information from each randomized trial about study features (title, year, author, study design and duration of follow-up, etc.), participants (mean age, sex, current smoker, etc.), interventions (control therapy and inhaler type, intervention therapy and inhaler type), and outcomes (death, moderate or severe exacerbations, the first time to exacerbation, mean change in FEV1, SGRQ (St George Respiratory Questionnaire) score, adverse events, serious adverse events, cardiovascular events and pneumonia events). When data could not be extracted from the published reports, we extrapolated from the supplementary material.

Quality score and risk of bias assessment

Cochrane Collaboration's tool was used to assess quality of each randomized trial and risk of bias. We analyzed included trials for allocation concealment, random sequence generation, blinding of outcome assessment, incomplete outcome data, selective reporting, blinding of participants and personnel, and other biases.

Data synthesis and statistical analysis

We used Revman 5.3 software for all statistical analyses. The degree of heterogeneity among RCTs was evaluated with the Q test and I^2 statistic. When I^2 values were ≥ 50%, we considered this as representing significant heterogeneity, and applied a random effects model. We combined continuous data using Inverse-variance test for hazard ratio (HR), rate ratio (RR), and mean difference (MD) with 95% confidence intervals (95% CIs) and combined dichotomous data using Mantel-Haenszel test for risk ratio (RR) with 95% confidence interval (95% CIs).

Results

We obtained 913 articles from our initial search, and 36 additional articles were identified through manual searches. At the end of the selection process, 6 RCTs[7] [8] [9] [10] [18] [19]were included in this meta-analysis. The flow diagram of the study selection process is shown in Fig. 1. A total of 25,171 COPD patients had been recruited for these 6 studies: 11,420 patients were treated with single-inhaler triple therapy, and 13,751 patients were treated with single-inhaler dual therapy (5,588 patients received LABA/LAMA and 8,163 patients received ICS/LABA). The summary of relevant studies and patient characteristics are provided in Table 1 and Table 2. Risk of bias for studies included is detailed in Fig. 2.

Table 1
Details of included RCTs

Number	Study	Study design	Duration of follow-up	Inclusion criteria	Exclusion criteria	Drugs, Doses(μg), Regimen, Device	No of patients
1	TRILOGY Singh,2016	A randomized, parallel group, double-blind, active-controlled study	52weeks	FEV1 < 50%; moderate or severe COPD exacerbation in the previous 12 months ≥ 1; CAT score ≥ 10, BDI score ≤ 10.	Asthma, history of allergic rhinitis; clinically significant cardiovascular conditions.	BDP/FOR/GLY (100/6/12.5) bid MDI	687
						BDP/FOR (100/6) bid MDI	680
2	FULFIL Lipson,2017	A phase 3, randomized, double-blind, double-dummy, parallel-group, multicenter study	24weeks	FEV1 < 50% and CAT score ≥ 10 or 50% ≤FEV1 < 80% and CAT score ≥ 10; moderate COPD exacerbation in the previous 12 months ≥ 2 or severe COPD exacerbation in the previous 12 months ≥ 1.	Asthma, unresolved pneumonia, severe COPD exacerbation.	FF/UMEC/VI (100/62.5/25) od DPI	911
						BUD/FOR (400/12) bid DPI	899
3	IMPACT Lipson,2018	A phase 3, randomized, double-blind, parallel-group, multicenter trial	52weeks	FEV1 < 50% and moderate or severe COPD exacerbation in the previous 12 months ≥ 1 or 50% ≤FEV1 < 80% and moderate COPD exacerbation in the previous 12 months ≥ 2 or severe COPD exacerbation in the previous 12 months ≥ 1.	NA	FF/UMEC/VI (100/62.5/25) od DPI	4151
						FF/VI (100/25) od DPI	4134
						UMEC/VI (62.5/25) od DPI	2070
4	KRONOS Ferguson,2018	A randomized, double-blind, parallel-group, phase 3 randomized controlled trial	24weeks	25% ≤FEV1 < 80%;CAT score ≥ 10.	Asthma, diagnosis of any respiratory disease.	BUD/GLY/FOR (320/18/9.6) bid MDI	639
						GLY/FOR (18/9.6) bid MDI	625
						BUD/FOR (320/9.6) bid MDI	314
5	TRIBUTE Papi,2018	A randomized, parallel-group, double-blind, double-dummy, active-controlled phase 3b study	52weeks	FEV1 < 50%; a moderate or severe COPD exacerbation in the previous 12 months ≥ 1; CAT score ≥ 10.	Asthma; clinically significant cardiovascular disorders.	BDP/FOR/GLY (100/6/10) bid MDI	764
						IND/GLY (85/43) od DPI	768
6	ETHOS Rabe,2020	A phase 3, randomized, double-blind, parallel-group, multicenter trial	52weeks	40 years ≤ age ≤ 80 years, CAT ≥ 10,25% ≤FEV1 ≤ 65%, smoking history ≥ 10 pack-years, FEV1 < 50% and moderate or severe COPD exacerbation in the previous 12 months ≥ 1or 50% ≤FEV1 and moderate COPD exacerbation in the previous 12 months ≥ 2 or severe COPD exacerbation in the previous 12 months ≥ 1.	Current diagnosis of asthma.	BUD/GLY/FOR (320/18/9.6) bid MDI	2144
						BUD/GLY/FOR (160/18/9.6) bid MDI	2124
						BUD/FOR (320/9.6) bid MDI	2136
						GLY/FOR (18/9.6) bid MDI	2125

Table 2
Patient baseline characteristics

Number	Study	Drugs, Doses(μg), Regimen, Device	No of patients	Age means (SD)	Male (%)	Current smoker (%)	Postbronchodilator FEV1, % Predicted (SD)	Moderate/severe COPD exacerbation in previous 12 months, n (%) 0	Moderate/severe COPD exacerbation in previous 12 months, n (%) 1	M C e p m 2
1	TRILOGY Singh,2016	BDP/FOR/GLY (100/6/12.5) bid MDI	687	63.3(7.9)	74	47	36.9(8.4)	NA	NA	N
		BDP/FOR (100/6) bid MDI	680	63.8(8.2)	77	47	36.2(8.6)	NA	NA	N
2	FULFIL Lipson,2017	FF/UMEC/VI (100/62.5/25) od DPI	911	64.2(8.56)	74	44	45.5(12.97)	34	28	3
		BUD/FOR (400/12) bid DPI	899	63.7(8.71)	74	44	45.1(13.64)	35	28	3
3	IMPACT Lipson,2018	FF/UMEC/VI (100/62.5/25) od DPI	4151	65.3(8.2)	67	35	45.7(15.0)	< 1	45	5
		FF/VI (100/25) od DPI	4134	65.3(8.3)	66	34	45.5(14.8)	< 1	46	5
		UMEC/VI (62.5/25) od DPI	2070	65.2(8.3)	66	35	45.4(14.7)	< 1	45	5
4	KRONOS Ferguson,2018	BUD/GLY/FOR (320/18/9.6) bid MDI	639	64.9(7.8)	72	40.1	50.2(14.3)	73.4	19.6	7
		GLY/FOR (18/9.6) bid MDI	625	65.1(7.7)	68.8	41.1	50.2(13.8)	75.7	17.3	7
		BUD/FOR (320/9.6) bid MDI	314	65.2(7.2)	71.3	36.6	50(14)	74.8	19.4	5
5	TRIBUTE Papi,2018	BDP/FOR/GLY (100/6/10) bid MDI	764	64.4(7.7)	72	46	36.4(8.0)	NA	80	2
		IND/GLY (85/43) od DPI	768	64.5(7.7)	72	43	36.4(8.1)	NA	82	1
6	ETHOS Rabe,2020	BUD/GLY/FOR (320/18/9.6) bid MDI	2144	64.6(7.6)	59	42.6	43.6(10.3)	0.1	44	5
		BUD/GLY/FOR (160/18/9.6) bid MDI	2124	64.6(7.6)	61.2	40.8	43.1(10.4)	0.1	43.9	5
		BUD/FOR (320/9.6) bid MDI	2136	64.6(7.6)	60	40.5	43.4(10.4)	0.1	42.8	5
		GLY/FOR (18/9.6) bid MDI	2125	64.8(7.6)	58.7	40.4	43.5(10.2)	0.1	42.8	5

Number	Study	Drugs, Doses(μg), Regimen, Device	No of patients	Age means (SD)	Male (%)	Current smoker (%)	Postbronchodilator FEV1, % Predicted (SD)	Moderate/severe COPD exacerbation in previous 12 months, n (%) 0	Moderate/severe COPD exacerbation in previous 12 months, n (%) 1	M C e p n 2
BDP/FOR/GLY: beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide;										
BUD/GLY/FOR: budesonide/glycopyrronium bromide/formoterol fumarate;										
FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol;										
BDP/FOR: beclomethasone dipropionate/formoterol fumarate;										
BUD/FOR: budesonide/formoterol fumarate;										
UMEC/VI: umeclidinium bromide/vilanterol;										
GLY/FOR: glycopyrronium bromide/formoterol fumarate;										
IND/GLY: indacaterol/glycopyrronium bromide.										
OD: once daily;										
BID: twice daily;										
MDI: metered-dose inhaler formulation;										
DPI: dry powder inhaler formulation;										
FEV1: forced expiratory volume in 1 second;										
BDI: Baseline Dyspnea Index;										
CAT: COPD assessment test.										

Efficacy endpoints

This meta-analysis suggested that single-inhaler triple therapy was associated with a lower all-cause mortality than single-inhaler dual therapy (risk ratio, 0.83; 95% CI 0.71-0.98; P=0.03; I^2 = 0%). Compared with patients receiving LABA/LAMA, those on ICS/LAMA/LABA had a significantly lower mortality rate (RR, 0.70; 95% CI 0.56-0.88; P□0.01; I^2 = 0%); no significant difference was found however between ICS/LAMA/LABA and ICS/ LABA (RR, 1.00; 95% CI 0.79-1.26; P□0.05; I^2 = 0%) (Figure 3).

Use of single-inhaler triple therapy was associated with a significant decrease in risk of moderate or severe COPD exacerbations, compared to single-inhaler dual therapy (rate radio, 0.78; 95% CI 0.73-0.83; P < 0.01; I^2 = 70%). This was also the case when comparing specifically ICS/LAMA/LABA vs. ICS/LABA (RR, 0.85; 95% CI 0.81-0.88; P < 0.01; I^2 = 1%) and comparing ICS/LAMA/LABA vs. LABA/LAMA (RR, 0.74; 95% CI 0.67-0.81; P < 0.01; I^2 = 71%) (Figure 4).

Time to first exacerbation was significantly longer in patients under single-inhaler triple therapy, compared with those on single-inhaler dual therapy (hazard radio, 0.86; 95% CI 0.84-0.89; P < 0.01; I^2 = 0%) (Figure 4).

FEV1 (trough FEV1 compared to baseline value, ml) increased significantly more under single-inhaler triple therapy obviously (P<0.01) than in COPD patients treated by ICS/LABA (mean difference, 103.4 ML; 95% CI 64.65-142.15; P < 0.01; I^2 = 94%) or LABA/LAMA (MD, 38.40 ML; 95% CI 7.05-69.75; P < 0.05; I^2 = 86%) (Figure 4).

Improvement in health-related quality of life (SGRQ total score) for single-inhaler triple therapy was statistically higher than with single-inhaler dual therapy. (MD, -1.48; 95% CI -1.75--1.22; P < 0.01; I^2 = 0%) (Figure 4).

Safety endpoints

Single-inhaler triple therapy was not associated with an increase in risk of adverse events (risk radio, 1.01; 95% CI 1.00-1.03; P□0.05; I^2 = 4%) (Figure 5) or serious adverse events (RR, 0.97; 95% CI 0.93-1.02; P□0.05; I^2 = 0%) when compared with single-inhaler dual therapy (Figure 5).

This was also the case for cardiovascular events (RR, 0.98; 95% CI 0.91-1.07; P□0.05; I^2 = 0%) (Figure 5). Risk of pneumonia did not differ between ICS/LAMA/LABA and ICS/LABA (RR, 1.04; 95% CI 0.87-1.23; P□0.05; I^2 = 36%), but use of ICS/LAMA/LABA was associated with a significant increase in the risk of pneumonia compared with LABA/LAMA (RR, 1.55; 95% CI 1.35-1.80; P□0.01; I^2 = 0%) (Figure 5).

Discussion

This systematic review aimed to investigate the long-term effects (≥ 24 weeks) of single-inhaler triple therapy, compared with single-inhaler dual therapy for the treatment of COPD. Our results suggest that the ICS/LAMA/LABA combination was more effective in reducing all-cause mortality, risk of moderate or

severe COPD exacerbations and prolonging time of first exacerbation than ICS/LABA or LABA/LAMA combinations. Furthermore, single-inhaler triple therapy had a significantly higher impact on both lung function (FEV1 trough) and health-related quality of life (HRQL: SGRQ score), compared to single-inhaler dual therapy. However, risk of pneumonia was significantly higher with ICS/LAMA/LABA than with LABA/LAMA.

Two recent meta-analyses showed that single-inhaler triple therapy was more effective in reducing acute exacerbations, and improving lung function and HRQL, compared with single-inhaler dual therapy.[20] [21] However, to the best of our knowledge, this meta-analysis is the first to show a reduction in all-cause mortality in stable COPD with fixed-dose triple therapy vs ICS/LABA or LABA/LAMA combinations.

The goal of COPD management is to decrease the risk of exacerbations and mortality.[1] Exacerbations are major determinants of patient's health status and strong predictors of mortality. [22] The present study concluded that, compared with single-inhaler dual therapy, single-inhaler triple therapy reduced the frequency of moderate and severe exacerbations by 22%. In IMPACT [9] (FF/UMEC/VI vs. UMEC/VI) and ETHOS [19] (BUD/GLY/FOR (320-µg– budesonide) vs. GLY/FOR) analyses, the risk of death from any cause was reduced by 29% and 46%, respectively. The all-cause mortality reduction by ICS/LAMA/LABA may be due to the reduction in total exacerbations. In ETHOS [19] study, compared with GLY/FOR, BUD/GLY/FOR (320-µg– budesonide) largely reduced the frequency of moderate and severe exacerbations by 24%. IMPACT [9] study illustrated 25% of decrease in the rate of COPD exacerbations when comparing FF/UMEC/VI and UMEC/VI and 34% of reduction in COPD hospitalizations for this comparison. Perhaps, the decline in exacerbation events can improve patients' health and decrease the rate of hospitalization,[23] thus decreasing associated morbidity and mortality in COPD patients. However, some included RCTs did not display that single-inhaler triple therapy improved mortality compared with LABA/LAMA, partly due to the short follow-up period. Of these, the KRONOS[18] study was only of 24 weeks in duration, and it was limited in the reporting of such final health outcomes. It is also partly due to differences in the inclusion criteria of patients. In IMPACT [9] and ETHOS [19] studies, all-cause mortality exhibited a difference, which may be due to the high-risk nature of part of the included population experiencing cardiovascular events. In the 52 weeks TRIBUTE [8] study, the patients suffering from clinically significant cardiovascular disorders were excluded. Single-inhaler triple therapy may have direct or indirect effects on cardiovascular comorbidities in COPD patients, which possibly has been confirmed by the results before, suggesting that the risk of non-respiratory fatal events was significantly decreased with ICS/LAMA/LABA versus LABA/LAMA.[24]

Our findings suggest that single-inhaler triple therapy was statistically more effective than single-inhaler dual therapy in terms of lung function and quality of life. According to Jones 2013[25] and Bateman 2014[26], the consensus on the minimal clinically important differences (MCID) for trough FEV1 is 60mL, and, for SGRQ, 4 points of the total score. Thus, the benefit of single-inhaler triple therapy on trough FEV1 (81 ml) outweighed the MCID. This was not the case however for HRQL.

Patients under single-inhaler triple therapy showed a significant increase in risk of pneumonia vs. single-inhaler dual therapy. Results differed when comparing the two sub-groups. Risk of pneumonia was higher when taking ICS/LAMA/LABA than for the LABA/LAMA group: Differences were not significant when ICS/LAMA/LABA vs. ICS/LABA group. This confirms previous findings [20] [21]

The GOLD guidelines recommend that triple therapy be considered for the most severe COPD patients. [3] Patients using multiple devices are more likely to have an inappropriate inhalation technique. [12] Also, previous research has shown that COPD patients have a lower adherence to treatment persistence with multiple inhaler therapy than single-inhaler therapy.[27] [28] Single-inhaler therapy is simpler, and thus may lead to better compliance and improve clinical outcomes for COPD patients [29] and therefore decrease healthcare resource utilization. [11] [15] If these outcomes are achieved without increasing costs, this may reduce economic and healthcare resource burden.[14]

Our research has some limitations. Firstly, some of the included RCTs were performed over only 24 weeks, thus limiting their relevance for outcomes such as all-cause mortality. Secondly, both analyzed RCTs illustrated similar criteria for eligible patients, while with some differences, thus resulting in that patients suffer from different severity and complication. Further studies are needed to determine whether any specific subgroup of COPD patients is more likely to benefit from single-inhaler triple therapy. Finally, patients obtained dual or triple therapies at baseline; it is therefore unclear whether the abrupt discontinuation of previous medication could have contributed to our results.

In conclusion, our meta-analysis suggests a beneficial effect of single-inhaler triple therapy versus single-inhaler dual therapy in terms of mortality, frequency of moderate or severe COPD exacerbations, and lung function for symptomatic COPD patients. However, ICS/LAMA/LABA is associated with an increased risk of pneumonia when compared to a dual therapy of LABA/LAMA.

Declarations

Author contributions:

H. L. and H. X. completed the literature search, assessed the studies for inclusion eligibility, were directly involved in the data collection for the article, and did the statistical analysis. H. L. wrote the first draft of the article, in consultation with Y. G. and J. J. for data interpretation. All authors revised the report and approved the final version before submission. Y. G. had ultimately responsible for the decision of whether to submit for publication.

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Figures

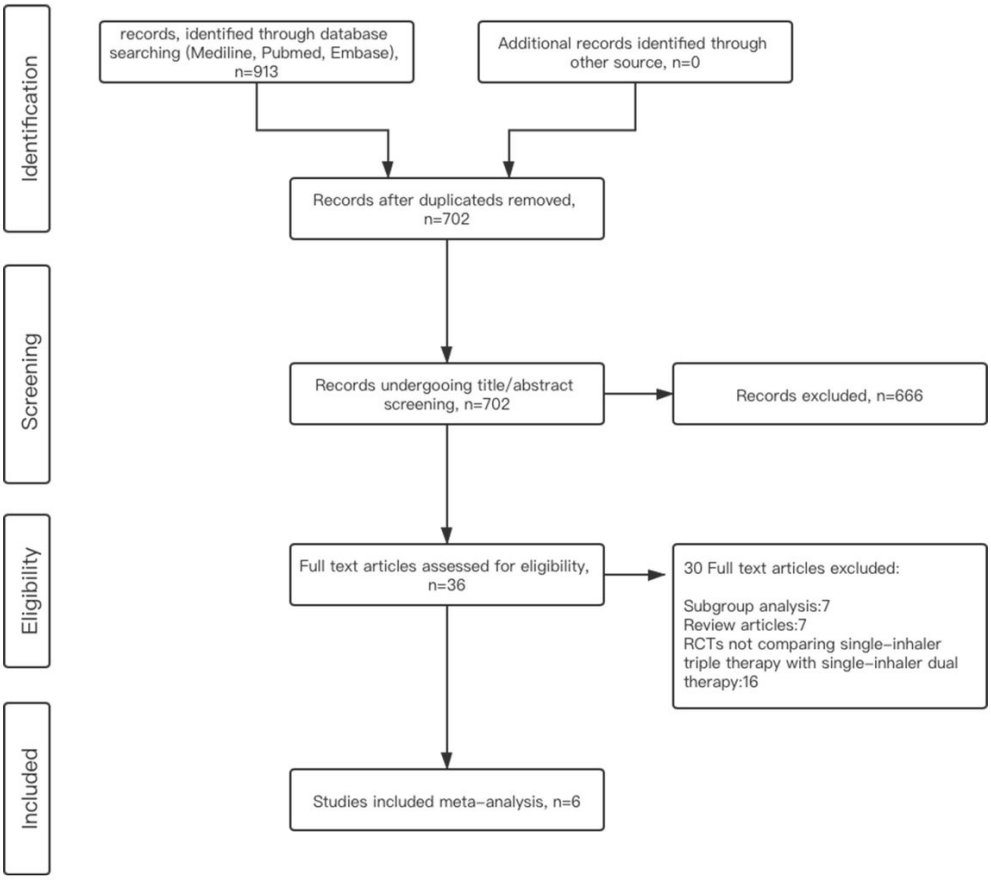

Figure 1

The flow diagram of the study selection process

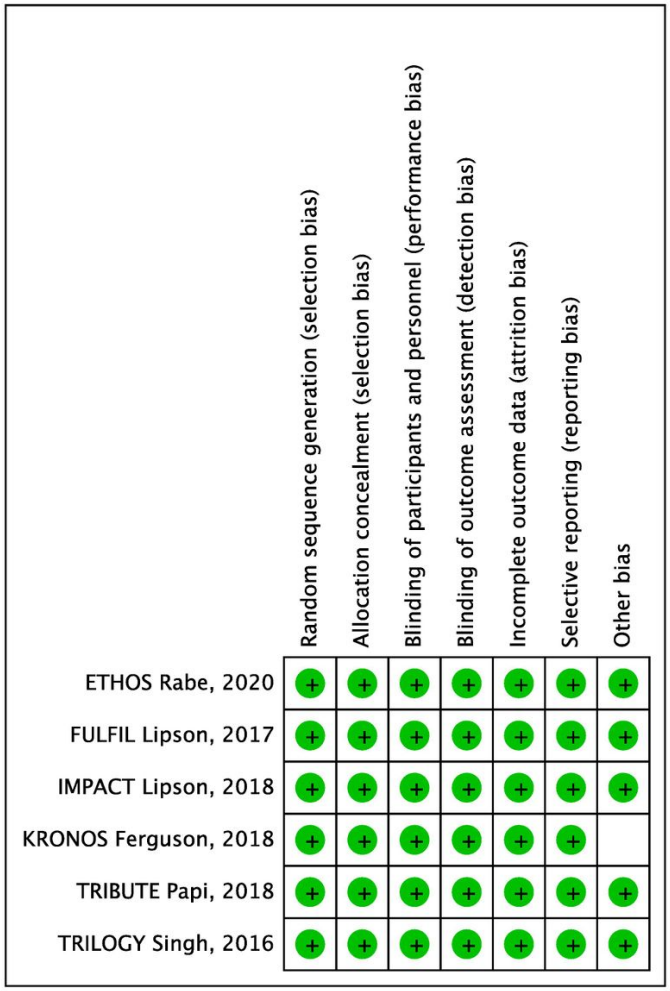

Figure 2

Risk of bias for studies

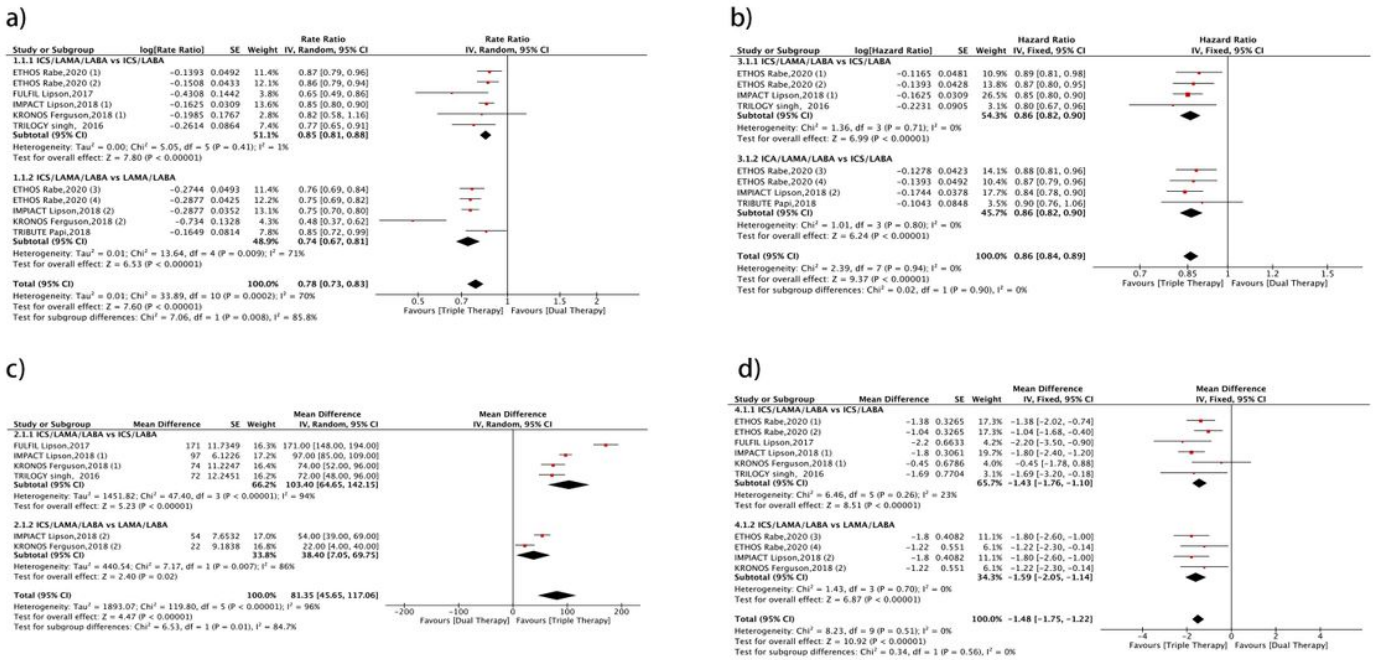

Figure 3

Efficacy endpoints

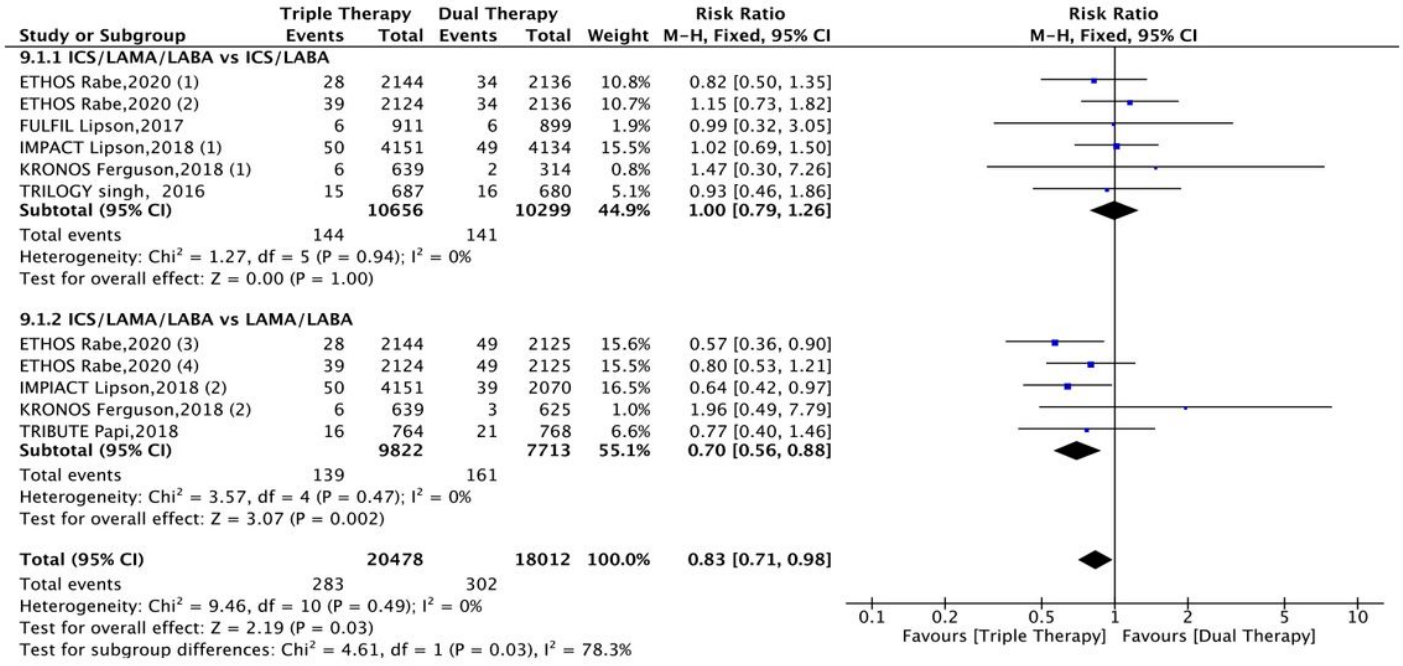

Figure 4

All cause mortality

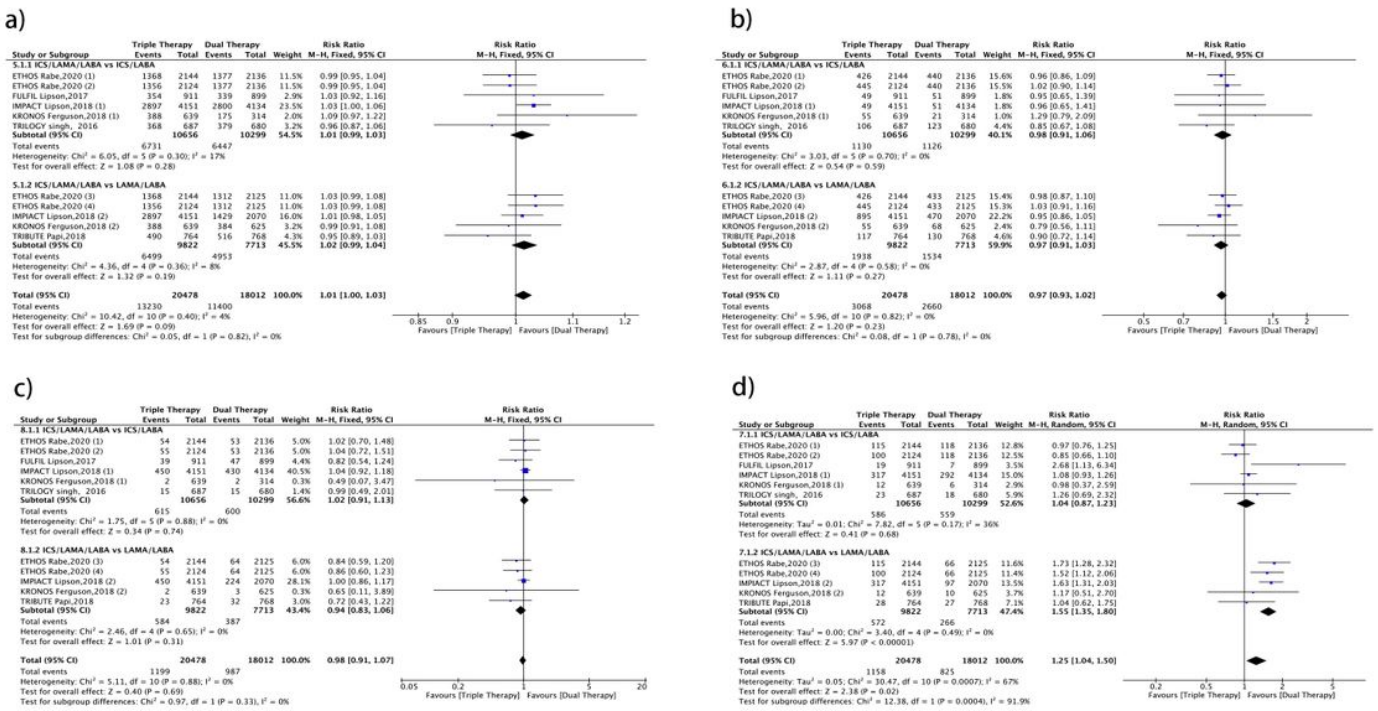

Figure 5

Safety endpoints