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ORIGINAL ARTICLE

Triple vs. dual therapy in patients with COPD: systematic review and meta-analysis

Terapia triple vs. dual en pacientes con EPOC: revisión sistemática y metanálisis

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Abstract

Introduction: *There is uncertainty about the best risk-benefit profile for treatment with triple therapy in patients with COPD.* **Objective:** *Identify the available scientific evidence on the effectiveness and safety of triple therapy compared to dual therapy in patients with COPD.* **Method:** *A systematic review of the literature was conducted according to the Cochrane methodology using the Medline, Embase and Central databases.* **Results:** *Acute exacerbations were evaluated in six studies, rate ratio of 0.74 (0.68-0.81), representing a reduction of 26% and mortality was evaluated in six studies showing a decrease of 29%, relative risk of 0. 71 (0.56-0.91) with triple therapy. Pneumonia was evaluated in seven studies, showing an increase in events with triple therapy, relative risk of 1.54 (1.30-1.81). Adverse events were evaluated in ten studies with no differences found. Discussion: Triple therapy reduced exacerbations and mortality consistent with what was described in previous reviews. Adverse events were similar between both therapies. An increase in pneumonia episodes, a worsening of dyspnea and FEV1 was found with the use of triple therapy.* **Conclusion:** *Triple therapy is an important alternative in patients with persistent exacerbations and highly symptomatic despite dual therapy. It is a safe therapy, but the occurrence of pneumonia must be monitored specifically.*

Keywords: *COPD. Triple therapy. Dual therapy. Systematic review. Meta-analysis.*

Resumen

Introducción: *Existe incertidumbre sobre el mejor perfil riesgo-beneficio para el tratamiento con triple terapia en pacientes con EPOC.* **Objetivo:** *Identificar la evidencia científica disponible sobre la efectividad y seguridad de la triple terapia en comparación con la terapia dual en pacientes con EPOC.* **Método:** *Se realizó una revisión sistemática de la literatura según la metodología Cochrane utilizando las bases Medline, Embase y Central. Resultados: Las exacerbaciones agudas se evaluaron en seis estudios, razón de tasas de 0.74 (0.68-0.81), lo que representa una reducción del 26%, y la mortalidad se evaluó en seis estudios, evidenciándose una disminución del 29%, riesgo relativo de 0.71 (0.56-0.91) con triple terapia. La neumonía se evaluó en siete estudios, mostrando un aumento de eventos con triple terapia, riesgo relativo de 1.54 (1.30-1.81). Los eventos adversos se evaluaron en diez estudios, sin encontrarse diferencias.* **Discusión:** *La triple terapia redujo las exacerbaciones y la mortalidad de forma consistente con lo descrito en revisiones previas. Los eventos adversos fueron*

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similares entre ambas terapias. Se encontró un incremento de los episodios de neumonía, un empeoramiento de la disnea y del FEV1 con el uso de la triple terapia. **Conclusión:** *La triple terapia es una alternativa importante en pacientes con exacerbaciones persistentes y muy sintomáticos a pesar de la terapia dual; es una terapia segura, pero se debe vigilar la ocurrencia de neumonía específicamente.*

Palabras clave: *EPOC. Triple terapia. Terapia dual. Revisión sistemática. Metaanálisis.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease characterized by airflow obstruction associated with chronic inflammation and airway remodeling.[1,2] It is a major cause of morbidity and mortality worldwide and has a substantial impact on patients' quality of life.[2] In 2015, an estimated 300,000,000 cases and 3,170,000 deaths occurred worldwide.[3] COPD is the third leading cause of death globally[2] and is associated with increased health care costs, constituting a major public health problem.[1,2,4-7]

Dual therapy (DT) with long-acting bronchodilators, including long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), has improved the treatment of COPD; however, a considerable proportion of patients continue to experience exacerbations and persistent symptoms despite adequate treatment.[8] These patients are characterized by severe symptoms, recurrent exacerbations, and, in some cases, elevated type 2 (T2) inflammation in up to 40%,[9] manifested by increased blood eosinophil counts.[10] In this context, triple therapy (TT), such as fluticasone/umeclidinium/vilanterol, beclomethasone/formoterol/glycopyrronium, and budesonide/glycopyrronium/formoterol, which consists of adding an inhaled corticosteroid (ICS) to DT, has emerged as a potentially more effective option for improving disease control, particularly in high-risk patients.[2,7,8]

A systematic review of randomized clinical trials published in 2020[11] compared TT with DT in patients with COPD and reported a 25% reduction in the risk of acute exacerbations, although with an increased risk of pneumonia. New evidence not included in the previous systematic review[12,13] appears to show that adding an ICS to DT improves lung function and reduces exacerbations and mortality.

To compare the potential benefits and harms of adding an ICS to DT in high-risk patients with COPD, we used the systematic review published in 2020[11] as the basis for this update and performed subgroup and sensitivity analyses to provide additional information that may modify or support the use of TT in patients with COPD.

Methods

Study design

The protocol for this systematic literature review and meta-analysis (SLR-MA) was registered in PROSPERO.[14] This report was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement[15] (supplementary data 1) and the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.[16,17]

This review followed Cochrane methodology.[18]

Literature search

An electronic literature search was conducted in MEDLINE (via PubMed), Embase (via Elsevier), and CENTRAL (via Ovid) from July 2019 through February 2022. Furthermore, a manual search was performed to identify potentially eligible studies. The search strategies were reviewed by a librarian experienced in systematic reviews and used a combination of Medical Subject Headings (MeSH) terms and keywords related to the population and interventions of interest. Some of the terms included in the search strategies were "chronic obstructive pulmonary disease" and "LABA/LAMA/ICS" (supplementary data 2 and 3).

Eligibility criteria

The included studies evaluated adults aged >18 years with symptomatic stable COPD, persistent dyspnea and/or exercise intolerance, recurrent exacerbations, and, in some cases, peripheral eosinophilia (supplementary data 3).

Inclusion criteria

Randomized controlled trials (RCTs) using any randomization design, such as parallel or crossover

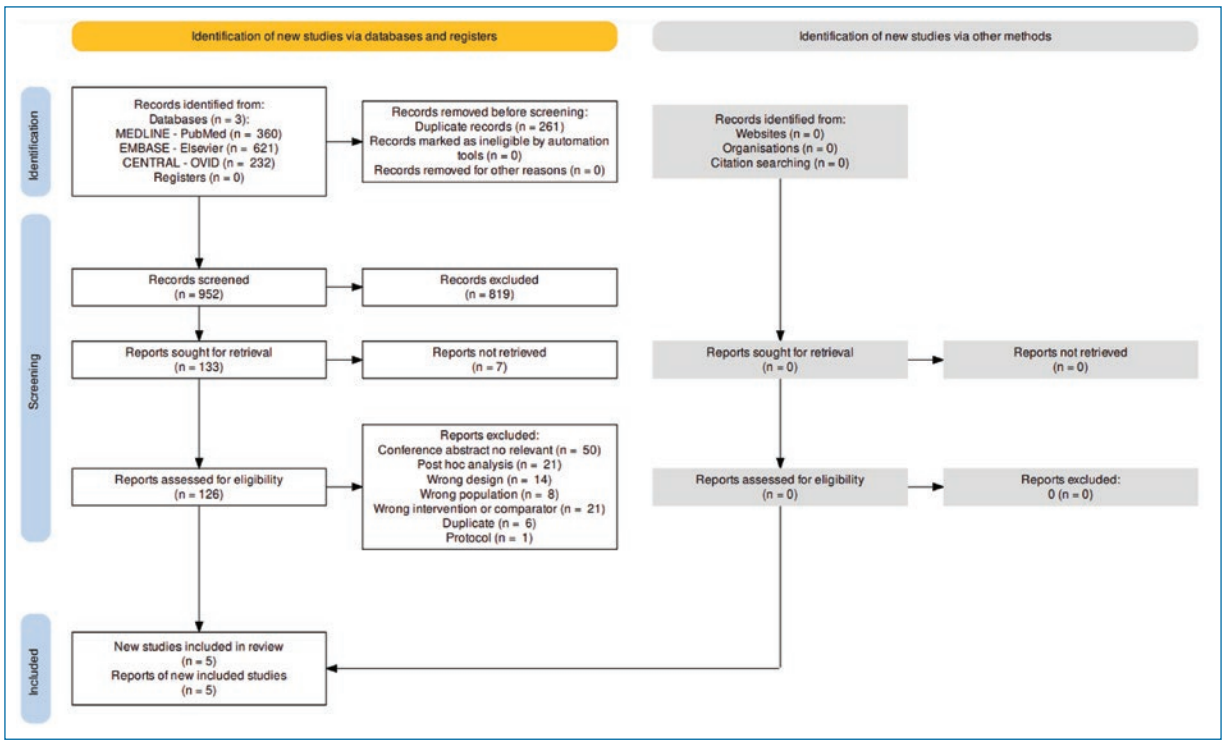


Figure 1. PRISMA flow diagram. *RCTs included from the 2020 review: 5. RCTs identified in the updated search strategy: 5. Total RCTs included: 10. RCT: randomized controlled trial.

designs, comparing TT with DT were included. The search was not restricted to hospitalized or outpatient populations. No restrictions were imposed on follow-up duration or study length (supplementary data 2 and 3).

Exclusion criteria

RCTs were excluded if they enrolled pregnant or breastfeeding patients, patients with COPD and unstable or decompensated comorbidities, patients with asthma or chronic pulmonary diseases other than COPD, such as interstitial lung disease or pulmonary fibrosis, active malignancy, or uncontrolled mental illness.

Study selection

Five reviewers independently and in duplicate assessed the studies identified through title and abstract screening and full-text review using Covidence software.[19] When a study could not be excluded based on title and abstract, or when disagreement persisted, the full text was reviewed. Studies were included when at least 2 reviewers agreed that they met the inclusion criteria. In the event of persistent disagreement, a third author reviewed the study and determined whether it should be included, or consensus was reached among the reviewers involved. Before title and abstract screening, interreviewer agreement was assessed using Rayyan software[20] by calculating Cohen κ (kappa statistic).[21,22]

Outcomes

The following outcomes were included: mortality, acute exacerbations, pneumonia, hospitalizations, dyspnea, physical activity, health-related quality of life, forced expiratory volume in 1 second (FEV1), and adverse events (Supplementary data 3).

Data extraction

Two reviewers independently used a standardized data collection form in Microsoft Excel and verified the consistency and clarity of the data. Discrepancies were resolved through discussion with a third reviewer. The following data were extracted from each included study: study design, population characteristics, intervention and comparator characteristics, outcomes, and funding information.[15]

Table 1. Characteristics of the included studies that treated patients with COPD with triple therapy vs dual therapy

Study	Population	Study design	Study period	Intervention	Duration	Participants	Controls	Primary outcome
Aaron et al.[39]	> 35 years, moderate-to-severe COPD and at least 1 exacerbation in the previous year, smoking history, FEV1/FVC ratio < 0.70, and postbronchodilator FEV1 < 65% of the predicted value	Randomized, double-blind, placebo-controlled trial (parallel group)	2003-2006	Tiotropium 18 µg once daily plus Advair (fluticasone/ salmeterol) 250/50 µg, 2 inhalations twice daily (open triple therapy)	52 weeks	145	148	No differences in exacerbations were found between the tiotropium plus salmeterol group (64.8%; 95% CI, –12.8 to 8.8) and the tiotropium plus fluticasone/ salmeterol group (60.0%; 95% CI, –8.2 to 13.8).
Cazzola et al.[40]	> 50 years, controlled COPD, current or former smokers. Baseline FEV1 < 50% of predicted and postbronchodilator FEV1 < 70%	Randomized, double-blind, double-dummy trial (parallel group)	2006	FSC 500/50 mg Diskus, 1 inhalation twice daily + tiotropium 18 mg HandiHaler, 1 inhalation daily (open triple therapy)	12 weeks	29	26	At the end of the study, trough FEV1 improved significantly from baseline by 141 mL ($p < 0.05$) in the tiotropium group, 140 mL ($p < 0.05$) in the FSC group, and 186 mL ($p < 0.05$) in the FSC + tiotropium group
Ferguson et al. (KRONOS)[41]	40-80 years, current or former smokers, symptomatic COPD despite ≥ 2 inhaled maintenance therapies for at least 6 weeks before screening	Phase 3, randomized, double-blind, multicenter trial (parallel group)	2015-2018	BGF MDI 320/18/9.6 µg (BGF MDI) (fixed triple therapy)	24 weeks	640	627	Estimated rates of moderate or severe exacerbations were 0.46 per year for BGF MDI, 0.95 per year for GFF (glycopyrrolate/FORM) MDI, 0.56 per year for BFF MDI, and 0.55 per year for BUD/ FORM DPI
Lipson et al. (IMPACT)[42]	> 40 years with symptomatic COPD, CAT ≥ 10, FEV1 < 50% of predicted and a history of at least 1 moderate or severe exacerbation in the previous year, or FEV1 50%-80% of predicted and at least 2 moderate exacerbations or 1 severe exacerbation in the previous year	Phase 3, randomized, double-blind, multicenter trial (parallel group)	2014-2017	Once-daily fluticasone furoate (inhaled corticosteroid), 100 µg; umeclidinium (LAMA), 62.5 µg; and vilanterol (LABA), 25 µg (fixed triple therapy)	52 weeks	4151	2070	The rate of moderate or severe exacerbations with triple therapy was 0.91 per year vs 1.21 per year among patients assigned to umeclidinium/vilanterol. Rate ratio with triple therapy, 0.75; 95% CI, 0.70-0.81; 25% difference; $p < 0.001$

(Continues)

Table 1. Characteristics of the included studies that treated patients with COPD with triple therapy vs dual therapy *(continuation)*

Study	Population	Study design	Study period	Intervention	Duration	Participants	Controls	Primary outcome
Papi et al. (TRIBUTE)[43]	> 40 years; current or former smokers; COPD; FEV1/FVC ratio < 0.7; FEV1 < 50% of predicted; at least 1 moderate or severe exacerbation in the previous 12 months; CAT score ≥ 10	Phase 3b, randomized, double-blind, double-dummy, active-controlled trial (parallel group)	2015-2017	Beclomethasone dipropionate/ FORM fumarate/ glycopyrronium (BDP/FF/G), 87 µg/5 µg/9 µg twice daily (fixed triple therapy)	52 weeks	764	768	Adjusted rates of moderate-to-severe exacerbations were 0.50 per patient-year (95% CI, 0.45-0.57) in patients receiving BDP/FF/G and 0.59 per patient-year (95% CI, 0.53-0.67) in those receiving IND/GLY
Siler et al.[35]	> 40 years; current or former smokers; FEV1/FVC ratio <0.7; predicted FEV1 < 70%	Randomized, double-blind, placebo-controlled trial (parallel group)	2013-2014	Umeclidinium (UMEC, 125 mg) + FF/VI (100/25 mg) (Argentina, Canada, Chile, Romania, and the United States) (open triple therapy)	12 weeks	207	206	The results of these 2 studies demonstrated that adding umeclidinium (62.5 and 125 mg) to FF/VI (100/25 mg) provided statistically significant and clinically meaningful improvements in lung function compared with placebo + FF/VI in patients with COPD
Siler et al.[35]	> 40 years; current or former smokers; FEV1/FVC ratio < 0.7; predicted FEV1 < 70%	Randomized, double-blind, placebo-controlled trial (parallel group)	2013-2014	Umeclidinium (UMEC, 125 mg) + FF/VI (100/25 mg) (Czech Republic, Germany, Republic of Korea, and the United States) (open triple therapy)	12 weeks	207	206	The results of these 2 studies demonstrated that adding umeclidinium (62.5 and 125 mg) to FF/VI (100/25 mg) provided statistically significant and clinically meaningful improvements in lung function compared with placebo + FF/VI in patients with COPD
Rabe et al. (ETHOS)[36]	40-80 years; CAT ≥ 10; symptomatic COPD despite at least 2 inhaled maintenance therapies; FEV1/FVC ratio < 0.7; postbronchodilator FEV1 25%-65% of predicted; smoking history; and a history of at least 1 moderate or severe exacerbation, at least 2 moderate exacerbations, or at least 1 severe exacerbation in the previous year	Randomized, double-blind trial (parallel group)	2015-2019	Twice-daily inhaled triple therapy consisting of an inhaled corticosteroid (BUD, 320 µg or 160 µg), a LAMA (glycopyrrolate, 18 µg), and a LABA (FORM, 9.6 µg) (open triple therapy)	52 weeks	2157	2139	Twice-daily triple therapy with BUD (160 or 320 µg), glycopyrrolate, and formoterol resulted in a lower rate of moderate or severe COPD exacerbations than glycopyrrolate/FORM or BFF

(Continues)

Table 1. Characteristics of the included studies that treated patients with COPD with triple therapy vs dual therapy *(continuation)*

Study	Population	Study design	Study period	Intervention	Duration	Participants	Controls	Primary outcome
Rabe et al. (ETHOS)[36]	40-80 years; CAT ≥ 10; symptomatic COPD despite at least 2 inhaled maintenance therapies; FEV1/FVC ratio < 0.7; postbronchodilator FEV1 25%-65% of predicted; smoking history; and a history of at least 1 moderate or severe exacerbation, at least 2 moderate exacerbations, or at least 1 severe exacerbation in the previous year	Randomized, double-blind trial (parallel group)	2015-2019	Twice-daily inhaled triple therapy consisting of an inhaled corticosteroid (BUD, 320 µg or 160 µg), a LAMA (glycopyrrolate, 18 µg), and a LABA (formoterol, 9.6 µg) (open triple therapy); quality-of-life assessment	52 weeks	2157	2139	Triple therapy with BGF (BUD [160 or 320 µg], glycopyrrolate, and FORM) improved symptoms and health-related quality of life compared with dual therapies over 24 and 52 weeks in patients with moderate-to-very-severe COPD
van den Berge et al.[38]	40-80 years; current or former smokers; moderate-to-severe COPD; FEV1/FVC ratio < 0.70; postbronchodilator FEV1 > 30% and < 80% of predicted; and blood eosinophil count > 150 cells/mm^3	Phase 3b, randomized, double-blind crossover trial	2019	BGF, 320/18/9.6 µg twice daily (fixed triple therapy)	4 weeks	22	23	As assessed using FRI, triple therapy with BGF resulted in greater increases in airway volume and greater reductions in airway resistance compared with GFF

BFF: budesonide/formoterol; BGF: budesonide/glycopyrrolate/formoterol fumarate; BUD: budesonide; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; DPI: dry powder inhaler; FEV1: forced expiratory volume in 1 second; FF/VI: fluticasone furoate/vilanterol; FORM: formoterol; FRI: functional respiratory imaging; FSC: fluticasone propionate/salmeterol; FVC: forced vital capacity; GFF: glycopyrrolate/formoterol fumarate; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; MDI: metered-dose inhaler.

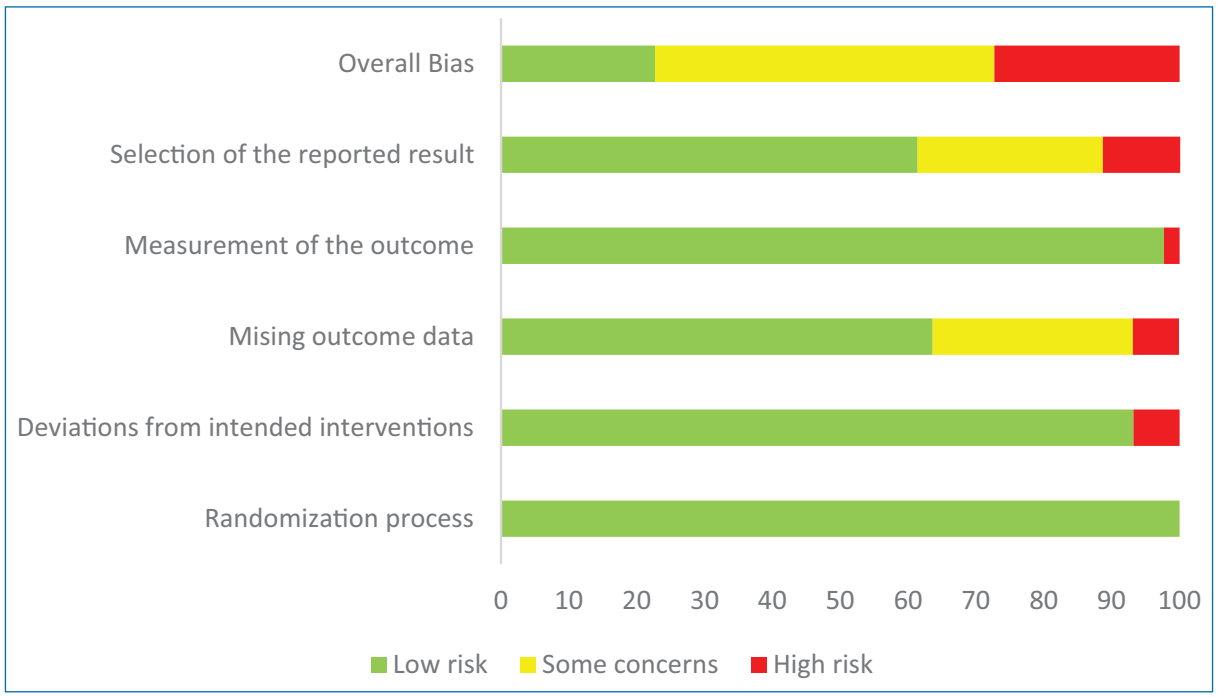


Figure 2. Summary of the risk-of-bias assessment by domain using the Cochrane RoB 2 tool (intention-to-treat analysis).

Risk-of-bias assessment

The reviewers independently assessed risk of bias in duplicate for each included study using the Cochrane Risk of Bias 2 tool.[23]

Data analysis

Outcomes were analyzed according to the intention-to-treat principle. Using a Mantel-Haenszel random-effects model and inverse-variance method, relative risks (RRs) and mean differences (MDs), with their corresponding 95% CIs, were calculated for dichotomous and continuous variables, respectively. Results for each outcome were presented using forest plots. All analyses were performed using Review Manager software (RevMan version 5.4).[24] No imputation was performed when study data were not reported. Summary-of-findings tables were generated using GRADEpro GDT software.[17]

Subgroup and sensitivity analyses

A prespecified subgroup analysis was performed using I^2[25] and the interaction test. The Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) was used to assess the credibility of effect modification.[26] Subgroup analysis compared TT delivered in a single device (fixed combination) with TT delivered through >1 device (open combination). I^2 was interpreted according to the recommendations of the Cochrane Handbook.[18] Subgroup analyses were conducted for outcomes in which heterogeneity of at least 30% was identified.

A sensitivity analysis was performed to assess the robustness of the results by considering studies at high vs low risk of bias.

Certainty of the evidence

Independently and in duplicate, reviewers assessed the certainty of the evidence using the GRADE approach[27] by evaluating the following domains for each outcome: risk of bias,[28] imprecision,[29] inconsistency,[30] indirectness,[31] and publication bias.[32] The certainty of evidence for each outcome was rated as high, moderate, low, or very low. Findings for each outcome were presented using standardized language that reflected both the magnitude of the effect and the certainty of the body of evidence.[16,27,33,34]

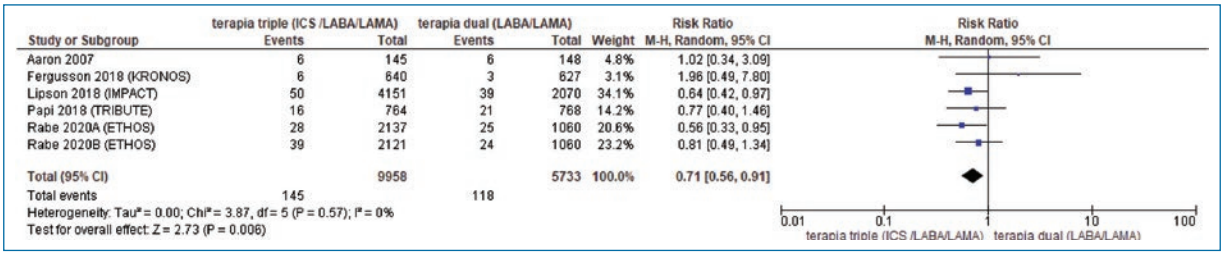


Figure 3. Meta-analysis of clinical trials comparing triple therapy with dual therapy for reducing mortality. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; RCT: randomized controlled trial.

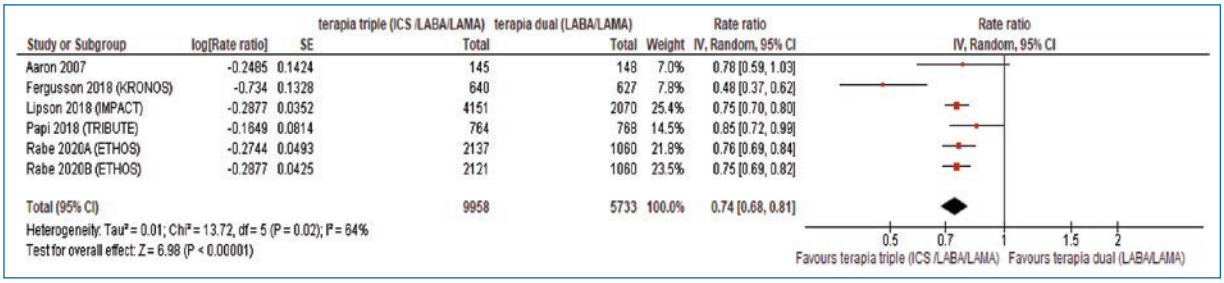


Figure 4. Meta-analysis of clinical trials comparing triple therapy with dual therapy for reducing acute exacerbations. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists.

Results

This literature update identified a total of 1213 citations, of which 216 were excluded as duplicates. A total of 952 studies underwent title and abstract screening, and 126 were assessed in full text. The full text could not be obtained for 7 citations. One study published in 2015 that had not been included in the 2020 SLR reported results from 2 RCTs.[35] Overall, 5 studies reported in 4 publications met the inclusion criteria (Fig. 1).[35-38]

Four of these studies were parallel-group RCTs,[35-37] and 1 was a crossover study[38] (Table 1). Interreviewer agreement before title and abstract screening was 82.5%.

Including 5 RCTs from the previous 2020 SLR-MA,[39-43] a total of 10 RCTs were ultimately included in this review. These studies evaluated 32,757 patients; 10,479 received TT and 8352 received DT. The most common TT regimen among the included studies was fluticasone/umeclidinium/vilanterol as a fixed combination, while the most common DT regimen was glycopyrronium/formoterol.[36,42] A total of 21 new publications reporting secondary or post hoc analyses of studies identified in the 2020 review were identified. Of these, 15 reports[8,44-48] were derived from the IMPACT trial, 4 from the KRONOS trial,[41] and 2 from the ETHOS trial.[49] These studies did not report additional information beyond that contained in the 5 publications included in 2020 and were therefore not considered for data extraction or analysis.

Risk of bias

A summary of the risk-of-bias assessment is presented in figure 2 and supplementary data 4.

Some included studies raised some concerns or were at high risk of bias, particularly in the domains of selective outcome reporting and missing outcome data.[36,37,41]

Outcomes

Mortality

Six RCTs[36,37,39,41-43] including 15,691 patients reported the effect of TT on mortality. Compared with DT, TT probably reduces mortality rate by 29% (moderate-certainty evidence; RR, 0.71; 95% CI, 0.56-0.91; I^2, 0%) (Fig. 3).

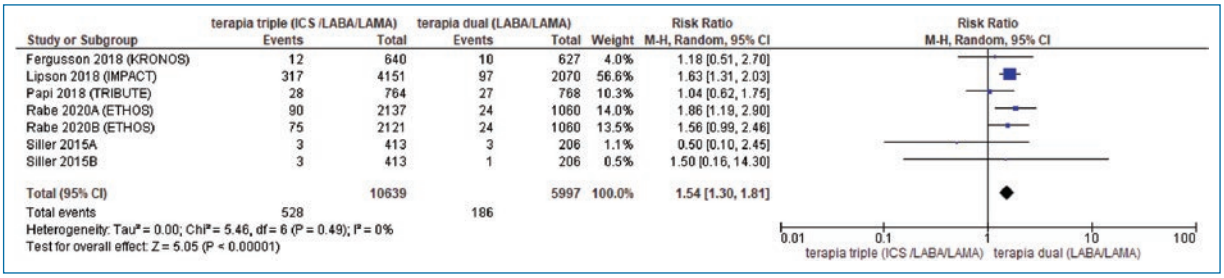


Figure 5. Meta-analysis of clinical trials comparing triple therapy with dual therapy for pneumonia. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists.

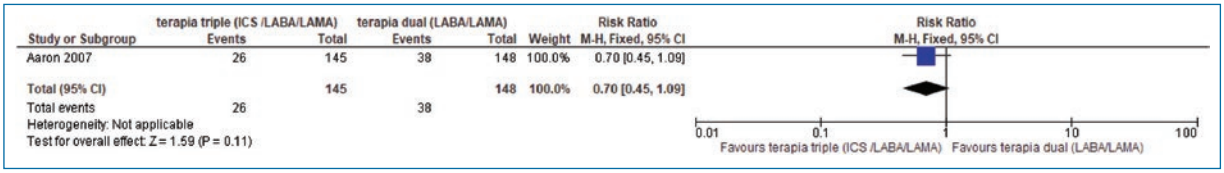


Figure 6. Clinical trial comparing triple therapy with dual therapy for reducing hospital admissions due to acute exacerbations. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist.

Acute exacerbations

Six RCTs[36,37,39,41-43] including 15,691 patients reported acute exacerbations. TT probably reduces acute exacerbations by 26% (moderate-certainty evidence; rate ratio, 0.74; 95% CI, 0.68-0.81) (Fig. 4). More than 65% of the weight of this estimate was accounted for by 3 studies.[36,37,42]

Pneumonia

Seven RCTs[36,37,39,41-44] including 16,636 patients reported pneumonia. The meta-analysis suggests that TT probably increases the incidence of pneumonia by 54% compared with DT (moderate-certainty evidence; RR, 1.54; 95% CI, 1.30-1.81) (Fig. 5).

Hospitalizations

One RCT[49] including 293 patients reported hospital admissions due to acute exacerbations. There were no differences in the number of hospitalizations for acute exacerbations between patients on TT and those on DT (moderate-certainty evidence; RR, 0.70; 95% CI, 0.45-1.05) (Fig. 6). The same study reported all-cause hospitalizations, with no differences between groups (moderate-certainty evidence; RR, 1.19; 95% CI, 0.84-1.69) (Supplementary data 5, Fig. 1).

Dyspnea

Four studies[13,47,49] including 7872 patients reported dyspnea at the end of follow-up. DT probably reduces dyspnea compared with TT (moderate-certainty evidence; MD, 0.28; 95% CI, 0.17-0.39) (Fig. 7). Two of the 4 studies contributed > 80% of the weight to this estimate.[13] When dyspnea was assessed as the mean change from baseline to the end of follow-up, 1 RCT[50] found no differences between TT and DT (low-certainty evidence; MD, 0.28; 95% CI, 0.17-0.39) (Supplementary data 5, Fig. 2).

Health-related quality of life

Three studies[13,37] including 12,599 patients reported the effect of TT compared with DT on improvement in quality of life, assessed as the mean change from baseline to the end of follow-up.[13,37] TT probably improves quality of life compared with DT (moderate-certainty evidence; MD, –1.51; 95% CI, –1.98 to –1.05) (Fig. 8). One RCT[37] including 6221 patients also reported a probable improvement in quality of life among those receiving TT when the outcome was assessed as the mean value at the end of follow-up (high-certainty evidence; MD, –1.80; 95% CI, –2.66 to –0.94) (Supplementary data 5, Fig. 3).

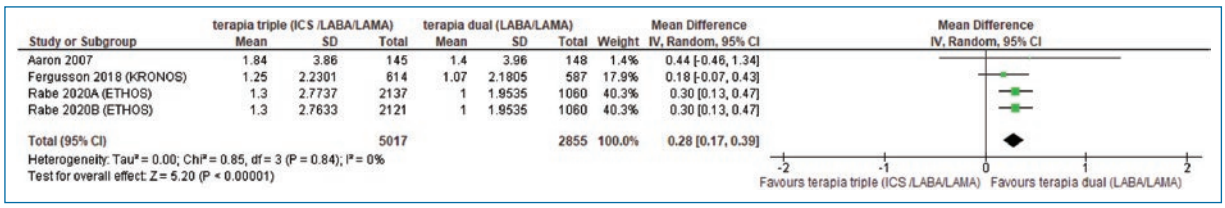


Figure 7. Meta-analysis of clinical trials comparing triple therapy with dual therapy for reducing dyspnea at the final follow-up assessment. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMAs: long-acting muscarinic antagonists.

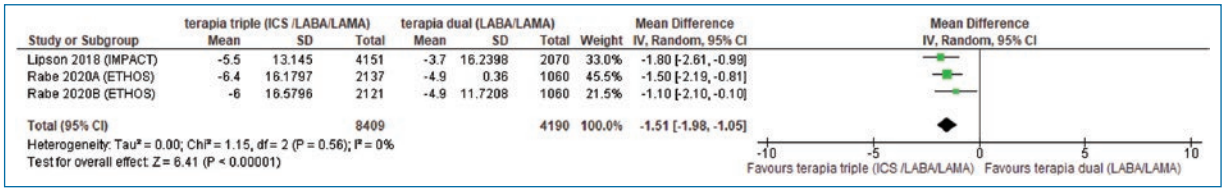


Figure 8. Meta-analysis of clinical trials comparing triple therapy with dual therapy for improving quality of life, measured as the mean change from baseline to the end of follow-up. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists.

Forced expiratory volume in 1 second

Three studies[14,37,50] including 6322 patients reported FEV1 as the mean change from baseline to the end of follow-up. DT probably increases mean FEV1 compared with TT (moderate-certainty evidence; MD, 52.63; 95% CI, 39.63-65.63) (Fig. 9). One RCT[37] including 6221 patients similarly reported an increase in FEV1 at the end of follow-up favoring DT over TT (high-certainty evidence; MD, –1.80; 95% CI, –2.66 to –0.94) (Supplementary data 5, Fig. 4).

Adverse events (number of adverse events)

Ten studies[12-14,37,47,49-51] including 17,030 patients reported approximately 10,117 adverse events, including common cold, bronchitis, oral candidiasis, sinusitis, headache, and cardiovascular events. A total of 6570 events occurred in the TT group compared with 3547 in the DT group. TT did not increase the overall number of adverse events compared with DT (moderate-certainty evidence; RR, 1.01; 95% CI, 0.97-1.06) (Fig. 10).

Other outcomes

No clinical trial reported information on the prioritized outcome of physical activity.

Subgroup analysis

The subgroup analysis showed relative effect modification between TT delivered in a single device (fixed combination) and therapy delivered through > 1 device (open combination) for the outcome of acute exacerbations, favoring TT (test for subgroup differences: χ^2 = 0.49; df = 1; P = .48) (supplementary data 6, Fig. 1). These differences were not observed for mortality, pneumonia, or adverse events (supplementary data 6, Figs. 2, 3, and 4, respectively). Assessment of the credibility of effect modification using the ICEMAN instrument suggested that the benefit of the intervention for exacerbations was maintained regardless of whether TT was delivered as an open or fixed regimen. No significant differences were reported for the remaining outcomes (Supplementary data 7).

Sensitivity analysis

A sensitivity analysis was performed according to high vs low risk of bias among the studies. Evidence favoring TT for exacerbations remained after exclusion of studies at high risk of bias (rate ratio, 0.75; 95% CI, 0.72-0.79). No evidence of a difference between TT and DT was found after excluding studies at low risk of bias (rate ratio, 0.64; 95% CI, 0.37-1.12). For mortality, a difference favoring TT was also observed after excluding

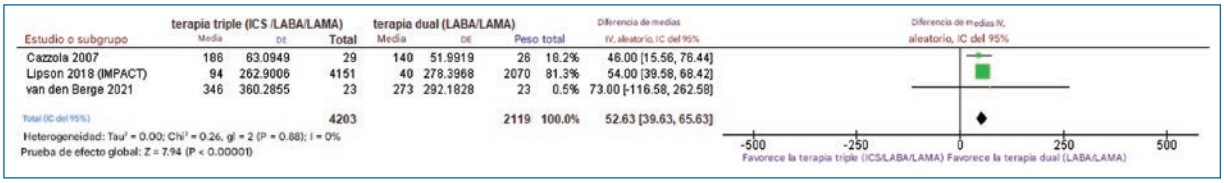


Figure 9. Meta-analysis of clinical trials comparing triple therapy with dual therapy for improving forced expiratory volume in 1 second, measured as the mean change from baseline to the end of follow-up. ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists.

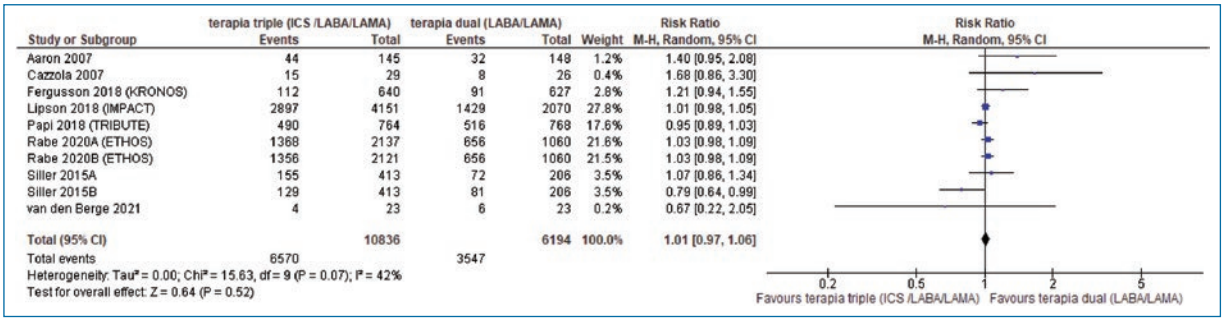


Figure 10. Meta-analysis of clinical trials comparing triple therapy with dual therapy for adverse events (number of adverse events). ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists.

studies at high risk of bias (RR, 0.68; 95% CI, 0.52-0.89). The difference favoring TT was particularly important when study quality was higher. There were no differences in adverse events in the sensitivity analysis according to study risk of bias (Supplementary data 8).

Certainty of the evidence

The certainty of evidence was moderate for most evaluated outcomes, including mortality, acute exacerbations, pneumonia, and adverse events. It was low for dyspnea and high for quality of life and FEV1. Figure 11 illustrates the summary of findings for each outcome according to each domain of the GRADE approach.

Discussion

This meta-analysis was based on the systematic review by Manoj et al. (2020). It found a possible 29% reduction in mortality with TT, although the certainty of the evidence for this outcome was moderate. It is important to note that this finding was not replicated across all studies included in the meta-analysis and that the duration of follow-up in some studies was limited to 1 year. This finding contrasts with the real-world cohort study by Suissa et al. (2021), which found an increase in all-cause mortality and exacerbations among TT users.[50]

Furthermore, the meta-analysis found that TT in high-risk patients with COPD may reduce acute exacerbations by 26% compared with DT, a finding consistent with other systematic reviews.[12] Moreover, these results are consistent with those reported by Manoj et al. (2020), who found a 25% reduction in the risk of acute exacerbations with TT.[11] In addition, the systematic review by Langham et al. (2019) found a reduction in the annual rate of moderate or severe exacerbations ranging from 15% to 52% compared with LAMA/LABA.[6] The systematic review by López et al. (2019) found variable improvements in exacerbations with TT, ranging from nonsignificant effects to a 41% reduction.[51] The consistency of these findings across different studies suggests that TT may be an effective strategy for reducing exacerbations in high-risk patients with COPD.[52]

Overall, no significant differences were found in treatment-related adverse events between TT and DT. A 54% increase in pneumonia rates was observed among patients on TT; this finding is consistent with former studies that have also reported an increased

Figure 11. Certainty of the evidence assessed using GRADE for critical outcomes

Question: Triple therapy (ICS/LABA/LAMA) compared with dual therapy (LABA/LAMA) for patients with COPD

Evaluation of certainty							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triple therapy (ICS/LABA/LAMA)	Dual therapy (LABA/LAMA)	Relative effect	Absolute (IC 95%)		
Mortality (all causes)												
6	Randomized trials	Serious*	Not serious	Not serious	Not serious	None	145/9958 (1.5%)	118/5733 (2.1%)	RR 0.71 (0.56 a 0.91)	6 fewer per 1000 (9 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Acute exacerbations												
6	Randomized trials	Serious*	Not serious	Not serious	Not serious	None	-/9958	-/5733	Incidence rate ratio, 0.74 (0.68-0.81)	-- per 1000 patient-years (from -- to --)	⊕⊕⊕◯ Moderate	CRITICAL
Pneumonia												
7	Randomized trials	Serious†	Not serious	Not serious	Not serious	None	528/10639 (5.0%)	186/5997 (3.1%)	RR 1.54 (1.30 a 1.81)	17 more per 1000 (9 more to 25 more)	⊕⊕⊕◯ Moderate	CRITICAL
Hospital admissions (assessed as acute COPD exacerbations)												
1	Randomized trials	Serious‡	Not serious	Not serious	Not serious	None		38/148 (25.7%)	RR 0.97 (0.65 a 1.43)	8 fewer per 1000 (90 fewer to 110 more)	⊕⊕⊕◯ Moderate	CRITICAL
Hospital admissions (all causes)												
1	Randomized trial	Serious‡	Not serious	Not serious	Not serious	None	48/145 (33.1%)	41/148 (27.7%)	RR 1.19 (0.84 a 1.69)	53 more per 1000 (44 fewer to 191 more)	⊕⊕⊕◯ Moderate	CRITICAL
Dyspnea (assessed at the end of the follow-up period)												
4	Randomized trials	Serious§	Not serious	Not serious	Not serious	None	5017	2855	-	MD, 0.28 higher (0.17 higher to 0.39 higher)	⊕⊕⊕◯ Moderate	CRITICAL
Dyspnea (assessed as the mean change from baseline to final value)												
1	Randomized trial	Serious	Not serious	Not serious	Serious	None	29	26	-	MD, 0.34 lower (0.80 lower to 0.12 higher)	⊕⊕◯◯ Low	CRITICAL

(Continues)

Figure 11. Certainty of the evidence assessed using GRADE for critical outcomes *(continuation)*

Question: Triple therapy (ICS/LABA/LAMA) compared with dual therapy (LABA/LAMA) for patients with COPD

Evaluation of certainty							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Triple therapy (ICS/LABA/LAMA)	Dual therapy (LABA/LAMA)	Relative effect	Absolute (IC 95%)		
Health-related quality of life (assessed as the mean change from baseline to final value)												
3	Randomized trials	Serious[††]	Not serious	Not serious	Not serious	None	8409	4190	-	MD, 1.51 lower (1.98 lower to 1.05 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Health-related quality of life (assessed at the end of the follow-up period)												
1	Randomized trial	Not serious	Not serious	Not serious	Not serious	None	4151	2070	-	MD, 1.8 lower (2.66 lower to 0.94 lower)	⊕⊕⊕⊕ High	CRITICAL
FEV1 in mL (assessed as the mean change from baseline to final value)												
3	Randomized trials	Serious[§]	Not serious	Not serious	Not serious	None	4203	2119	-	MD, 52.63 higher (39.63 higher to 65.63 higher)	⊕⊕⊕◯ Moderate	CRITICAL
FEV1 in mL (assessed at the end of the follow-up period)												
1	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	4151	2070	-	MD, 54 higher (39.01 higher to 68.99 higher)	⊕⊕⊕⊕ High	CRITICAL
Adverse events (number of adverse events)												
10	Randomized trials	Serious[‡‡]	Not serious	Not serious	Not serious	None	6570/10836 (60.6%)	3547/6194 (57.3%)	RR 1.01 (0.97 a 1.06)	6 more per 1000 (17 fewer to 34 more)	⊕⊕⊕◯ Moderate	CRITICAL
Physical activity (exercise capacity, 6-minute walk) – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

*Two studies were rated as having a high risk of bias. One study had concerns regarding the reporting of missing data, and the other because of bias in outcome measurement.

[†]Two studies were rated as having a high risk of bias. One study had selective reporting of an outcome, and the other had concerns regarding the reporting of missing participant follow-up data.

[‡]One study was rated as having some concerns because missing participant follow-up data were not clearly reported.

[§]One study was rated as having a high risk of bias because of selective outcome reporting.

[¶]One study was rated as having a high risk of bias because of deviations from the intended interventions.

[**]Serious imprecision. The 95% CI is consistent with the possibility of both an important benefit and significant harm without reaching the optimal information size.

[††]Two studies were rated as having some concerns because of selective outcome reporting.

[‡‡]Three studies were rated as having a high risk of bias: 1 because of deviations from the intended interventions, 1 because of selective outcome reporting, and 1 because of bias in outcome measurement.

COPD: chronic obstructive pulmonary disease; FEV1:forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; MD: mean difference; OR: odds ratio; RR: relative risk; 95% CI: 95% confidence interval.

risk of pneumonia with TT, particularly in patients receiving inhaled corticosteroid therapy with fluticasone furoate. However, a post hoc analysis of the IMPACT study by Dransfield et al. suggests that there may be a favorable risk-benefit balance when the occurrence of pneumonia is weighed against the reduction in exacerbations achieved in symptomatic patients with a history of recurrent exacerbations.[52]

The subgroup analysis showed that both fixed TT and open TT significantly reduced acute exacerbations. This finding suggests that TT may be effective regardless of the type of combination used. This analysis showed no significant differences in pneumonia, adverse events, or mortality. The sensitivity analysis yielded conflicting results.

Conclusions

This meta-analysis suggests that TT may be an effective therapeutic option for reducing acute exacerbations and mortality in high-risk patients with COPD. The increased risk of pneumonia associated with TT should be taken into consideration, although the overall risk-benefit balance favors the use of TT. Additional larger and longer-term studies are needed to confirm these findings and to assess the long-term efficacy and safety of TT.

Authors' contributions

Dr. Jorge Eliécer Rivas Ibargüen contributed to data analysis, interpretation, and writing of the first and subsequent drafts of the article.

Dr. Carolina Ocampo Salgado contributed to data analysis and interpretation of the first and subsequent drafts of the article.

Dr. Diana Marcela Chaparro Martínez contributed to data analysis for the first and subsequent drafts of the article.

Dr. Fredy Leonardo Carreño contributed to data analysis for the first and subsequent drafts of the article.

Dr. Andrés Fernando Rodríguez Gutiérrez contributed to data analysis for the first and subsequent drafts of the article.

Sebastián Castaño Duque contributed to the design and implementation of the search strategy for the article.

Dr. Olga Milena García Molares contributed to the study design, data analysis, interpretation, and writing of the first and subsequent drafts of the article.

Dr. Juan José Yepes Núñez contributed to the study design, data analysis, interpretation, and writing of the first and subsequent drafts of the article.

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Conflicts of interest

The authors have read and approved the final manuscript for submission and declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data. Given the nature of the study, individual informed consent was not required. Relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that no type of generative artificial intelligence was used in the writing or creation of content for this manuscript.

Supplementary data

Supplementary data is available at DOI: 10.24875/NCTE.M25000037. This data is provided by the corresponding author and published online for the benefit of the reader. The content of the supplementary data is the sole responsibility of the authors.

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