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Clinically Important Deterioration (CID) and Ageing in COPD: A Systematic Review and Meta-Regression Analysis According to PRISMA Statement

Gian Marco Manzetti[1], Josuel Ora[1], Arianna Sepiacci[1], Mario Cazzola[1], Paola Rogliani[1], Luigino Calzetta[2]

[1]Department of Experimental Medicine, Unit of Respiratory Medicine, University of Rome "Tor Vergata", Rome, Italy; [2]Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy

Correspondence: Luigino Calzetta, Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy, Email luigino.calzetta@unipr.it

Purpose: Clinically important deterioration (CID) is a composite endpoint developed to quantify the impact of pharmacological treatment in clinical trials for Chronic Obstructive Pulmonary Disease (COPD), also showing a prognostic value. CID is defined as any of the following condition: forced expiratory volume in 1 s decrease ≥100 mL from baseline, and/or St. George's Respiratory Questionnaire total score increase ≥4-unit from baseline, and/or the occurrence of a moderate-to-severe exacerbation of COPD. Although most COPD patients experience a clinical worsening as they get older, to date, no specific studies assessed the correlation between ageing and CID in COPD. Therefore, the aim of this study was to investigate the impact of ageing on CID in COPD patients.

Patients and Methods: Data obtained from 55219 COPD patients were extracted from 17 papers, mostly post-hoc analyses. A pairwise meta-analysis and a meta-regression analysis were performed according to PRISMA-P guidelines to quantify the impact of pharmacological therapy on CID and to determine whether ageing might modulate the risk of CID in COPD patients.

Results: Inhaled treatments resulted generally effective in reducing the risk of CID in COPD (relative risk: 0.81, 95% confidence interval 0.79–0.84; $P < 0.001$). The meta-regression analysis indicated a trend toward significance ($P = 0.063$) in the linear relationship between age and the risk of CID. Of note, age significantly ($P < 0.05$) increased the risk of CID when associated with lower post-bronchodilator FEV_1. These results were not affected by a significant risk of bias.

Conclusion: This quantitative synthesis suggests that inhaled therapy is effective in reducing the risk of CID in COPD, although such a protective effect may be affected in older patients with impaired lung function. Further studies specifically designed on CID in COPD are needed to confirm these results.

Keywords: ageing, clinically important deterioration, chronic obstructive pulmonary disease, elderly, meta-analysis, inhaled therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is defined by the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as a heterogeneous lung condition characterized by chronic respiratory symptoms and a persistent, often progressive, airflow obstruction.[1] The need for a multi-dimensional approach, assessing lung function, acute exacerbations, and quality of life of COPD patients, led to the development of the composite clinically important deterioration (CID) endpoint in 2016.[2] In its original formulation, a CID was defined as any of the following: a decrease of ≥100 mL from baseline in forced expiratory volume in 1 s (FEV_1) and/or a ≥4-unit increase from baseline in St. George's Respiratory Questionnaire (SGRQ) total score and/or the occurrence of a moderate-to-severe exacerbation of COPD (AECOPD). AECOPD was defined as an acute worsening of COPD symptoms requiring the use of additional treatment.[2]

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The CID concept has proven itself as a reliable tool to quantify the impact of pharmacological treatment in several post-hoc analyses of randomized controlled trials (RCTs),[3] overcoming the exclusive effect on FEV_1, which might correlate weakly with patient reported outcomes (PRO).[4] Throughout the years, the composite CID endpoint also showed a prognostic value[5] and alternative definitions, including, among the others, the COPD Assessment test (CAT) score[6] and the Transition Dyspnea Index (TDI),[7] were developed.

COPD patients can experience a rather fast decline in lung function over the years, ranging from 33 to 66 mL/year in FEV_1 according to different studies.[8,9] However, this annual rate is below the 100 mL decrease considered by the original CID definition, which is indeed intended to be greater than the expected functional decline; for this reason, this value is considered the minimal clinically important difference (MCID) for FEV_1 in COPD.[10]

According to the well-known Fletcher–Peto curve[11] and to more recent retrospective evidence, the FEV_1 decrease could accelerate with ageing.[12] As a matter of fact, this trend can be identified also in healthy subjects, where the median FEV_1 decline is 22.4 mL/year, ranging from 3 mL/year in the 40–49 years decade to 34 mL/year in the 70–79 years decade, as reported by a recent systematic review.[13]

Likewise, older COPD patients have a higher risk of future AECOPD and a higher mortality for acute exacerbations,-[14,15] showing an age-related dysfunction of the immune system.[16] Moreover, elderly COPD patients are more likely to suffer from comorbidities,[17] that per se increase the risk of moderate and severe AECOPD.[18]

Conversely, ageing does not seem to affect health-related quality of life (HRQL) in COPD patients, since younger patients, aged 50–64 years, actually score higher in SGRQ than patients aged 65–80 years, probably due to a higher impact of dyspnea.[19]

Despite this evidence, to date, no specific studies have been carried out to assess the correlation between ageing and CID in COPD patients.

The meta-regression analysis is a statistical method which usually follows a traditional meta-analysis: on one hand, it is mainly used to identify possible confounding factors in a meta-analysis, on the other hand, meta-regression analysis can also be used as a tool to investigate if and how a specific variable, such as ageing, may modulate certain outcomes.[20–23]

Therefore, the aim of this systematic review and meta-regression analysis was to investigate the impact of ageing on CID in COPD patients, according to the current PRISMA statement.[24]

Materials and Methods

Search Strategy and Study Eligibility

This systematic review and meta-regression analysis was performed according to PRISMA-P guidelines.[24] The PRISMA 2020 flow diagram is shown in Figure 1. The PRISMA-P checklist is reported in Table S1.[24]

A comprehensive literature search was carried out for Phase III RCTs or post-hoc analyses of RCTs written in English and assessing CID in COPD patients.

The patient problem, intervention, comparison, and outcome (PICO) framework were used for the literature search.[26] The "Patient problem" included COPD; the 'Intervention' regarded inhaled therapy; the 'Comparison' was performed vs placebo (PCB) or across different inhaled drugs; the 'Outcome' was the association between CID and ageing.

The search was performed in MEDLINE and Scopus to find relevant studies published up to February 9th, 2023.

The following search string was used in the database was: ((clinically important deterioration) OR CID) AND COPD. References of previous high-quality reviews were checked to identify further RCTs, if any.[5]

Eppi-Reviewer 4 (EPPI-Centre Software. London, UK) was used to manage data in literature and facilitate the collaboration across reviewers for the selection of the studies.

Study Selection

Phase III RCTs or post-hoc analyses of RCTs that analyzed CID in COPD patients were included in the systematic review and meta-regression analysis. Trials not including at least FEV_1 decline, SGRQ increase, and AECOPD in the

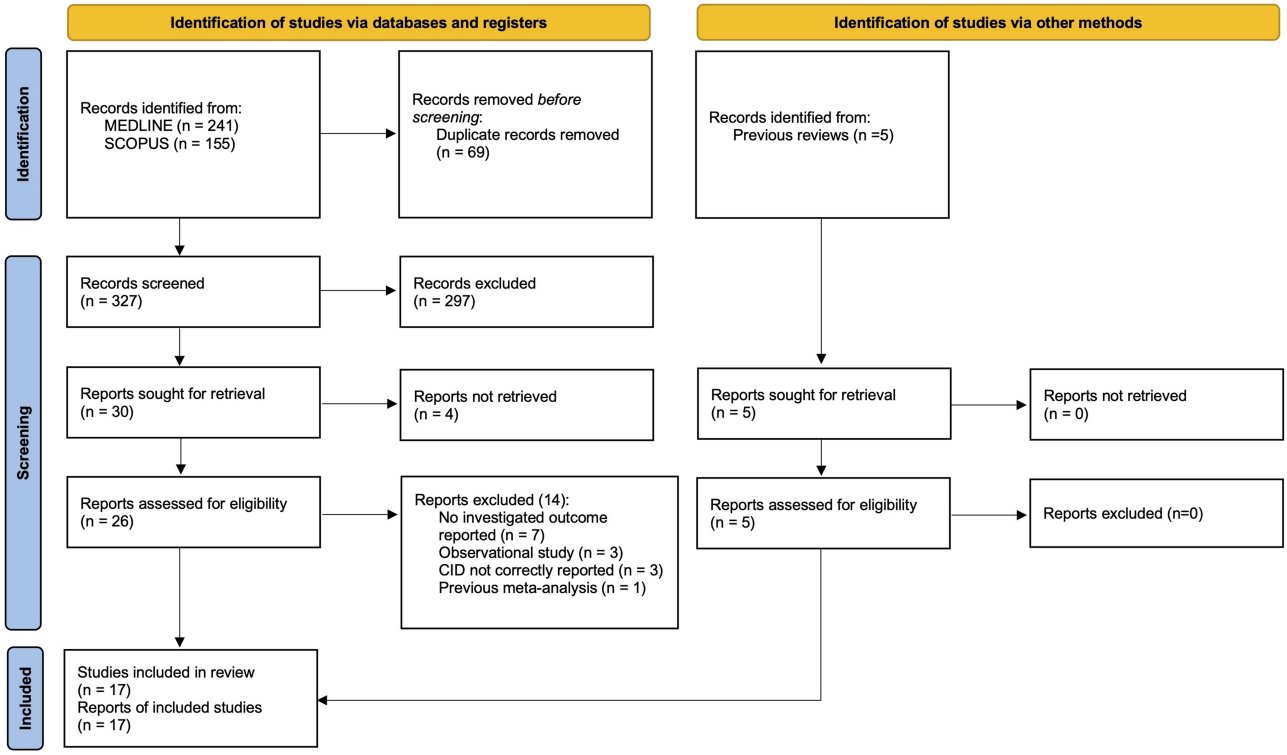

Figure 1 PRISMA 2020 flow diagram for the identification of the studies included in the systematic review.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[25]
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

CID definition were excluded from the analysis. Two reviewers (GMM and LC) independently checked for study selection and any difference in opinion was resolved by consensus.

Data Extraction

Data from the Phase III or RCTs post-hoc analyses included in this systematic review and meta-regression analysis were extracted from journal articles, and/or Supplementary Data Files, and/or the ClinicalTrials.gov database.

Data were checked for reference, clinical trial ID, duration and characteristics of the study, number of analyzed patients, treatments administered including the doses of medications, regimen of administration, main inclusion criteria, age, gender, smoking habit, post-bronchodilator FEV_1, AECOPD, SGRQ, COPD assessment test (CAT), modified medical research council dyspnea scale (mMRC), and Jadad Score.[27]

Data were extracted according to the DECiMAL recommendations.[28] Cohen's Kappa score was used to assess the inter- and intra-rater reliability for data abstraction (≥0.80: excellent agreement; ≥0.61 and <0.80: substantial agreement; ≥0.41 and <0.61 moderate agreement; <0.41 poor agreement).[29]

Endpoint

The primary endpoint of systematic review and meta-regression analysis was to assess the risk of CID according to ageing.

Data Synthesis and Analysis

A pairwise meta-analysis was carried out to quantify the risk of CID in COPD patients enrolled in RCTs. Obtained results were reported as relative risk (RR) and 95% confidence interval (95% CI).

A common effect size cannot be assumed because data were extracted from a series of studies performed by investigators operating independently. Therefore, the binary DerSimonian-Laird random-effects model was used to balance the study weights and correctly assess the effect estimates and relative 95% CI. Subgroup analyses were carried out according to specific inhaled treatments.

A meta-regression analysis via random-effect method was also performed to investigate whether ageing, alone or in association with other potential effect modifiers, might modulate the risk of CID in COPD. The meta-regression analysis was carried out by plotting the outcome variables obtained from the pairwise meta-analysis with the explanatory variables reported in the included studies.[20–23] The resulting regression coefficient indicates how strongly the explanatory variables may modify the effect induced by a specific treatment.[22] The meta-regression analysis reports a positive or negative correlation between the effect estimates and the potential effect modifiers for statistically significant regression coefficient. In this study, meta-regression analysis was used to investigate the impact of ageing on CID.

Study Quality, Bias, and Quality of Evidence

The risk of bias for the included studies was quantified via Jadad score, ranging from 1 to 5 (score ≤2: low quality; score = 3: medium quality; score ≥4: high quality).[27]

Heterogeneity (I^2) was assessed to analyze the between-study dissimilarity, as previously reported.[20]

Funnel plot and Egger's test were performed to investigate the origin and risk of publication bias related to significant and/or substantial (I^2>50%) level of heterogeneity if more than 10 studies were included in the meta-analysis.[30–33]

The quality of the evidence was assessed according to GRADE system (++++: high quality; +++: moderate quality; ++: low quality; +: very low quality).[34]

Two reviewers (GMM and LC) independently assessed the study quality, bias, and quality of evidence and any difference in opinion was resolved by consensus.

Software and Statistical Significance

Open-MetaAnalyst Was Used to Perform

The pairwise meta-analysis and meta-regression analysis were analyzed via Open-MetaAnalyst software[20] and the quality of evidence assessed via the GRADEpro GDT software.[34] The statistical significance was identified for P value <0.05.

Results

Study Characteristics

Of the 332 potentially relevant records identified in the initial search, 17 studies were deemed eligible for qualitative and quantitative syntheses.[2,6,7,35–48] Full-text papers were published between 2016 and 2021.

Data obtained from 55219 COPD patients were extracted from 15 post-hoc analyses of RCTs, a subgroup analysis of a RCT,[40] and a RCT prospectively assessing the CID composite endpoint.[42] The duration of the studies ranged from 3 to 48 months and the age of the COPD populations enrolled in the studies ranged from 62.8 to 65.3 years.

A certain level of study population overlap was detected across the post-hoc analyses. Namely, the SHINE trial[49] was analyzed in both the studies by D'Urzo et al[45] and Anzueto et al,[7] the ZEP117115 trial[50] was included in both the post-hoc analyses by Maleki-Yazdi et al[48] and Singh et al,[2] the study by Chen et al[40] was a subgroup analysis of the PINNACLE-4 trial,[51] which was also included in the post-hoc analysis by Zheng et al.[39]

Different treatments were analyzed as following: long-acting bronchodilators (LABD) vs PCB,[2,37–40,45,47] long-acting muscarinic antagonist (LAMA) vs long-acting β_2-adrenoceptor agonist (LABA),[2,40] dual bronchodilation vs PCB,[2,39,40,47] dual bronchodilation vs LABD,[2,7,36,39,40,42,47,48] dual bronchodilation vs inhaled corticosteroid (ICS)/LABA,[35,46] ICS/LABA vs LABD,[41] triple combination vs LABD,[43] triple combination vs dual bronchodilation,[35,43] triple combination vs ICS/LABA.[6,35,43,44]

The main characteristics of the studies included in the systematic review and meta-regression analysis are reported in Table 1, whereas Table 2 shows the different CID definitions for study.

Table 1 Main Characteristics of the Studies Included in the Systematic Review and Meta-Regression Analysis

Study, Year, PMID, and Reference	Number Identifier	Study Characteristics	Study Duration (Months)	Number of Analysed Patients	Drugs, Doses and Regimen of Administration	Main inclusion Criteria	Age (Years)	Male (%)	Current Smokers (%)	Smoking History (Pack-Years)	Baseline Post-Broncho-Dilator FEV_1 (% Predicted)	AECOPD in the Previous Year (Rate)	Baseline SGRQ	Baseline CAT Score	Baseline mMRC Dyspnea Score	Jadad Score
Han et al 2021 33718490[35]	NCT02164513 (IMPACT)	Post-hoc analysis of the multicenter, randomized, double-blind, parallel-group, phase III IMPACT study	12.0	10,355	FF/UMEC/VI 100/62.5/25 μg QD vs FF/VI 100/25 μg QD vs UMEC/VI 62.5/25 μg QD	COPD, age >40 years, CAT score ≥10, FEV_1 ≤50% of predicted AND ≥1 moderate or severe exacerbation in the previous year or FEV_1 of ≥50–≤80% predicted AND ≥2 moderate or ≥1 severe exacerbation in the previous year	65.3	66.3	34.6	NA	45.6	NA	50.6	20.1	NA	5
Rabe et al 2021 33175291[36]	NCT01431274 (TONADO1); NCT01431287 (TONADO2)	Post-hoc analysis of the multicenter, randomized, double-blind, parallel-group, phase III replicate trials TONADO 1 and TONADO 2	12.0	2055	T/O 2.5/5 or 5/5 μg QD vs T 2.5 μg QD or 5 μg vs O 5 μg QD.	Moderate-to-very severe COPD (GOLD 2–4), age ≥40 years, smoking history of >10 pack-years	63.7	72.2	37.3	NA	49.5	NA	NA	NA	NA	5 (TONADO1); 5 (TONADO2)
Kerwin et al 2020 33061349[37]	NCT02347761 (GOLDEN 3); NCT02347774 (GOLDEN 4)	Post-hoc analysis of pooled data from the multicenter, randomized, double-blind, placebo-controlled phase III trials GOLDEN3 and GOLDEN4	3.0	1293	GLY 25 mcg and 50 mcg BID vs PCB	Moderate-to-very-severe COPD (post-bronchodilator, FEV_1 ≤80% of predicted, FEV_1 >0.7 L, and FEV_1/FVC ratio <0.70), age ≥40 years, current or past smokers (≥10 pack-years)	63.2	56.0	52.9	NA	NA	NA	48.8	NA	NA	3 (GOLDEN 3); 3 (GOLDEN 4)
Rabe et al 2020 32646424[38]	NCT00144339	Post-hoc analysis of the multicenter, randomized, double-blind, parallel-group trial UPLIFT	48.0	5652	T 18 μg QD vs PCB	Moderate-to-very severe COPD (GOLD 2–4), age ≥40 years, smoking history of ≥10 pack-years	NA	NA	NA	NA	NA	NA	NA	NA	NA	5
Zheng et al 2020 32164675[39]	NCT01854645 (PINNACLE-1); NCT01854658 (PINNACLE-2); NCT02343458 (PINNACLE-4)	Post-hoc analysis of pooled data from the multicenter randomized, international, double-blind, placebo-controlled phase III trials PINNACLE-1, −2 and −4	6.0	4983	GLY/FOR 14.4/9.6 μg BID vs GLY 14.4 μg BID vs FOR 9.6 μg BID vs PCB	Moderate- to-very severe COPD according to ATS (post-bronchodilator, FEV_1 <80% of predicted, and FEV_1/FVC ratio <0.70), age >40 years, current or past smokers (≥10 pack-years)	63.3	61.9	50.7	49.2	NA	NA	44.0	17.3	1.8	5 (PINNACLE-1); 5 (PINNACLE-2); 4 (PINNACLE-4)
Chen et al 2020 32021143[40]	NCT02343458 (PINNACLE-4)	Chinese subgroup analysis of the multicenter randomized, double-blind, placebo-controlled, parallel-group Phase III trial PINNACLE-4	6.0	466	GLY/FOR 14.4/9.6 μg BID vs GLY 14.4 μg BID vs FOR 9.6 μg BID vs PCB	COPD according to ATS 2004, FEV_1/FVC ratio <0.70 and FEV1 <80% predicted, age 40–80 years, smoking history of ≥10 pack-years	63.5	95.7	33.3	36.9	53.7	NA	34.1	11.8	NA	4
Bafadhel et al 2020 31924197[41]	NCT00206167 (SUN); NCT00206154 (SHINE); NCT00419744 (US3); NCT02157935 (RISE)	Post-hoc analysis of pooled data from the multicenter randomized, double-blind, double-dummy, parallel-group trials SUN, US3, SHINE and RISE	12.0 (SUN, US3); 6.0 (SHINE, RISE).	3576	BUD/FOR 160/4.5 μg BID vs FOR 4.5μg BID	COPD, age ≥40years, current or past smokers (≥10 pack-years), confirmed airflow obstruction, history of ≥1 exacerbation	63.2	61.3	42.3	NA	42.0	1.6	52.7	NA	NA	4 (SUN); 5 (SHINE); 5 (US3); 4 (RISE)

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Table 1 (Continued).

Study, Year, PMID, and Reference	Number Identifier	Study Characteristics	Study Duration (Months)	Number of Analysed Patients	Drugs, Doses and Regimen of Administration	Main inclusion Criteria	Age (Years)	Male (%)	Current Smokers (%)	Smoking History (Pack-Years)	Baseline Post-Broncho-Dilator FEV_1 (% Predicted)	AECOPD in the Previous Year (Rate)	Baseline SGRQ	Baseline CAT Score	Baseline mMRC Dyspnea Score	Jadad Score
Maltais et al 2019 31666084[42]	NCT03034915 (EMAX)	Multicenter, randomized, double-blind, double-dummy, 3-arm parallel group EMAX study	6.0	2425	UMEC/VI 62.5/25 μg QD vs UMEC 62.5 μg QD vs SAL 50 μg BID	COPD (FEV_1/FVC ratio <0.7), age ≥ 40 years, post-salbutamol FEV_1 of ≥30–≤80% predicted, CAT score ≥10, ≤1 moderate exacerbation (requiring oral or systemic corticosteroids and/or antibiotics) and no severe exacerbations (requiring hospitalization) in the previous year	64.6	59.0	50.0	26.5	55.4	NA	44.7	19.2	NA	5
Singh et al 2019 30880943[43]	NCT01917331 (TRILOGY); NCT01911364 (TRINITY); NCT02579850 (TRIBUTE)	Post-hoc analysis of pooled data from the multicenter randomized, double-blind, active controlled, trial TRILOGY, the multicenter randomized, double-blind, double-dummy active controlled, parallel group trial TRINITY and the multicenter randomized, double-blind, double-dummy, active controlled, parallel group, phase IIIb Trial TRIBUTE	12.0	5588	TRILOGY: BDP/FOR/GLY 87/5/9 μg 2 inhalations BID vs BDP/FOR 87/5 μg 2 inhalations BID; TRINITY: BDP/FOR/GLY 87/5/9 μg 2 inhalations BID vs T 18 μg QD vs BDP/FOR 87/5 μg 2 inhalations BID + T 18 μg QD; TRIBUTE: BDP/FOR/GLY 87/5/9 μg 2 inhalations BID vs IND/GLY 85/43 μg QD	TRILOGY: age ≥40years, FEV1 of <50% predicted post-bronchodilator, FEV1/FVC <70%, at least one moderate or severe COPD exacerbation in the previous 12 months, use of ICS+LABA, ICS+LAMA, LABA+LAMA or LAMA at least 2 months before screening, CAT ≥10, BDI ≤10; TRINITY: age ≥40years, current or past smokers, FEV_1 of <50% predicted post-bronchodilator, FEV_1/FVC <70%, at least one moderate or severe COPD exacerbation in the previous 12 months, use of ICS+LABA, ICS+LAMA, LABA+LAMA or LAMA at least 2 months before screening, CAT ≥10. TRIBUTE: age ≥40years, current or past smokers, FEV_1 of <50% predicted, post-bronchodilator FEV_1/FVC <70%, at least one moderate or severe COPD exacerbation in the previous 12 months, use of ICS+LABA, ICS +LAMA, LABA+LAMA or LAMA at least 2 months before screening, CAT ≥10	63.6	75.0	46.7	NA	NA	1.2	51.7	21.3	NA	5 (TRILOGY); 5 (TRINITY); 5 (TRIBUTE)

Naya et al 2018 30191464[44]	NCT01772134 (AC4116135); NCT01772147 (AC4116136); NCT01957163 (200109); NCT02119286 (200110)	Post-hoc analysis of pooled data from the multicenter, randomized, double-blin, parallel-group, phase III trials AC4116135, AC4116136, 200109 and 200110	3.0	1637	AC4116135 and AC4116136: UMEC 62.5 µg QD + SAL/FP 500/50 µg BID vs PCB + SAL/FP 500/50 µg BID; 200109 and 200110: UMEC 62.5 µg QD + FF/VI 100/ 25 µg QD vs PCB + FF/VI 100/ 25 µg QD	COPD according to ATS 2004, age ≥40years, Group B or D according to GOLD 2016, current or past smokers (≥10 pack-years), mMRC grade≥2, FEV_1 of ≤70% predicted post-bronchodilator, FEV_1/ FVC <70%	63.9	65.2	47.5	47.7	45.8	NA	44.6	NA	NA	5 (AC4116135); 5 (AC4116136); 5 (200109); 5 (200110)
Naya et al 2018 30302335[6]	NCT02345161 (FULFIL)	Post-hoc analysis of the multicenter, randomized, double-blind, double-dummy placebo-controlled parallel-group trial FULFIL	6.0	1810	FF/UMEC/VI 100/ 62.5/25 µg QD + PCB BID vs BUD/FOR 400/ 12 µg BID + PCB QD	COPD, age ≥40years, Group D according to GOLD 2015 (FEV_1 <50% predicted and CAT ⩾10 or patients with FEV_1 ⩾50% to <80% predicted and CAT ⩾10, and either at least two moderate exacerbations or at least one severe exacerbation in the past year)	63.9	74.1	43.9	39.3	45.3	NA	51.3	NA	NA	5
D'Urzo et al 2018 29795478[45]	NCT01005901 (GLOW1), NCT00929110 (GLOW2), NCT01613326 (GLOW5), NCT01202188 (SHINE)	Post-hoc analysis of the multicenter, randomized, double-blind, placebo-controlled, phase III trial GLOW1, the multicenter, randomized, double-blind, placebo-controlled with open-label, parallel group phase III trial GLOW2, the blinded, double-dummy, parallel group trial GLOW5 and the multicenter randomized, double-blind, placebo and active controlled, trial SHINE	3.0 (GLOW5); 6.0 (SHINE, GLOW1); 12.0 (GLOW2)	2936	GLOW1: GLY 50 µg QD vs PCB GLOW2; GLY 50 µg QD vs open-label T 18 µg QD vs PCB GLOW5: GLY 50 µg QD vs T 18 µg QD SHINE: IND/GLY 110/50 µg QD vs IND 150 µg QD vs GLY 50 µg QD vs open-label T 18 µg QD vs PCB;	COPD, age ≥40 years, current or past smokers of (≥10 pack- years), post-bronchodilator FEV_1 ≥30–<80% predicted, and post-bronchodilator FEV_1/ FVC ratio <0.70	63.8	73.3	41.2	NA	54.9	NA	48.0	NA	NA	4 (GLOW1), 5 (GLOW2), 5 (GLOW5), 5 (SHINE)
Anzueto et al 2018 29925383[46]	NCT01782326 (FLAME)	Post-hoc analysis of the multicenter, randomized, double-blind, double-dummy, parallel-group trial FLAME	12.0	3362	IND/GLY 110/50 µg QD vs SAL/FP 50/500 µg BID	COPD, age ≥40 years, post-bronchodilator FEV_1 ≥25% and<60% predicted, documented history of ≥1 COPD exacerbation in the previous 12 months, mMRC grade≥2.	64.5	76.0	39.6	NA	44.0	NA	47.2	NA	NA	5
Singh et al 2017 28558833[47]	NCT01462942 (ACLIFORM); NCT01437397 (AUGMENT)	Post-hoc analysis of pooled data from the multicenter randomized, double-blind, placebo-controlled, active-controlled, parallel group, phase III trials ACLIFORM and AUGMENT	6.0	2680	AB/FOR 400/12 µg BID vs AB/ FOR 400/6 µg BID vs AB 400 µg BID vs FOR 12 µg BID vs PCB	Stable moderate to severe COPD (FEV_1/FVC ≤70% post bronchodilator, FEV_1 of ≥30–<80%predicted post bronchodilator), age ≥40years, current or past smokers.	63.6	60.0	49.2	46.4	53.7	0.4	46.0	NA	NA	5 (ACLIFORM); 4 (AUGMENT)

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Table 1 (Continued).

Study, Year, PMID, and Reference	Number Identifier	Study Characteristics	Study Duration (Months)	Number of Analysed Patients	Drugs, Doses and Regimen of Administration	Main inclusion Criteria	Age (Years)	Male (%)	Current Smokers (%)	Smoking History (Pack-Years)	Baseline Post-Broncho-Dilator FEV_1 (% Predicted)	AECOPD in the Previous Year (Rate)	Baseline SGRQ	Baseline CAT Score	Baseline mMRC Dyspnea Score	Jadad Score
Anzueto et al 2017 28496316[7]	NCT01202188 (SHINE); NCT01709903 (LANTERN); NCT01315249 (ILLUMINATE)	Post-hoc analysis of the pooled data from the multicenter randomized, double-blind, placebo and active controlled, trial SHINE, the multicenter, randomized, double-blind, double-dummy, placebo controlled, parallel-group trial LANTERN and the multicenter, randomized, double-blind, double-dummy, parallel-group, placebo controlled trial ILLUMINATE	6.0	2217	SHINE: IND/GLY 110/50 µg QD vs IND 150 µg QD vs GLY 50 µg QD vs open-label T 18 µg QD vs PCB; LANTERN: 110/50 µg QD vs SAL/FP 50/500 µg BID vs PCB; ILLUMINATE: IND/GLY 110/50 µg QD vs SAL/FP 50/500 µg BID vs PCB	SHINE: Moderate to very severe COPD according to GOLD 2017, age ≥40years, post-bronchodilator FEV_1 ≥30% and<80% predicted, post-bronchodilator, FEV1/FVC <70%; LANTERN: age ≥40years, current or past smokers (≥10 pack-years), post-bronchodilator FEV_1 ≥30% and<80% predicted, post-bronchodilator, FEV_1/FVC <70%; ILLUMINATE: age ≥40years, current or past smokers (≥10 pack-years), post-bronchodilator FEV_1 ≥40% and<80% predicted, post-bronchodilator, FEV_1/FVC <70%	64.1	79.6	37.1	NA	55.3	NA	NA	NA	NA	5 (SHINE); 5 (LANTERN); 5 (ILLUMINATE)
Maleki-Yazdi et al 2017 27796912[48]	NCT01316900 (DB2113360); NCT01316913 (DB2113374); NCT01777334 (ZEP117115)	Post-hoc analysis of pooled data from the multicenter randomized, blinded, double-dummy, parallel-group trials DB2113360, DB2113374 and ZEP117115	6.0	1747	ZEP117115: UMEC/VI 62.5/25 µg QD vs T 18 µg QD; DB2113360: UMEC/VI 62.5/25 µg QD vs T 18 µg QD vs VI 25 µg QD vs, UMEC/VI 125/25 µg QD; DB2113374: UMEC/VI 62.5/25 µg QD vs T 18 µg QD vs UMEC 125 µg QD vs, UMEC/VI 125/25 µg QD	COPD according to ATS 2004, age ≥40years, mMRC grade≥2, FEV_1 of ≤70% predicted post-bronchodilator, FEV_1/FVC <70%. Maintenance-naïve population: no maintenance therapy for ≥30 days before screening.	63.2	68.1	51.3	45.6	47.0	NA	NA	NA	NA	4 (DB2113360); 4 (DB2113374); 5 (ZEP117115)
Singh et al 2016 27445468[2]	NCT01313650 (DB2113373); NCT01777334 (ZEP117115)	Post-hoc analysis of the pooled data from the multicenter randomized, double-blind, parallel-group, phase III trials DB2113373 and ZEP117115	6.0	2437	DB2113373 (StudyA): UMEC/VI 62.5/25 µg QD vs UMEC 62.5 µg QD vs VI 25 µg QD vs PCB; ZEP117115: (Study B) UMEC/VI 62.5/25 µg QD vs T 18 µg QD	COPD according to ATS 2004, age ≥40years, mMRC grade≥2, FEV_1 of ≤70% predicted post-bronchodilator, FEV_1/FVC <70%.	62.8	69.6	52.2	45.5	47.0	NA	49.1	NA	NA	5 (DB2113373); 5 (ZEP117115)

Abbreviations: AB, aclidinium bromide; AECOPD, acute exacerbation of COPD; ATS, American Thoracic Society; BDP, beclomethasone dipropionate; BID, bis in die, twice daily; BUD, budesonide; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FF, fluticasone furoate; FOR, formoterol fumarate; FP, fluticasone propionate; FVC, forced vital capacity; GLY, glycopyrronium bromide or glycopyrrolate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council dyspnea scale; NA, not available; O, olodaterol; PCB, placebo; PMID, PubMed IDentifier; QD, quaque die, once daily; SAL, salmeterol; SGRQ, St. George's Respiratory Questionnaire; T, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

Table 2 Different CID Definitions Used in the Studies Included in the Systematic Review and Meta-Regression Analysis

Study, Year, PMID, and Reference	FEV_1 Decline and/or	Exacerbations and/or	SGRQ Increase and/or	CAT Increase and/or	Other Items
Han et al 2021 33718490[35]	≥100 mL (12 months study follow-up)	A moderate/ severe exacerbation (12 months study follow-up)	Increase ≥4 units in SGRQ (12 months study follow-up)	≥2 units increase in CAT (12 months study follow-up)	
Rabe et al 2021 3317529[36]	≥100 mL (12 months study follow-up)	A moderate/ severe exacerbation (12 months study follow-up)	Increase ≥4 units in SGRQ (12 months study follow-up)	NA	NA
Kerwin et al 2020 33061349[37]	≥100 mL post-bronchodilator FEV_1 (3 months study follow-up) ≥100 mL over the first 6 months	A moderate or severe healthcare resource utilization-related exacerbation (3 months study follow-up)	Increase ≥4 units in SGRQ (3 months study follow-up)	NA	NA
Rabe et al 2020 32646424[38]	≥100 mL (pre-bronchodilator) during at least two consecutive assessments (5 or 6 months apart)	A moderate/ severe exacerbation (48 months study follow-up)	Increase ≥4 units in SGRQ during at least two consecutive assessments (5 or 6 months apart)	NA	NA
Zheng et al 2020 32164675[39]	≥100 mL (6 months study follow-up)	A moderate or severe exacerbation (6 months study follow-up)	Increase ≥4 units in SGRQ (6 months study follow-up)	NA	NA
Chen et al 2020 32021143[40]	≥100 mL (6 months study follow-up)	A moderate or severe exacerbation (6 months study follow-up)	Increase ≥4 units in SGRQ (6 months study follow-up)	NA	NA
Bafadhel et al 2020 31924197[41]	≥100mL pre-dose (6.5 months study follow-up for SHINE and RISE trials, 13 months for SUN and US3 trials)	A moderate or severe exacerbation after the first dose of study medication (6.5 months study follow-up for SHINE and RISE trials, 13 months for SUN and US3 trials)	Increase ≥4 units in SGRQ (6.5 months study follow-up for SHINE and RISE trials, 13 months for SUN and US3 trials)	NA	NA
Maltais et al 2019 31666084[42]	Definition A and B: ≥100 mL Definition C: NA (6 months study follow-up)	Definition A, B and C: moderate or severe exacerbation (6 months study follow-up)	Definition A and C: Increase ≥ 4 units in SGRQ Definition B: NA 6 months study follow-up)	Definition A: NA Definition B and C: ≥2 units increase in CAT (6 months study follow-up)	Definition A and B: NA Definition C: ≥1 unit decrease in TDI (6 months study follow-up)

(*Continued*)

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Table 2 (Continued).

Study, Year, PMID, and Reference	FEV_1 Decline and/or	Exacerbations and/or	SGRQ Increase and/or	CAT Increase and/or	Other Items
Singh et al 2019 30880943[43]	Classic and TRILOGY definition: ≥ 100 mL (12 months study follow-up) Sustained: if maintained at all subsequent visits	Classic and TRILOGY definition: A moderate/ severe exacerbation or death (12 months study follow-up) Alternative sustained CID definition: if accompanied by a CID in FEV1 and/or SGRQ at all subsequent visits (and/or TDI focal score in the additional TRILOGY analysis), or study discontinuation due to the event, or at least one further exacerbation	Classic and TRILOGY definition: Increase ≥ 4 units in SGRQ (12 months study follow-up) Sustained: if maintained at all subsequent visits	Classic and TRILOGY definition: NA	Classic definition: NA TRILOGY definition: ≥1 unit decrease in TDI focal score Sustained: if maintained at all subsequent visits
Naya et al 2018 30191464[44]	≥100 mL (3 months study follow-up)	A moderate/ severe exacerbation (3 months study follow-up)	Increase ≥ 4 units in SGRQ (3 months study follow-up)	NA	NA
Naya et al 2018 30302335[6]	SGRQ-containing CID and CAT-containing CID: ≥100 mL (6 months study follow-up)	SGRQ-containing CID and CAT-containing CID: a moderate/ severe exacerbation (6 months study follow-up)	SGRQ-containing CID: increase ≥ 4 units in SGRQ CAT-containing CID: NA (6 months study follow-up)	SGRQ-containing CID: NA CAT-containing CID: ≥2 units increase in CAT (6 months study follow-up)	SGRQ-containing CID and CAT-containing CID: NA
D'Urzo et al 201829795478[45]	≥100mL pre-dose (GLOW5: 3 months study follow-up; SHINE and GLOW1: 6 months study follow-up; GLOW2: 12 months study-follow-up)	A moderate to severe exacerbation (GLOW5: 3 months study follow-up; SHINE and GLOW1: 6 months study follow-up; GLOW2: 12 months study-follow-up)	Increase ≥ 4 units in SGRQ (GLOW5: 3 months study follow-up; SHINE and GLOW1: 6 months study follow-up; GLOW2: 12 months study-follow-up)	NA	NA
Anzueto et al 201829925383[46]	≥100mL pre-dose (12 months study follow-up)	A moderate to severe exacerbation (12 months study follow-up)	Increase ≥ 4 units in SGRQ (12 months study follow-up	NA	NA
Singh et al 2017 28558833[47]	≥100 mL pre-dose (6 months study follow-up)	A moderate/ severe exacerbation (6 months study follow-up)	Increase ≥ 4 units in SGRQ (6 months study follow-up	NA	≥1 unit decrease in TDI (6 months study follow-up)

Anzueto et al 2017 28496316[7]	Definition 1: ≥100 mL Definition 2: NA (6.5 months study follow-up) Sustained: if present on two consecutive visits at least 4 weeks apart, or on >50% of all subsequent visits	Definition 1 and 2: an on-treatment moderate-to-severe exacerbation (6.5 months study follow-up)	Definition 1 and 2: increase ≥ 4 units in SGRQ (6.5 months study follow-up) Sustained: if present on two consecutive visits at least 4 weeks apart, or on >50% of all subsequent visits	Definition 1 and 2: NA	Definition 1: NA Definition 2: ≥1 unit decrease in TDI (6.5 months study follow-up) Sustained: if present on two consecutive visits at least 4 weeks apart, or on >50% of all subsequent visits
Maleki-Yazdi et al 2017 27796912[48]	≥100 mL (6 months study follow-up) Sustained: ≥100 mL on two consecutive visits, or for ≥50% of all available subsequent visits	A COPD exacerbation (6 months study follow-up) Sustained: if leading to study withdrawal	Increase ≥ 4 units in SGRQ (6 months study follow-up) Sustained: if present on two consecutive visits, or for ≥50% of all available subsequent visits	NA	NA
Singh et al 2016 27445468[2]	≥100 mL (6 months study follow-up)	An on-treatment moderate-to-severe exacerbation (6 months study follow-up)	Increase ≥ 4 units in SGRQ (6 months study follow-up)	NA	NA

Abbreviations: CAT, COPD assessment test; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; PMID, PubMed IDentifier; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

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Pairwise Meta-Analysis

The overall pairwise meta-analysis indicated that the pharmacological treatment of COPD is effective in reducing the risk of CID in COPD (RR: 0.81, 95% CI 0.79–0.84; P < 0.001, GRADE +++) (Figure 2). The effect estimates were affected by high and significant heterogeneity (I^2 92.28%, P < 0.001).

More specifically, when compared to PCB, LABD and dual bronchodilation significantly (P < 0.001) reduced the risk of CID (RR: 0.76, 95% CI 0.70–0.84, GRADE +++ and RR: 0.67, 95% CI 0.60–0.76, GRADE +++, respectively). When compared to LABD, dual bronchodilation, ICS/LABA and triple combination significantly (P < 0.001) reduced the risk of CID (RR: 0.84, 95% CI 0.80–0.87, GRADE +++, RR: 0.89, 95% CI 0.86–0.93, GRADE ++++ and RR: 0.89, 95% CI 0.86–0.92, GRADE ++++, respectively). Triple combination significantly (P < 0.001) reduced the risk of CID (RR: 0.92, 95% CI 0.90–0.95, GRADE ++++) compared to dual bronchodilation. When compared to ICS/LABA, dual bronchodilation and triple combination significantly reduced the risk of CID (RR: 0.91, 95% CI 0.86–0.97, P < 0.01, GRADE +++ and RR: 0.76, 95% CI 0.66–0.87, P < 0.001, GRADE +++, respectively). Only the comparison between LAMA and LABA did not significantly modulate in the risk of CID (RR: 0.94, 95% CI 0.80–1.11, P > 0.05, GRADE +++).

The study arms comparing the same treatment groups were excluded from the pairwise meta-analysis. Namely, the study by Zheng et al, Maltais et al and Singh et al[39,42,47] included a subgroup comparing a long-acting muscarinic antagonist (LAMA) and a LABA, both belonging to the LABDs. The post-hoc analysis by Singh et al[43] included the TRINITY trial,[52] comparing two different triple combinations, while the study by D'Urzo et al[47] compared different LAMAs.

Meta-Regression Analysis

An overall meta-regression analysis was performed for age, to assess whether it might modulate the risk of CID in COPD patients. Although age was not a significant (P > 0.05) potential effect modifier, it resulted a trend toward significance (P = 0.063) in the linear relationship with respect to the RR of CID (slope: 0.051, Figure 3).

When considering specific treatment subgroups, age was a significant (P < 0.05) potential effect modifier for CID only for dual bronchodilation vs PCB and dual bronchodilation vs ICS/LABA subgroups (slope: 0.268 and 0.103, respectively).

The impact of age on CID was also analyzed in association with other characteristics of the study population, namely, gender, smoking habit, post-bronchodilator FEV_1, AECOPD, SGRQ, CAT, and mMRC. Only when associated with post-bronchodilator FEV_1, age significantly modulated the risk of CID (P = 0.027, slope = 0.061), indicating that the pharmacological treatment of COPD is less effective in older patients with reduced lung function. When associated with the other population characteristics, age did not result in a significant modulating factor (P > 0.05).

Among the study characteristics, the duration of the trials represented a significant (P < 0.001) albeit modest potential effect modifier for the risk of CID in COPD (slope: 0.008, Figure S1), suggesting a greater impact of pharmacological treatment in shorter-term studies.

Bias and Quality of Evidence

All studies (100.0%) were ranked as being of medium- to high-quality in agreement with Jadad score (Table 1). One study was of medium quality (Jadad score = 3),[37] and all the others were of high quality (Jadad score >3).

The assessment of the quality of evidence carried out via the GRADE system reported a general moderate (+++) to high-quality (++++) of evidence.

The visual inspection of the funnel plot confirmed the presence of overall heterogeneity, with data reported in an apparent symmetric way. Nevertheless, Egger's test indicated that the overall effect estimates resulting from this meta-analysis were not affected by significant bias and confirmed symmetry for the reported data. Details on the funnel plots and Egger's test analyses are reported in Figure 4.

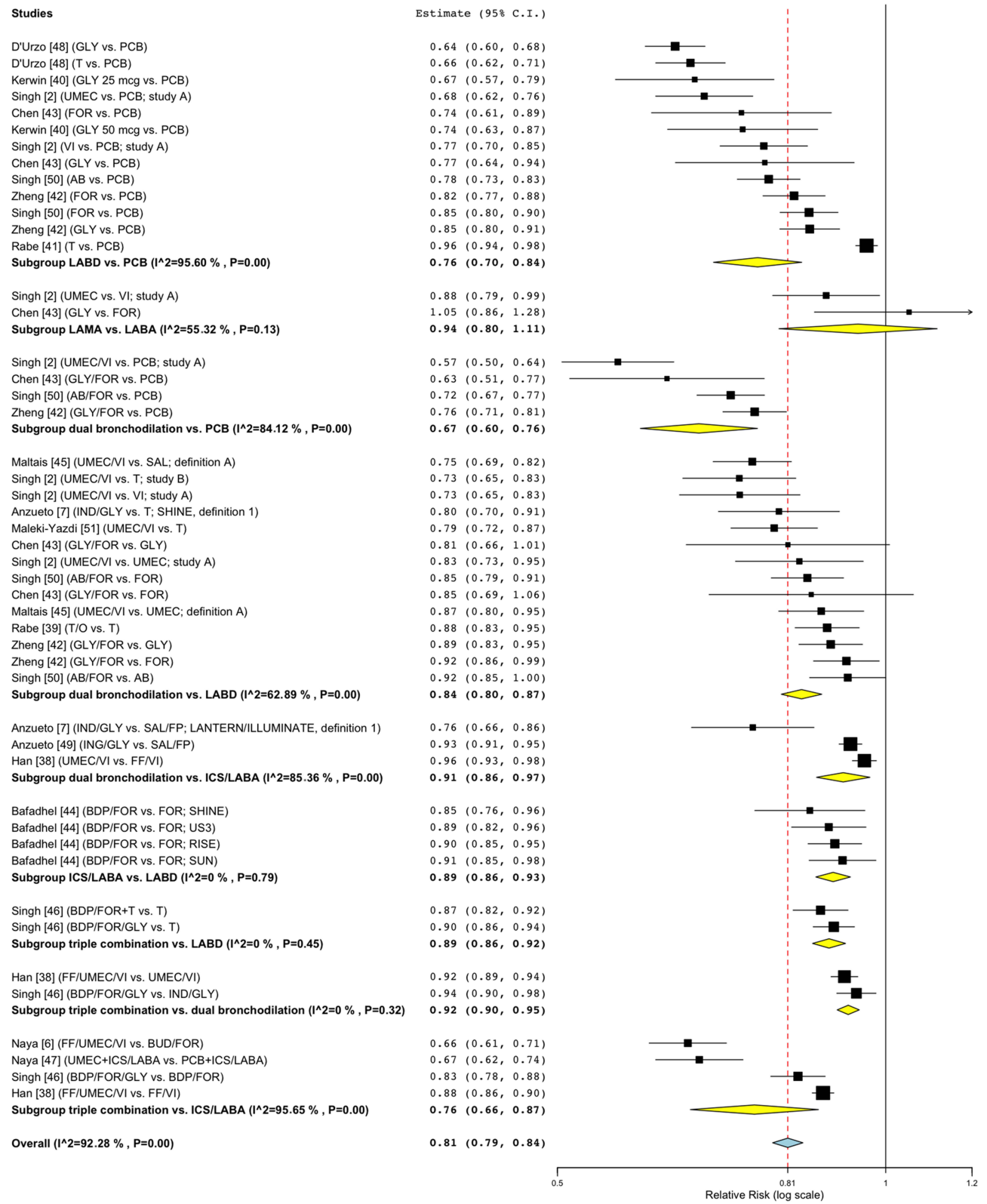

Figure 2 Forest plot of meta-analysis concerning the impact of pharmacological treatment on the risk of CID in COPD.

Notes: The subgroup and overall effect estimates resulting from the meta-analysis are reported in bold; the red-dashed line indicates the average relative risk resulting for the overall effect estimate.

Abbreviations: AB, aclidinium bromide; BUD, budesonide; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium bromide or glycopyrrolate; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2-adrenoceptor agonist; LABD, long-acting bronchodilators; LAMA, long-acting muscarinic antagonist; O, olodaterol; PCB, placebo; SAL, salmeterol; T, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

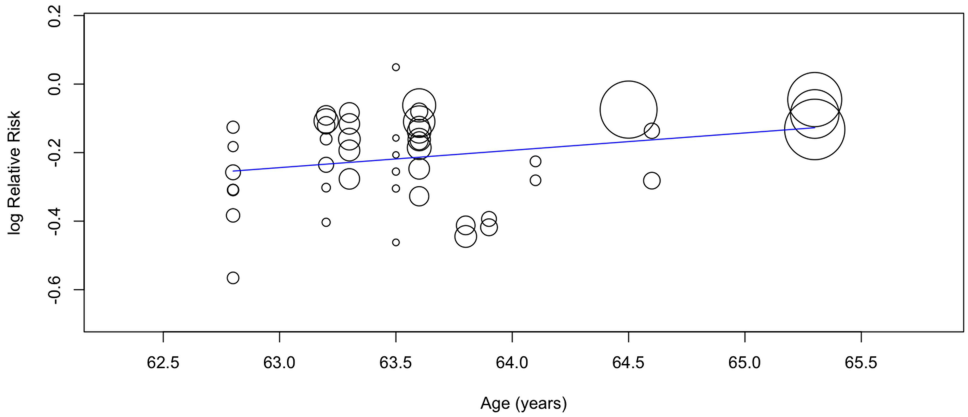

Figure 3 Graphical representation of the meta-regression analysis for age with respect to the risk of CID.
Note: The size of the circles is proportional to the sample weights.
Abbreviation: CID, clinically important deterioration.

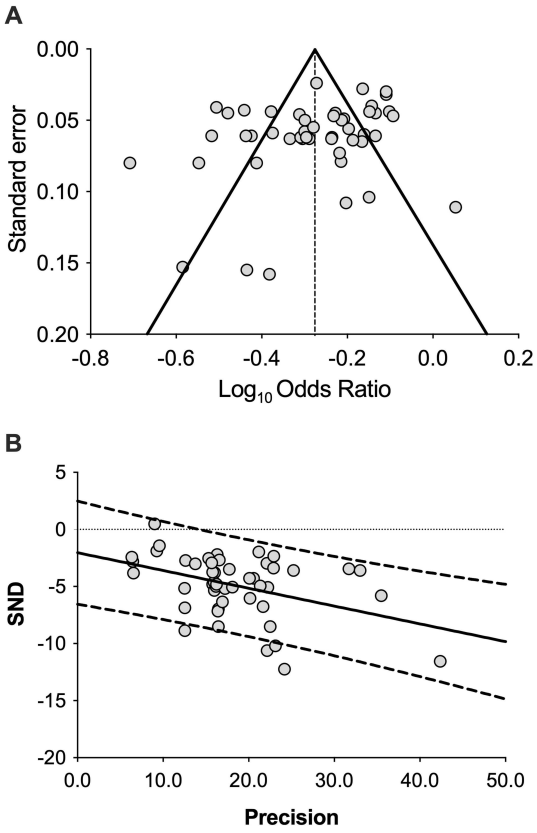

Figure 4 Funnel plot (**A**) and graphical representations of Egger's test (**B**).
Notes: Funnel plot represents a visual approach to check for the existence of publication bias by assessing the symmetry of study distribution, whereas Egger's test is a regression assay that permits to statistically quantify the extent of Funnel plot asymmetry; dotted lines in the Egger's test represent 90% prediction bands.
Abbreviation: SND, standard normal deviate.

Discussion

The findings of this quantitative synthesis indicate with moderate-to-high quality of evidence that the pharmacological treatment of COPD significantly reduces the risk of CID in the overall study population.

Moreover, three specific treatment subgroups, namely, LABD vs PCB, dual bronchodilation vs PCB, and triple combination vs ICS/LABA reached the minimal clinically important difference in the risk of CID, according to a detected RR value ≤0.75, as previously reported.[53,54] As expected, LAMA vs LABA did not modulate the risk of CID. Although data reported a certain level of heterogeneity, Egger's test excluded that results were affected by significant bias.

Thus, the findings of this quantitative synthesis support the use of CID as an outcome for pharmacological trials in COPD, as already suggested in previous narrative reviews.[3,5]

Of note, the meta-regression analysis indicated that age may represent a potential effect modifier for the impact of pharmacological treatment against the risk of CID in COPD, although just a trend towards significance was detected. As a matter of fact, despite the limited range of age between 62.5 and 65.5 years of the investigated population, it resulted that older patients may have a numerical greater risk of CID. Such a narrow age range is related to the intrinsic characteristics of the COPD populations enrolled in the primary RCTs, which evidently appear to differ from the broader demographic diversity detectable among real-life COPD patients. Therefore, it is expected that the impact of ageing could have a significant and detrimental impact on the risk of CID when considering a wider range of age in a real-life setting.

Interestingly, when the meta-regression analysis for age was carried out along with lung function, age significantly modulated the risk of CID when associated with post-bronchodilator FEV_1. On the other hand, the latter evidence suggests that older COPD patients with a larger impairment in lung function may experience a higher risk of CID.

In this regard, the Age, Dyspnea and airflow Obstruction (ADO) index was reported to be a prognostic factor in COPD.[55] Further evidence indicated that the ADO index may be a predictor of 3-year mortality in COPD.[56] It is important to underline that also the occurrence of a CID in the natural history of COPD patients correlates with all-cause mortality,[14,57] supporting the existence of a correlation between CID and age, especially when associated with lower FEV_1.

The evidence that older patients with impaired lung function are more prone to undergo a CID may have a substantial impact on daily clinical practice. In this respect, since the general population ageing is increasing as well as the age at death in COPD patients, and FEV_1 decline is greater in older patients,[9,58] it is expected that the prevalence of elderly COPD patients with poor clinical condition will increase in the future (Figure 5). This COPD population is per se

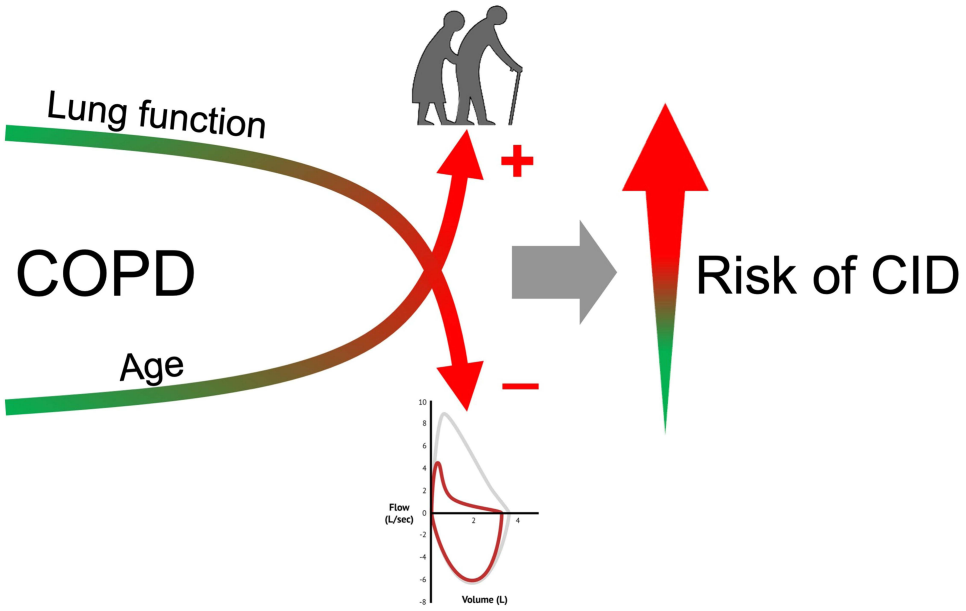

Figure 5 CID risk increases in older patients with worse lung function.
Notes: The meta-regression analysis suggested that age significantly modulates the risk of CID when associated with lower post-bronchodilator FEV_1.
Abbreviation: CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second.

characterized by a higher burden of comorbidities[17,59] that need to be managed properly, especially on the cardiovascular disease counterpart.[60,61] In this scenario, elderly COPD patients not only need to be screened and treated for comorbidities but might also benefit from a tight functional follow-up and an early pharmacological therapy in order to reduce the risk of CID.

The main limitations to this study are intrinsic to the quantitative synthesis methods, which are based on large sample approximations, and to the intrinsic weakness of the included studies.[62,63] Indeed, most of the studies were post-hoc analyses of RCTs, and only one was an RCT prospectively assessing the CID composite endpoint. Moreover, the studies spanned a duration ranging from 3 to 48 months, introducing a certain level of temporal heterogeneity that could potentially act as an effect modifier, suggesting greater efficacy of pharmacological treatment in shorter-term studies. Finally, also the limited age range may represent a limitation of our analysis.

Conclusion

This systematic review and meta-regression analysis indicates that inhaled therapy is effective in reducing the risk of CID in COPD, although such a protective effect may be affected in older patients with reduced lung function. Certainly, further studies designed to directly assess the impact of ageing on CID are needed to confirm these findings in COPD.

Abbreviations

AB, aclidinium bromide; ADO, Age, Dyspnea and airflow Obstruction; AECOPD, acute exacerbation of COPD; ATS, American Thoracic Society; BDP, beclomethasone dipropionate; BID, bis in die, twice daily; BUD, budesonide; CAT, COPD assessment test; CI, confidence interval; CID, clinically important deterioration; COPD, chronic obstructive pulmonary disease; DECiMAL, Data Extraction for Complex Meta-anALysis; FEV_1, forced expiratory volume in the first second; FF, fluticasone furoate; FOR, formoterol fumarate; FP, fluticasone propionate; FVC, forced vital capacity; GLY, glycopyrronium bromide or glycopyrrolate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HRQL, health-related quality of life; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; mMRC, modified medical research council dyspnea scale; NA, not available; O, olodaterol; PICO, Patient problem, Intervention, Comparison, and Outcome; PCB, placebo; PMID, PubMed Identifier; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; PRO, patient-reported outcome; QD, quaque die, once daily; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting β2-adrenoceptor agonist; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; SGRQ, St. George's Respiratory Questionnaire; T, tiotropium bromide; TDI, Transition Dyspnea Index; UMEC, umeclidinium bromide; VI, vilanterol.

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Author Contributions

All the authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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