Online Supplement

Inhaled Corticosteroids and Risk of Cardiovascular Disease in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Regression

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Table E1: Search terms

COPD	ICS	CVD
Chronic obstructive lung disease/	Budesonide/ Fluticasone/ Beclomethasone/ Inhaled corticosteroid	Myocardial infarction Heart failure Stroke Cardiovascular disease

Table E2: Patient characteristics of studies included

Study authors and year	Exposure	Mean age (SD)	% males	Ethnicity or Social Deprivation Scores (%)
Löfdahl et al. 2007 (14)	Placebo	52.4 (7.7)	72.2	
	BUD (800µg)	52.5 (7.5)	73.5	
Calverley et al. 2010 (15)	Placebo	65.1 (8.1)	76	
	FP (500 µg)	65.1 (8.4)	75	
	SAL/FP	65.0 (8.3)	75	
Vestbo et al. 2016 (16)	Placebo	65 (8)	75	
	FF (100µg)	65 (8)	74	
	FF/VI (100µg/50µg)	65 (8)	76	
Dransfield et al. 2018* (12)	Placebo	NA	NA	
	FF (100 µg)	NA	NA	
	FF/VI (100/(25 µg)	NA	NA	
Vaz Fragoso et al. 2019 (17)	Placebo	64.8 (8.2)	75.6	White: 81.5, American Hispanic: 3.3, African American: 1.5, Asian: 13.1, Other: 0.7
	Sal (50 µg)	64.8 (8.2)	76.7	White: 81.4, American Hospanic: 3.0, African American: 1.3, Asian: 13.4, Other: 1.0
	Fluticasone (500 µg)	64.8 (8.5)	75.5	White: 80.9, American Hispanic: 3.1, African American: 1.5, Asian: 13.6, Other: 0.9
	Fluticasone/Sal (500/50 µg)	64.8 (8.3)	74.8	White: 81.3, American Hispanic: 3.2, African American: 1.5, Asian: 13.1, Other: 0.8
Day et al. 2020* (11)	UMEC/VI (62.5/25µg)	65.2 (8.3)	66	
	FF/UMEC/VI (100/62.5/25µg)	65.3 (8.2)	67	
Huiart et al. 2005*(5)	No ICS use	77.7 (3.8)	50.8	
	ICS-combinations	77.7 (8.6)	65.5	
Short et al. 2011 (18)	SABA, SAMA, or SABA/SAMA	70.5 (10.2)	52.3	
	ICS mono	69.7 (9.8)	51.5	
	ICS + LAMA	69.1 (9.2)	44.3	

	ICS/LABA	68.9 (9.6)	54.9	
	ICS/LABA/LAMA	68.3 (8.9)	52.3	
Manoharan et al. 2014 (19)	LABA, LAMA or LABA/LAMA	70 (9)	51	
	ICS combinations	69.9 (9)	52	
Lin et al. 2015* (10)	Total population	NA	80.6	
Aljaafareh et al. 2016 (20)	Total poulation	NA	49.4	
Samp et al. 2017 (21)	LABA/LAMA	29.1% ≥ 65 years	54.4	
	LABA/ICS	59.0% ≥ 65 years	40.0	
Patel et al. 2020 (13)	LABA, LAMA or LABA/LAMA	72.1 (0.06)	64.4	IMD 1: 14.5; 2: 19.3; 3: 23.0; 4: 24.6; 5: 18.7
	Any LABA/ICS	71.5 (0.06)	63.4	IMD: 1: 14.7; 2: 19.2; 3: 22.6: 4: 24.2; 5: 19.4
Wang et al. 2021 (22)	IND/GLY	71.67	78.3	
	VI/UMEC	71.47	78.6	
	SAL/FP	71.79	77.1	
	FF/BUD	71.86	78.2	
	FF/BDP	71.81	77.3	
Rebordosa et al. 2022 (23)	LABA	69.4 (10.7)	50.1	IMD 1: 17.0; 2: 18.3; 3:19.8; 4: 20.9; 5: 24.0
	LABA/ICS	68.9 (11.5)	48.4	IMD 1: 16.1; 2: 17.9; 3: 19.2; 4: 21.7: 5: 25.1

Legend: NA (not applicable) when mean age or proportion of men could not be obtained from the manuscript alone. Only 1 paper included ethnicity estimates and 2 papers included IMD quintiles. IMD (Index of Multiple Deprivation)

Table E3: Risk of bias in RCT studies

Study Authors	Random sequence	Allocation concealment	Reporting bias	Other bias	Performance bias	Detection bias	Attrition bias
Calverley 2010	Low	Low	Low	Moderate	Low	Low	Low
Day 2020	Low	Low	Low	Low	Low	Low	Low
Vestbo 2016	Low	Low	Low	Low	Low	Low	Low
Lofdahl 2007	Low	Low	Low	Low	Low	Low	Low
Fragoso 2019	Moderate	Low	Low	Low	Low	Low	Low
Dransfield 2020	Moderate	Low	Low	High	Low	Low	Low

Table E4:Risk of bias in observational studies

Study Authors	Confounding bias	Selection bias	Classification bias	Deviation from intended intervention bias	Attrition bias	Measurement of outcome bias	Selection of reported results bias
Aljaafareh 2016	Moderate	Moderate	Low	Low	Low	Low	Low
Huiart 2005	Moderate	Low	Low	Low	Low	Low	Low
Lin 2015	Severe	Low	Low	Low	Low	Low	Low
Manohoran 2014	Low	Low	Low	Low	Low	Low	Low
Patel 2020	Moderate	Low	Low	Low	Low	Low	Low
Rebordosa 2021	Low	Moderate	Low	Low	Moderate	Low	Low
Samp 2017	Moderate	Moderate	Low	Low	Low	Low	Low
Short 2011	Low	Low	Low	Low	Low	Low	Low
Wang 2021	Moderate	Low	Low	Moderate	Low	Low	Low

Support for judgement for RCT studies

Author & year: Calverley 2010		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Low	Quote: "TORCH was a randomised, double-blind, placebo controlled study" Comment: Probably done
Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcomes measured in methods section were reported in results
Other sources of bias *Other bias*	Moderate	Quote: "No specific information was collected about whether patient-reported AEs had been objectively verified." Comment: Self reporting bias possible as participants reported events however mitigated as standard questions at intervals were asked
Blinding of participants and personnel *Performance bias*	Low	Quote: ''randomized, double-blind, placebo-controlled study''
Blinding of outcome assessment *Detection bias*	Low	Quote: ''likely cause of death which was adjudicated by an expert panel blinded to the study medication''
Incomplete outcome data *Attrition bias*	Low	Quote: "The proportion of patients who withdrew from the study was highest in the placebo group (44%) and lowest in the SFC group (34%) (SAL 37%, FP 39%)." Comment: ITT analysis was done

Author & year: Day 2020		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Low	Quote: ''Patients will be randomised using the proprietary RandAll software (GlaxoSmithKline), and assigned to treatment using the Randomisation and Medication Ordering System (RAMOS; GlaxoSmithKline).'' Comments: Refers to IMPACT trial and probably done
Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcome measures listed in the methods section were reported in the results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: ''IMPACT was a 52-week, randomized, double-blind, multicenter Phase III study''
Blinding of outcome assessment *Detection bias*	Low	Quote: ''a separate adjudication committee will be established to independently review

		and categorise the cause of each serious adverse event (SAE) and death in the study. The committee members will remain blinded to treatment.'' Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: "assess the CV safety of FF/UMEC/VI versus FF/VI and UMEC/VI in the intent-to-treat (ITT) population of the IMPACT trial" 6% withdrew from triple therapy, 8% withdrew from FF/Vi and 9% withdrew for UMEC/Vi

Author & year: Vestbo 2016		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Low	Quote: ''Participants were randomly assigned (1:1:1:1) through a centralised randomisation service " Comment: probably done
Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcome measures listed in the methods section were reported in the results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: "In this double-blind randomised controlled trial (SUMMIT)'' Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: ''only the database administrators having knowledge of treatment assignment.'' Comment: Probably done as investigators were unaware of the allocated treatment
Incomplete outcome data *Attrition bias*	Low	Quote:" More patients withdrew from study medication in the placebo group (29%) than in the three other groups: the lowest withdrawal rates were seen with combination therapy (23%)." Comments: ITT analysis and all randomised patients included, however withdrawal rates differed between groups

Author & year: Löfdahl 2007		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Low	Quote: ''EUROSCOP study was a 3-yr, double-blind, randomised, multicentre, placebo-controlled study'' Comment: Probably done

Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcome measures listed in the methods section were reported in the results
Other sources of bias *Other bias*	Low	No other sources of bias found
Blinding of participants and personnel *Performance bias*	Low	Quote: ''double blind, multicentre study'' Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: ''double blind'' Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: ''Among the 1,175 evaluated patients, 132 were discontinued due to an adverse event (70 budesonide, 62 placebo) and 131 were discontinued due to other reasons (65 budesonide, 66 placebo)'' Comment: Randomised patients were included in an ITT analysis, withdrawal rates similar between groups.

Author & year: Fragoso 2019		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Moderate	Quote: ''Of the original 6112 TORCH participants with GOLD-based moderate-to-severe COPD, 5688 (93.1%) had GLI-based moderate-to-severe COPD, which defined our primary analytical sample. We thus excluded 424 TORCH participants, of whom 420 had GLI-based restrictive-pattern, 3 had GLI-based normal-for age spirometry, and 1 had GLI-based mild COPD.'' Comment: Potential confounding introduced as authors acknowledge due to GLI reclassification of TORCH trial.
Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcome measures listed in the methods section were reported in the results
Other sources of bias *Other bias*	Low	No other sources of bias
Blinding of participants and personnel *Performance bias*	Low	Quote: ''double blind'' Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: ''Outcomes were centrally adjudicated by TORCH investigators, blinded to treatment assignment.'' Comment: Probably done
Incomplete outcome data *Attrition bias*	Low	Quote: ''All analyses of primary and secondary outcomes were performed

		according to a modified intention-to-treat principle. Comment: Authors suggest ITT analysis

Author & year: Dransfield 2018		
Domain	**Risk of bias**	**Support for judgement**
Random sequence generation Selection bias	Serious	Quote: 'The use of baseline β-blocker therapy at study entry was not randomized, and changes in β-blocker use during the trial were not captured precisely."
Allocation concealment *Selection bias*	Low	Comments: Double-blind, probably done
Selective reporting *Reporting bias*	Low	All outcome measures listed in the methods section were reported in the results
Other sources of bias *Other bias*	High	Quote: "As such, it remains possible that our results could be affected by residual bias, including confounding by indication, and causal interactions between β-blocker use and the response to inhaled treatments cannot be determined."
Blinding of participants and personnel *Performance bias*	Low	Quote: "In this double-blind randomised controlled trial (SUMMIT)'' Comment: Probably done
Blinding of outcome assessment *Detection bias*	Low	Quote: ''only the database administrators having knowledge of treatment assignment.'' Comment: Probably done as investigators were unaware of the allocated treatment
Incomplete outcome data *Attrition bias*	Low	Quote:" In addition, although compliance with the inhaled treatments was excellent (96 to 97% across treatment groups, regardless of whether the patient was receiving β-blockers at study entry), we do not know whether β-blockers were continued after enrollment or if patients were compliant Comments: ITT analysis was prespecified.

Support for judgement for observational studies

Author & year: Aljaafareh et al 2016		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Moderate	Comment: Used oxygen supplement instead of validated COPD severity measures
Bias in selection of participants into the study	Moderate	Comment: All participants from a private insurance company, poor external validity; COPD and CVD risk associated with Socio-Economic Status
Bias in classification of interventions	Low	Comment: Intervention clearly defined
Bias due to deviations from intended interventions	Low	Comment: No deviation from usual practice likely
Bias due to missing data	Low	Comment: Data were reasonably complete
Bias in measurement of outcomes	Low	Comment: The methods of outcome assessment were comparable across intervention groups; *and* outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants
Bias in selection of the reported result	Low	All outcomes measured reported

Author & year: Huiart et al 2005		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Moderate	Quote: ''To confound the association between ICS and AMI, current smoking would have to be associated with the use of ICS, even after adjusting for the number of exacerbations and concomitant respiratory medications.'' Comment: Analysis was adjusted for the number of exacerbations and the quantity of medication (COPD severity) but residual confounding may be present with smoking status
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention clearly defined
Bias due to deviations from intended interventions	Low	Comment: No deviations from usual practice mentioned
Bias due to missing data	Low	Comment: Data were reasonably complete
Bias in measurement of outcomes	Low	Comment: The methods of outcome assessment were comparable across intervention groups; *and* outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants
Bias in selection of the reported result	Low	All outcomes measured were reported

Author & year: Lin et al 2015		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Serious	Comment: COPD severity unaccounted for. Important confounding factors including smoking, drinking, body mass index was not recorded in data but were accounted for by a two-stage calibration approach.
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention clearly defined
Bias due to deviations from intended interventions	Low	Quote: Deviations beyond normal practice unlikely.
Bias due to missing data	Low	Comment: Outcome data was available for nearly all participants
Bias in measurement of outcomes	Low	Comment: Stroke risk measured in control and intervention groups unlikely to be biased.
Bias in selection of the reported result	Low	All outcomes measured were reported.

Author & year: Manoharan et al 2014		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Low	Quote: "We minimised confounding by including clinically important covariates in the analysis. Indeed, one strength of our database is that we were able to factor in severity markers such as FEV_1 and oxygen saturation." Comment: Did not perform a time-dependent analysis of the various treatments but otherwise has accounted for all clinically relevant covariates
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention clearly defined.
Bias due to deviations from intended interventions	Low	Comment: No deviation from usual practice likely
Bias due to missing data	Low	Comment: Data were reasonably complete. No mention of missing FEV1
Bias in measurement of outcomes	Low	Comment: The methods of outcome assessment were comparable across intervention groups; *and* outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants
Bias in selection of the reported result	Low	All outcomes measured were reported

Author & year: Patel et al 2020		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Low	Comment: Twenty three confounders adjusted for including COPD severity.
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention groups are well defined
Bias due to deviations from intended interventions	Low	Comment: co-interventions were balanced across treatment groups and intervention seemed to be implemented successfully, deviation from clinical practice unlikely
Bias due to missing data	Low	Quote: ''Co-variates with missing data were social deprivation score, smoking status and GOLD classification." Comment: Authors applied multiple imputations to account for missing data of covariates listed above and outcome data was otherwise available for nearly all participants.
Bias in measurement of outcomes	Low	Comment: The methods of outcome assessment were comparable across intervention groups
Bias in selection of the reported result	Low	All outcomes measured were reported.

Author & year: Rebordosa et al 2021		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Low	Comment: adjusted for all clinically relevant covariates appropriately
Bias in selection of participants into the study	Moderate	Comment: Selection of participants was based on characteristics observed before the start of intervention found in HES and CRPD GOLD (patient data from the primary health care setting). However, only patients with complete data were included.
Bias in classification of interventions	Low	Comment: Intervention clearly defined
Bias due to deviations from intended interventions	Low	Comment: Deviations beyond normal practice unlikely.
Bias due to missing data	Moderate	Comment: Patients were excluded if they had missing data on smoking or BMI
Bias in measurement of outcomes	Low	Comment: Authors state a consistent method for detecting heart failure and this method is applied to all groups
Bias in selection of the reported result	Low	All outcomes measured were reported.

Author & year: Samp et al 2017		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Moderate	Comment: Possible confounders like smoking status and FEV1 not included.
Bias in selection of participants into the study	Moderate	Quote: "Our source of data was health insurance claims from the Truven Health…" Comment: Potential for selection bias as participants with access to health insurance may be systematically different.
Bias in classification of interventions	Low	Comment: Intervention clearly defined
Bias due to deviations from intended interventions	Low	Comment: No deviations from usual practice were mentioned
Bias due to missing data	Low	Comment: Data were reasonably complete
Bias in measurement of outcomes	Low	Comment: The methods of outcome assessment were comparable across intervention groups; *and* outcome measures was unlikely to be influenced by knowledge of the intervention received by study participants
Bias in selection of the reported result	Low	Comment: All outcome measures were reported

Author & year: Short et al 2011		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Low	Comment: Cox-proportional hazards conducted on clinically relevant covariates.
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention clearly defined.
Bias due to deviations from intended interventions	Low	Comment: Deviations beyond normal practice unlikely.
Bias due to missing data	Low	Comment: Data available for nearly all participants.
Bias in measurement of outcomes	Low	Comment: Major outcome is all-cause mortality; low probability of bias in measurement.
Bias in selection of the reported result	Low	All outcomes measured reported.

Author & year: Wang et al 2021		
Domain	**Risk of bias**	**Support for judgement**
Bias due to confounding	Moderate	Quote: "We examined five dimensions of confounders according to a comprehensive literature review, including demographics, proxy indicators of COPD severity, health care uses, comorbidities, and comedications in the year before cohort entry" Comment: Whilst some COP severity confounders were adjusted for FEV1 was not.
Bias in selection of participants into the study	Low	Comment: Low risk of selection bias of participants into the study
Bias in classification of interventions	Low	Comment: Intervention groups are well defined
Bias due to deviations from intended interventions	Moderate	Quote: "LABA/LAMA or LABA/ICS initiators may have discontinued their inhaled medication as a result of exacerbations" Comment: Discontinued medication could have potentially biased the results if exacerbations were worse in one group
Bias due to missing data	Low	Comment: Data available for nearly all participants
Bias in measurement of outcomes	Low	Quote: "The adopted algorithms for identifying pneumonia, acute myocardial infarction, heart failure, and ischemic stroke have been validated with high accuracy" Comment: Probably done
Bias in selection of the reported result	Low	Comment: All outcomes measured were reported in results