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Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD

Y.K. Loke*, C.S. Kwok# and S. Singh¶

ABSTRACT: The effect of long-term inhaled corticosteroid (ICS) use on myocardial infarction (MI) and cardiovascular (CV) death in chronic obstructive pulmonary disease (COPD) remains uncertain.

We conducted a systematic search of MEDLINE, EMBASE, ISI, regulatory documents and manufacturers' trial registries for long-term (>24 weeks duration) randomised controlled trials (RCTs) or controlled observational studies reporting on CV outcomes or death with ICS use in COPD. A fixed effects model was used to calculate the relative risks (RRs) and 95% CIs.

23 RCTs with 24–160 weeks of follow-up were included. In the RCTs, ICS were not associated with a significantly reduced risk of MI (RR 0.95, 95% CI 0.73–1.23; p=0.68, I^2=0%), CV death (RR 1.02; 95% CI 0.81–1.27; p=0.89, I^2=0%), or mortality (RR 0.96, 95% CI 0.86–1.07; p=0.43, I^2=0%). In the observational studies, ICS use was associated with a significant reduction in CV death (two studies: RR 0.79, 95% CI 0.72–0, 86; p <0.0001, I^2=44%) and mortality (11 studies: RR 0.78, 95% CI 0.75–0.80; p<0.001, I^2=33%). Publication bias *via* funnel plot asymmetry was noted for mortality in the observational studies (Egger test, p=0.05).

We conclude that while observational studies suggest that ICS may potentially confer CV or mortality benefit, RCTs failed to show any significant effect of ICS therapy on MI or CV death. These conflicting findings need to be clarified through further research.

KEYWORDS: Cardiovascular effects, chronic obstructive pulmonary disease, inhaled corticosteroids, meta-analysis, mortality

AFFILIATIONS
*Dept of Clinical Pharmacology, #School of Medicine, University of East Anglia, Norwich, UK. ¶Dept of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

CORRESPONDENCE
S. Singh
Section on General Internal Medicine, Dept of Medicine
Johns Hopkins University School of Medicine; Suite 8063
E 1830 Monument St
Baltimore
MD 21287
USA
E-mail: ssingh31@jhu.edu

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Inhaled corticosteroids (ICS) such as fluticasone propionate, budesonide and beclometasone are widely used in chronic obstructive pulmonary disease (COPD) [1]. According to the current Global Initiative for Chronic Obstructive Lung Disease guidelines, ICS are indicated in combination with long acting β_2-agonists (LABA) in patients with moderate-to-severe COPD to reduce the frequency of exacerbations [2].

ICS may potentially reduce cardiovascular (CV) events by alleviating the systemic inflammation responsible for atherogenesis in patients with COPD [3]. CV and mortality benefits with ICS have been reported in observational studies in patients with COPD [4, 5]. However, it remains uncertain whether this beneficial effect is seen in randomised controlled trials (RCTs). CV disease is an important cause of morbidity and mortality among patients with COPD [6]. The strength of association between ICS use and CV events and mortality and the magnitude of any potential benefit needs critical evaluation.

Our primary objective was to systematically ascertain the risk of myocardial infarction (MI) or CV death associated with long-term use of ICS compared with control therapies in COPD. As a secondary objective, we aimed to ascertain the effects of ICS on overall mortality.

METHODS

Inclusion criteria

Our inclusion criteria for RCTs were as follws: 1) a study design consisting of parallel-group RCTs for any ICS (fluticasone, beclomethasone, budenoside or triamcinolone) of ⩾24 weeks duration; 2) study participants with COPD of any severity; 3) an ICS as the intervention drug *versus* control treatment, in which the comparison groups consisted of ICS *versus* placebo or ICS in combination with LABA

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versus LABA alone; and 4) the trials had to explicitly report data (including zero events) on the incidence of MI, CV death or overall mortality.

Controlled observational studies (case control, prospective cohort or retrospective cohort) reporting on MI or mortality with ICS exposure compared to those without ICS exposure in COPD were also evaluated.

Exclusion criteria

We restricted the analysis of RCTs to trials of >24 weeks duration to evaluate the long-term CV effects of ICS use. RCTs in patients with asthma or acute exacerbations of COPD were excluded.

Search strategy

An initial search which yielded 30 long-term RCTs of ICS from 651 citations was originally carried out in May 2008 as part of an earlier systematic review [7], covering PubMed and EMBASE by using the clinical trial filters in conjunction with drug and disease search terms (''fluticasone'' or ''budesonide'' or ''beclometasone'' or ''beclomethasone'') and ''chronic'' and ''obstructive''. Y.K. Loke and C.S. Kwok continued updating the search until April 30, 2009, and added the drug term ''triamcinolone'' to the above trial search with no language restrictions. A separate search string was used to identify observational studies: ''inhaled corticosteroids'' AND ''cohort OR case–control'' AND ''mortality OR death OR myocardial OR cardiovascular'' AND ''chronic obstructive''. Published and unpublished trials were retrieved from the Cochrane Database of systematic reviews, websites of the US Food and Drug Administration, European regulatory authorities, manufacturers' product information sheets and the manufacturers' clinical trials register of fluticasone and beclometasone (GlaxoSmithKline) [8], and budesonide (AstraZeneca) [9]. The bibliographies of included studies and the Web of Science Cited References search were used to identify relevant citing articles.

Study selection

Two reviewers (Y.K. Loke and C.S. Kwok) independently and in duplicate scanned all titles and abstracts that indicated the study was an RCT or observational study evaluating the use of ICS in patients with COPD. After obtaining full reports of potentially relevant RCTs and observational studies, the same two reviewers independently assessed eligibility from full text articles. Full consensus regarding eligibility and matching between journal publications and company trial reports was obtained after consultation with a third reviewer (S. Singh).

Study characteristics

A pre-specified protocol was used to record: the location and duration of the RCT (in weeks); the spirometric criteria used to diagnose COPD in participants; the primary outcome measure; the dose and frequency of ICS and control interventions; mean age and sex of participants; the severity of COPD in the participants as mean predicted forced expiratory volume in 1 s (FEV_1); previous ICS corticosteroid use; and the proportion of current smokers and patients with pre-existing CV disease or CV risk factors when available. The design and relevant data sources, duration of follow-up, the number of study participants and their selection criteria were recorded for the observational studies.

Risk of bias assessment

Two reviewers independently and in duplicate assessed the reporting of blinding, allocation concealment, withdrawals and the loss to follow-up in RCTs. To determine the strength of adverse event monitoring, the frequency and type of adverse event monitoring during the follow-up period were evaluated based on the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* on assessing adverse effects [10]. Information on the selection of participants, the comparability of cases and controls, and methods used in ascertaining exposure and outcomes, and the sources of support were extracted for the observational studies. The risk of publication bias was assessed using funnel plot and Egger's test. Evidence of asymmetry from Egger's test was considered to be a p-value <0.1 [11].

Outcome measures

The end-points of incidents of fatal and nonfatal MI and CV death were pre-specified as the co-primary outcome measures. A composite CV mortality end-point comprising of fatal MI, fatal stroke, sudden death, cardiac arrest and fatal arrhythmias was constructed for trials that did not report on the specific end-point of CV death but provided mortality data on individual CV end-points [12]. The CV end-points were ascertained through routine serious adverse events (life threatening, require hospitalisation or lead to significant disability or death) reported within each trial and may not have been prospectively defined in a uniform fashion across the trials, because none of the RCTs were prospectively designed to assess the CV risk of ICS use. The end-point of all-cause mortality or overall mortality (inclusive of CV death) was pre-specified as the secondary outcome measure.

Data extraction

Two reviewers independently and separately extracted data (including zero events) on MI, CV death and mortality among trial listings of adverse events or serious adverse events. Data in the clinical trials register and the regulatory documents were reconciled with data in the published journal article when possible, and authors were contacted for data clarification where needed. If there were multiple reports for a particular study, data from the recent versions were extracted. We avoided double counting of trials by cross checking published and unpublished studies. We extracted the crude and adjusted risk ratios for CV events and mortality from the observational studies. Two reviewers (Y.K. Loke and C.S. Kwok.) were independently involved in all stages of study selection, data extraction and risk of bias assessment. Discrepancies were resolved with 100% agreement after rechecking the source papers, further discussion among the reviewers, and consultation with a third reviewer (S. Singh), with full consensus obtained before drafting the article.

Statistical analysis

RevMan (version 5.021; Nordic Cochrane Center, Copenhagen, Denmark) was used to calculate relative risk (RR) and 95% CI for the outcome of MI, CV death and all-cause mortality. Outcome data on trial participants were analysed using a 2×2 format according to the ''intention to treat'' principle. All

reported p-values are two sided with significance set at <0.05. Statistical heterogeneity was assessed using the Cochrane I^2 statistic, with I^2 >25% indicating moderate statistical heterogeneity and I^2 >50% indicating a substantial level of heterogeneity [13]. We planned to pool data across studies using the fixed-effects models if substantial statistical heterogeneity was not present. If substantial statistical heterogeneity was present (I^2 >50%), we planned to explore sources of heterogeneity and the effect of individual study characteristics and subgroups on the risk estimates.

A predefined sensitivity analyses was performed to explore the influence on effect size of the choice of comparators, statistical models (fixed *versus* random effects), duration of the trials (limited to the trials >1 yr in duration), and the risk of bias by restricting the analysis to RCTs at low risk of bias (adequate sequence generation, allocation concealment and double-blinding, with clear reporting of loss to follow-up). We evaluated the effect of ICS dose by excluding data from intervention arms where participants were randomised to lower doses of ICS (fluticasone ⩽500 μg daily and budesonide ⩽400 μg daily).

Risk ratios (RR or hazard ratio, adjusted where available) from the observational studies were pooled separately from the RCTs, using the generic inverse variance method with fixed effects model. We assumed similarity between the risk ratio and OR because CV events and deaths were assumed to be rare events [14].

RESULTS

Trial characteristics

The flow chart of study selection is shown in figure 1. Of the 715 citations retrieved, 23 RCTs fulfilled our inclusion criteria [15–37]. Trial characteristics are shown in table 1. These trials enrolled a total of 23,396 participants with COPD, with 12,332 receiving ICS *versus* 11,064 controls. The duration of the trials ranged from 24 to 160 weeks, with 16 trials being longer than 52 weeks in duration [15–20, 22, 23, 25, 27–29, 32, 33, 36, 37]. The sample size was variable and the number of participants in the trials ranged from 186 [23] to 6,184 [18]. Inhaled fluticasone was evaluated in 16 trials [15–18, 20–27, 30, 31, 35, 37], inhaled budesonide in six trials [19, 28, 32–34, 36], and inhaled triamcinolone in only one trial [29]. Most trials enrolled participants with severe COPD, as the mean FEV_1 of the participants was <50% for the majority of trials, compared to >50% for only a few trials [28, 29, 35]. The majority of the participants were males, with proportions of current smokers ranging from 22% [35] to 90% [29]. COPD was consistently defined in the RCTs with spirometric criteria and the majority of trials excluded patients with asthma, except the Lung Health Study [29] which had <10% of participants with asthma in both arms. The trial by PAGGIARO *et al.* [31] had some patients with atopy [31], while SCO40041 [23] and SCO3002 did not specify these exclusions [25].

The trial quality was variable (table 2). All the RCTs had blinding of participants and personnel [15–37]. The loss to

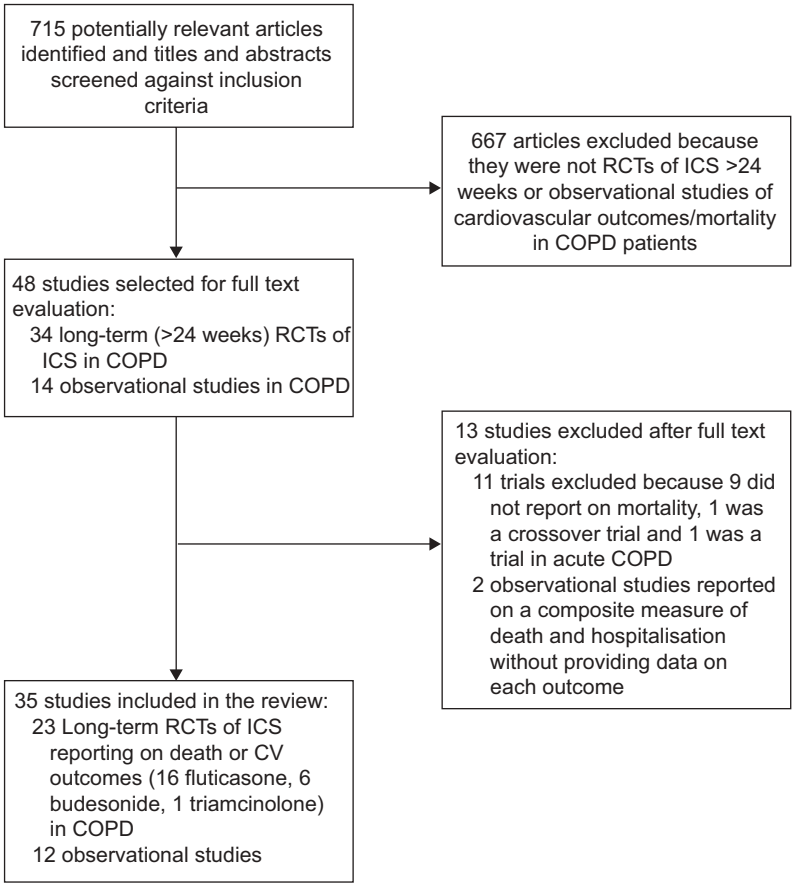

FIGURE 1. Flow chart showing the study selection. RCTs: randomised controlled trials; ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; CV: cardiovascular.

TABLE 1 Characteristics of randomised controlled trials included in the analysis of cardiovascular (CV) events and mortality

Study [Ref.]	Location	Treatment duration weeks	COPD criteria	Primary outcome	Concomitant cardiac conditions and exclusions	Drug	Male	Age yrs	FEV1 % pred	Prior ICS use	Current smokers
Aaron [15]#	27 centres in Canada	52	FEV1/FVC <70%	COPD exacerbation	HTN: 41.4 %; CAD: 22.8%; CHF: 3.5%	Salmeterol/fluticasone combination 50/500 μg *b.i.d.*	57.9	67.5±8.9	39.4±11.9	70.8	32.4
					HTN: 43.9%; CAD: 21.0%; CHF: 1.4% Excluded CHF with LV dysfunction	Salmeterol xinafoate 50 μg	57.4	67.6±8.2	38.0±13.1	78.8	24.3
Burge [16]	18 UK hospitals	156	FEV1/FVC <70%	Decline in FEV1	NA	Fluticasone propionate 500 μg *b.i.d.*	75	63.7±7.1	50.3±14.9	51.1	36.4
						Placebo	74.2	63.8±7.1	50.0±14.9	57.0	39.2
Calverley [17]	196 centres in 25 countries	52	ERS	FEV1	NA	Salmeterol/fluticasone combination 50/500 μg *b.i.d.*	75	62.7±8.7	44.8±14.7	50	52
						Salmeterol xinafoate 50 μg *b.i.d.*	70	63.2±8.6	44.3±13.8	49	51
						Fluticasone propionate 500 μg *b.i.d.*	70	63.5±8.5	45±13.6	54	53
						Placebo	75	63.4±8.6	44.2±13.7	52	47
Calverley [19]	109 centres in 15 countries	52	GOLD	FEV1 and HRQoL	NA	Formoterol 9 μg/budesonide 400 μg *b.i.d.*	78	64±NA	36±10	47	33
					Excluded any CV disorder	Formoterol 9 μg *b.i.d.*	75	63±NA	36±10	48	36
						Budesonide 400 μg *b.i.d.*	74	64±NA	36±10	51	39
						Placebo	75	65±NA	36±10	46	30
Calverley [18]	44 centres in 42 countries	156	ERS	Mortality	NA	Salmeterol/fluticasone combination 50/500 μg *b.i.d.*	75	65±8.3	44.3±12.3	47	43
						Salmeterol xinafoate 50 μg	76	65.1±8.2	43.6±12.6	45	43
						Fluticasone propionate 500 μg *b.i.d.*	75	65±8.4	44.1±12.3	47	43
						Placebo	76	65±8.2	44.1±12.3	51	43
Ferguson [20]	94 centres in North America	52	ATS	Rate of exacerbations	NA	Salmeterol/fluticasone combination 50/250 μg *b.i.d.*	58.3	64.9±9.0	39.8±13.9	15	40
						Salmeterol xinafoate 50 μg *b.i.d.*	52.0	65.0±9.1	50.6±15.4	18	38
FLTA3025 [21]	55 centres in the USA	24	ATS	FEV1	NA	Fluticasone propionate 500 μg *b.i.d.*	66	63.3±10	1301±500+	NA	NA
						Fluticasone propionate 250 μg *b.i.d.*	72	65.2±8.7	1240±486+	NA	NA
						Placebo	70	64.8±9.5	1221±502+	NA	NA
Hanania [26]	76 centres in the USA	24	ATS	FEV1	Excluded abnormal ECG	Salmeterol/fluticasone combination 50/250 μg *b.i.d.*	61	63±NA	41±11	23	43
						Salmeterol xinafoate 50 μg *b.i.d.*	58	64±NA	42±12	20	51
						Fluticasone propionate 250 μg *b.i.d.*	66	63±NA	42±11	28	48
						Placebo	58	65±NA	42±12	30	47
Kardos [27]	95 centres in Germany	52	GOLD	COPD exacerbations	NA	Salmeterol/fluticasone combination 50/500 μg *b.i.d.*	74	63.8±8.3	40.4±8.9	40.6	49.7
						Salmeterol xinafoate 50 μg *b.i.d.*	77.6	64±8.2	40.3±8.5	44.4	49.9
Lung Health Study [29]	10 centres	160	FEV1/FVC <70 %	Rate of decline in FEV1	Excluded recent MI	Triamcinolone 600 μg *b.i.d.*	64	56.2±6.8	64.9±13.5	NA	90.5
						Placebo	62.1	56.4±6.8	63.4±13.2	NA	89.8

TABLE 1 Continued

Study [Ref.]	Location	Treatment duration weeks	COPD criteria	Primary outcome	Concomitant cardiac conditions and exclusions	Drug	Male	Age yrs	FEV1 % pred	Prior ICS use	Current smokers
LOFDAHL [28]	39 centres in 9 EU countries	156	FEV1/FVC <70 %	Rate of decline in FEV1	32 (15 on budesonide, 15 on placebo with previous ischaemic cardiac events)	Budesonide 400 μg *b.i.d.*	73.5	52.5±7.5	76.8±12.4	NA	39.4 pack-yrs
						Placebo	72.2	52.4±7.7	76.9±13.2	NA	39.2 pack-yrs
MAHLER [30]	Multicentre trial in the USA	24	ATS	FEV1 and TDI	NA	Salmeterol/fluticasone combination 50/500 μg *b.i.d.*	62	61.9±NA	41±NA	28	46
						Salmeterol xinafoate 50 μg *b.i.d.*	64	63.5±NA	40±NA	31	46
						Fluticasone propionate 500 μg *b.i.d.*	61	64.4±NA	41±NA	25	46
						Placebo	75	64±NA	41±NA	18	54
PAGGIARO [31]	13 European centres	24	ERS	Exacerbations	NA	Fluticasone propionate 500 μg *b.i.d.*	99	62±NA	59±18	NA	49
						Placebo	78	64±NA	55±17	NA	49
RENNARD [32]	237 centres in 9 countries	52	FEV1/FVC <70%	FEV1	HTN 41.6%	Budesonide 160/ formoterol 4.5 μg *b.i.d.*	62.3	63.2±8.9	33.8±11.4	NA	34.8
					Cardiac disease 17.7%	Budesonide 80/ formoterol 4.5 μg *b.i.d.*	62.8	63.6±9.2	34.5±11.5	NA	37.0
					Cardiac failure 2.9%	Formoterol 4.5 μg *b.i.d.*	65.3	62.9±9.1	33.7±11.2	NA	41.2
						Placebo	65.3	62.9±9.1	35.5±11.9	NA	39.5
SCO100250 [22]	98 centres in the USA and Canada	52	FEV1/FVC <70%	Rate of exacerbations	NA	Salmeterol/fluticasone combination 50/250 μg *b.i.d.*	51	65.4±NA	<50§	NA	NA
						Salmeterol xinafoate 50 μg *b.i.d.*	57	65.3±NA	<50§	NA	NA
SCO100470 [24]	135 centres in Europe and Asia-Pacific	24	GOLD	FEV1 and TDI score	NA	Salmeterol/fluticasone combination 50/250 μg *b.i.d.*	78.3	63.5±9.3	1654±459+	NA	42
						Salmeterol xinafoate 50 μg *b.i.d.*	77.2	63.7±9.0	1681±465+	NA	44
SCO40041 [23]	31 centres in the USA	156	GOLD	Bone mineral density	NA	Salmeterol/fluticasone combination 50/250 μg *b.i.d.*	59.7	65.4±8.36	<70%	NA	NA
						Salmeterol xinafoate 50 μg *b.i.d.*	62.7	65.9±9.52	<70%	NA	NA
SFCT01/ SCO30002 [25]¶	49 centres in Italy and Poland	52	FEV1/VC <88%	Time to exacerbations	NA	Fluticasone propionate 500 μg *b.i.d.*	83.9	64.6±8.7	NA	NA	NA
						Placebo	80	65.7±9.0	NA	NA	NA
SZAFRANSKI [33]	89 centres in 11 countries	52	GOLD	Number of severe exacerbations and FEV1	NA	Budesonide/formoterol 160/4.5 μg 2 inhalations *b.i.d.*	76	64±NA	36±NA	26	30
					Excluded if relevant CV disorder	For 4.5 μg 2 inhalations *b.i.d.*	76	63±NA	36±NA	28	38
						Budesonide 200 μg 2 inhalations *b.i.d.*	80	64±NA	37±NA	24	36
						Placebo	83	65±NA	36±NA	26	34
TASHKIN [34]	194 sites in 5 countries	26	FEV1/FVC <70%	FEV1	NA	Budesonide 320/ formoterol 9 μg *b.i.d.*	67.9	63±NA	33.7±11.8	NA	40.8
						Budesonide 160/ formoterol 9 μg	64.4	63±NA	34.1±10.9	NA	39.5
						Budesonide 160 μg + formoterol 4.5 μg	74.2	64±NA	33.5±10.7	NA	37.3
						Budesonide 160 μg	67.6	63±NA	33.5±10.8	NA	40.0
						Formoterol 4.5 μg	65.5	64±NA	33.6±11.3	NA	38.4
						Placebo	69.0	63±NA	34.6±10.5	NA	36.0

TABLE 1 Continued

Study [Ref.]	Location	Treatment duration weeks	COPD criteria	Primary outcome	Concomitant cardiac conditions and exclusions	Drug	Male	Age yrs	FEV1 % pred	Prior ICS use	Current smokers
VAN DER VALK [35]	Pulmonary clinics	26	ATS	Exacerbations and HRQoL	Cardiac insufficiency excluded	Fluticasone propionate 500 µg *b.i.d.*	85.4	64.1±6.8	57.5±14.1	86.2	22.0
						Placebo	83.5	64±6.7	56.1±14.8	80.2	33.0
VESTBO [36]	Community in Denmark	156	FEV1/VC<70%	Rate of FEV1 decline	NA	Budesonide 400 µg *b.i.d.*	58.6	59.0±8.3	86.2±20.6	NA	75.9
						Placebo	62.1	59.1±9.7	86.9±21.1	NA	77.2
WOUTERS [37]	39 centres in the Netherlands	52	FEV1/VC <88%	Rate of FEV1 decline	Excluded if they had MI, angina or heart failure 3 months prior to entry	Salmeterol/fluticasone combination 50/500 µg *b.i.d.*	73	63±7.9	47.4±13.9	85	39
						Salmeterol xinafoate 50 µg *b.i.d.*	75	64±7.7	48.2±12.9	87	35

Data are presented as % or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; % pred: % predicted; ICS: inhaled corticosteroid; FVC: forced vital capacity; HTN: hypertension; CAD: coronary artery disease; CHF: chronic heart failure; LV: left ventricle; NA: not available; ERS: European Respiratory Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HRQoL: health-related quality of life; ATS; American Thoracic Society; EU: European Union; ECG: electrocardiogram; MI: myocardial infarction; TDI: transitional dyspnoea index; VC: vital capacity. #: treatment with tiotropium bromide 18 µg·day^{-1} in both arms and an additional tiotropium arm; ¶: also had an additional salmeterol/fluticasone combination arm; +: FEV1 <50% pred, exact mean and SD data were unavailable.

follow-up was variable and ranged from no loss to follow-up (0 %) [35–37] to 4.9 % [16]. Similarly, the withdrawal rates were variable and ranged from <1% [35] to 52% [16]. Nine RCTs provided detailed descriptions regarding blinding, adequate sequence generation, allocation concealment, and clear reporting of loss to follow-up and were at low risk of bias [15–18, 27, 31, 35–37]. The remaining 14 RCTs were at unclear risk of bias [19–21, 22–26, 28–30, 32–34]. 23 RCTs reported on overall mortality [15–37], of which 20 trials reported on MI [15–18, 20–28, 30–32, 34–37] and 20 trials reported on CV death [15–18, 20–31, 34–37]. Data on MI, CV death and overall mortality in the RCTs are shown in table 3.

Main findings

ICS use was not associated with a significant effect on the risk of MI (105 (1.0%) out of 10,222 *versus* 107 (1.2%) out of 8,951 for control; RR 0.95 (95% CI 0.73–1.23); p=0.68) (fig. 2). There was no evidence of statistical heterogeneity among the included trials (I^2=0%) [15–18, 20–28, 30–32, 34–37].

ICS use was not associated with a significant effect on the risk of CV death (149 (1.8%) out of 8,274 *versus* 145 (1.9%) out of 7,705 for control; RR 1.02 (95% CI 0.81–1.27); p=0.89) (fig. 3). There was no evidence of statistical heterogeneity among the included trials (I^2=0%) [15–18, 20–31, 34–37].

ICS use was not associated with a significant effect on the risk of mortality (580 (5.2%) out of 11,241 *versus* 596 (5.8%) out of 10,211 for control; RR 0.96 (95% CI 0.86–1.07); p=0.43) [15–37]. There was no evidence of statistical heterogeneity among the included trials (I^2=0%).

Sensitivity analysis

These estimates were robust to the choice of comparators in subgroup analysis. ICS use was not associated with a significant effect on the risk of MI when combined ICS+LABA was compared to LABA alone (RR 0.92 (95% CI 0.63–1.35), p=0.67; I^2=0%) or when ICS was evaluated against placebo (RR 0.97 (95% CI 0.67–1.40), p=0.87; I^2=0%). Similarly, ICS use was not associated with a significant effect on the risk of CV death when combined ICS+LABA was compared to LABA alone (RR 1.12 (95% CI 0.79–1.58), p=0.53; I^2=0%) or when ICS was evaluated against placebo (RR 0.95 (95% CI 0.71–1.27), p=0.74; I^2=0) Combined ICS and LABA use did not significantly reduce MI (RR 1.09 (95% CI 0.68–1.75), p=0.71; I^2=0%) or CV death (RR 0.81 (95% CI 0.58–1.12), p=0.20; I^2=0%) against placebo. The random effects analysis on MI (RR 0.92 (95% CI 0.70–1.20), p=0.52; I^2=0%) and CV death (RR 1.01 (95% CI 0.81–1.27), p=0.90; I^2=0%) associated with ICS use yielded effect sizes similar in magnitude and direction to those from the fixed-effects analysis.

The sensitivity analysis on MI (RR 0.95 (95% CI 0.72–1.24), p=0.70; I^2=0%) and CV death (RR 1.02 (95% CI 0.82–1.28), p=0.84; I^2=2%) associated with ICS use in trials of ⩾52 weeks duration [15–20, 22, 23,25 27–29, 32, 33, 36, 37] was similar in magnitude and direction to the overall estimates. The sensitivity analysis on MI (RR 0.91 (95% CI 0.67–1.24), p=0. 56; I^2=0%) and CV death (RR 1.00 (95% CI 0.79–1.25), p=0.97; I^2=9%) associated with ICS use in RCTs at low risk of bias [15–18, 27, 31, 35–37] was similar in magnitude and direction to the overall estimates. The exclusion of trial

TABLE 2 Risk of bias assessment of included randomised controlled trials of inhaled corticosteroids in chronic obstructive pulmonary disease (COPD)[#]

Study [Ref.]	Sequence generation	Allocation concealment	AE monitoring	Drug	Withdrawal rates	Lost to follow-up
Aaron [**15**]	Adequate, central allocation	Adequate	AE captured by monthly telephone questionnaire and checklist	Salmeterol/fluticasone combination=145 Salmeterol xinafoate=148	15 (10.3) 20 (13.5)	2 (1.3) 2 (1.3)
Burge [**16**]	Adequate, computer generated, stratified by centre	Adequate	AEs and SAEs recorded throughout the study	Fluticasone propionate=372 Placebo=370	160 (43.0) 195 (52.7)	16 (4.3) 18 (4.9)
Calverley [**17**]	Adequate, computer generated	Adequate	AE or SAE occurring during therapy	Salmeterol/fluticasone combination=358 Salmeterol xinafoate=372 Fluticasone propionate=374 Placebo=361	89 (24.9) 119 (32.0) 108 (29.0) 140 (38.8)	8 (2.2) 8 (2.2) 8 (2.1) 6 (1.7)
Calverley [**19**]	Unclear	Unclear	AEs recorded at 1, 2, 3, 6, 9 and 12 months of treatment	Formoterol/budesonide=254 Formoterol=255 Budesonide=257 Placebo=256	74 (29) 111 (44) 102 (40) 106 (41)	4 (1.6) 4 (1.6) 4 (1.6) 6 (2.3)
Calverley [**18**]	Adequate, schedule central allocation	Adequate	AEs reviewed at each visit	Salmeterol/fluticasone combination=1533 Salmeterol xinafoate=1521 Fluticasone propionate=1534 Placebo=1524	522 (34.1) 561 (36.9) 587 (38.3) 673 (44.2)	29 (1.9) 15 (1.0) 24 (1.6) 21 (1.4)
Ferguson [**20**]	Unclear	Unclear	AE collected at start and end	Salmeterol/fluticasone combination=394 Salmeterol xinafoate=388	117 (29.7) 149 (38.4)	10 (2.5) 10 (2.6)
FLTA3025 [**21**]	Unclear	Unclear	AEs and SAEs recorded at each visit	Fluticasone propionate=434 Placebo=206	147 (33.9) 79 (38.3)	NA NA
Hanania [**26**]	Unclear	Unclear	AE reporting at each visit	Salmeterol/fluticasone combination=178 Salmeterol xinafoate=177 Fluticasone propionate=183 Placebo=185	53 (30) 57 (32) 49 (27) 59 (32)	NA NA NA NA
Kardos [**27**]	Adequate, centrally generated block	Adequate	AEs and SAEs recorded during run in and follow-up	Salmeterol/fluticasone combination=507 Salmeterol xinafoate=487	99 (19.5) 103 (21.1)	4 (0.8) 3 (0.6)
Lofdahl [**28**]	Unclear	Unclear	Angina pectoris, MI, CAD and myocardial ischaemia reported as AE and SAE	Budesonide=634 Placebo=643	176 (27.7) 189 (29.4)	NA NA
Lung Health Study [**29**]	Unclear	Unclear	AEs every 3 months Reviewed deaths to determine cause of death	Triamcinolone=559 Placebo=557	28 (5.0) 38 (6.8)	NA NA
Mahler [**30**]	Unclear	Unclear	AEs and SAEs documented	Salmeterol/fluticasone combination=165 Salmeterol xinafoate=160 Fluticasone propionate=168 Placebo=181	52 (31.5) 45 (28.2) 68 (40.5) 69 (38.1)	NA NA NA NA
Paggiaro [**31**]	Adequate, computer generated	Adequate	AE defined as untoward medical occurrence during treatment	Fluticasone propionate=142 Placebo=139	19 (13.3) 27 (19.4)	0 2 (1.4)
Rennard [**32**]	Unclear	Unclear	AEs, vital signs and ECGs at study visit	Budesonide 320 μg/formoterol 9 μg *b.i.d.*=494 Budesonide 160μg/formoterol 9 μg *b.i.d.*=494 Formoterol=495 Placebo=481	134 (27.1) 143 (28.9) 157 (31.7) 175 (36.3)	9 (1.8) 12 (2.4) 12 (2.4) 13 (2.7)
SCO100250 [**22**]	Unclear	Unclear	AEs and SAEs recorded after study medication but no later than last date after study medication	Salmeterol/fluticasone combination=394 Salmeterol xinafoate=403	125 (31.7) 156 (38.7)	NA NA
SCO100470 [**24**]	Unclear	Unclear	AEs and SAEs recorded at each study visit	Salmeterol/fluticasone combination=518 Salmeterol xinafoate=532	59 (11.4) 74 (13.9)	NA NA

TABLE 2 Continued

Study [Ref.]	Sequence generation	Allocation concealment	AE monitoring	Drug	Withdrawal rates	Lost to follow-up
SCO40041 [23]	Unclear	Unclear	On therapy AEs and SAEs monitored	Salmeterol/fluticasone combination=92	36 (39.1)	NA
				Salmeterol xinafoate=94	39 (41.5)	NA
SFCT01/ SCO30002 [25]	Unclear	Unclear	All AEs occurring after subject consented to participate until end of follow-up	Fluticasone propionate=131	34 (26.0)	NA
				Placebo=125	40 (32.0)	NA
Szafranski [33]	Unclear	Unclear	AEs detected at visits 2–8, with ECGs at visits 1, 6 and 8	Budesonide/formoterol=208	59 (28)	NA
				Formoterol=201	64 (32)	NA
				Budesonide=198	62 (31)	NA
				Placebo=205	90 (44)	NA
Tashkin [34]	Unclear	Unclear	AEs, vital signs and ECGs at study visit	Budesonide 160 μg/formoterol 4.5 μg *b.i.d.*=277	NA	NA
				Budesonide/formoterol=281	NA	NA
				Budesonide + formoterol=287	NA	NA
				Budesonide=275	NA	NA
				Formoterol=284	NA	NA
				Placebo=300	NA	NA
van der Valk [35]	Adequate, permuted blocks, stratified	Adequate	3- and 6-month follow-up	Fluticasone propionate=123	1 (0.8)	0
				Placebo=121	1 (0.8)	0
Vestbo [36]	Adequate, computer generated	Adequate	Participants seen every 3 months	Budesonide=145	36 (24.8)	0
				Placebo=145	51 (35.2)	0
Wouters [37]	Adequate	Adequate	AE collected at start and end of treatment	Salmeterol/fluticasone combination=189	34 (18.0)	0
				Salmeterol xinafoate=184	46 (25.0)	0

Data are presented as n or n (%). AE: adverse event; SAE: serious adverse event; NA: not available; MI: myocardial infarction; CAD: coronary artery disease; ECG: electrocardiogram. #: all randomised controlled trials were double blinded.

arms with lower doses of ICS use did not change the direction or magnitude of the estimates for MI (RR 0.88 (95% CI 0.66–1.16), p=0.36; I^2=0%) and CV death (RR 1.03 (95% CI 0.81–1.28), p=0.82; I^2=5%).

Observational studies

12 observational studies were included [4, 5, 38–47]. Details of the included studies and the risk of bias are shown in table 4. Confounding was potentially present in several studies, with differences in baseline characteristics between the study groups [5, 40, 43, 44, 46]. ICS exposure was estimated from dispensing records and dosages were usually extrapolated from the amounts dispensed [39, 43]. It was uncertain if patients with concomitant asthma were reliably excluded (misclassification bias) [40]. Immortal time bias, when patients exposed to ICS had an inappropriate interval of immortality compared with patients exposed to controls that did not have this interval, was a potential bias in certain studies [4, 40, 42–45]. Some studies were funded by manufacturers of ICS [41, 44, 45, 47].

ICS were not associated with a significantly reduced risk of MI (RR 0.83, 95% CI 0.63–1.08) in one observational study reporting on MI [39]. Two observational studies reported a significant association between ICS exposure and reduction in CV death, but did not specify details on the causes of death [4, 5]. Pooled analysis of these two studies yielded an RR of 0.79 (95% CI 0.72–0.86, p<0.0001) for CV death, with moderate statistical heterogeneity (I^2=44%) (fig. 4a). 11 observational studies reported on overall mortality [4, 5, 38, 40–47]. ICS use was associated with a significantly reduced risk of death in a meta-analysis of these 11 observational studies (RR 0.78, 95% CI 0.75–0.80; p<0.0001) (fig. 4b) [4, 5, 38, 40–47]. However, there was evidence of moderate statistical heterogeneity among the included studies (I^2=33%).

Publication bias

The funnel plot for mortality appeared to be symmetrical for the RCTs (fig. 5a) and showed asymmetry for the observational studies (fig. 5b). The Egger's test for publication bias was nonsignificant for RCTs (p=0.23), with evidence of significant publication bias in the observational studies (Egger's test p=0.05).

DISCUSSION

Our meta-analysis has found conflicting evidence on the effects of ICS therapy on cardiovascular events and mortality in patients with COPD. We were unable to demonstrate a significant beneficial effect of ICS therapy on MI or CV death in RCTs. In contrast, our meta-analysis showed significant relative reductions (magnitude of ~20%) in the risk of CV and all-cause mortality with ICS-exposed patients in the observational studies.

Methodological issues

Publication or outcome reporting bias in the observational studies may partly account for the differences in results between the observational studies and RCTs. The meta-analysis of observational studies was limited to available published studies, and journal publications may favour manuscripts with positive results [48]. In contrast, our meta-analysis of RCTs

TABLE 3 Cardiovascular (CV) events and all-cause mortality in randomised controlled trials of inhaled corticosteroids in chronic obstructive pulmonary disease

Study [Ref.]	Intervention	Total participants	Participants		
			MI	CV death	Overall mortality
AARON [15]#	Salmeterol/fluticasone combination	145	1	0	6
	Salmeterol xinafoate	148	2	1	6
	Placebo	156	2	1	4
BURGE [16]¶	Fluticasone propionate	376	8	10	32
	Placebo	375	9	12	36
CALVERLEY [17]¶	Salmeterol/fluticasone combination	358	3	0	2
	Salmeterol xinafoate	372	2	0	3
	Fluticasone propionate	374	1	1	3
	Placebo	361	1	3	7
CALVERLEY [19]	Formoterol/budesonide	254	NA	NA	5
	Formoterol	255	NA	NA	13
	Budesonide	257	NA	NA	6
	Placebo	256	NA	NA	5
CALVERLEY [18]¶,+	Salmeterol/fluticasone combination	1546	28	60	193
	Salmeterol xinafoate	1542	36	45	205
	Fluticasone propionate	1552	30	61	246
	Placebo	1544	28	71	231
FERGUSON [20]¶	Salmeterol/fluticasone combination	394	2	2	6
	Salmeterol xinafoate	388	3	1	3
FLTA3025 [21]¶	Fluticasone propionate	434	1	0	0
	Placebo	206	1	0	0
HANANIA [26]¶	Salmeterol/fluticasone combination	178	0	0	0
	Salmeterol xinafoate	177	0	0	0
	Fluticasone propionate	183	1	0	0
	Placebo	185	0	0	0
KARDOS [27]¶	Salmeterol/fluticasone combination	507	3	1	7
	Salmeterol xinafoate	487	2	3	9
Lung Health Study [29]	Triamcinolone	559	NA	6	15
	Placebo	557	NA	2	19
LOFDAHL [28]	Budesonide	634	9	2	8
	Placebo	643	14	1	10
MAHLER [30]¶	Salmeterol/fluticasone combination	165	0	0	0
	Salmeterol xinafoate	160	0	0	0
	Fluticasone propionate	168	0	0	0
	Placebo	181	0	0	3
PAGGIARO [31]¶	Fluticasone propionate	142	1	0	0
	Placebo	139	1	0	2
RENNARD [32]	Budesonide/formoterol	988	5	NA	9
	Formeterol	495	2	NA	2
	Placebo	481	1	NA	4
SCO100250 [22]¶	Salmeterol/fluticasone combination	394	2	0	4
	Salmeterol xinafoate	403	1	0	6
SCO100470 [24]¶	Salmeterol/fluticasone combination	518	0	0	3
	Salmeterol xinafoate	532	1	2	3
SCO40041 [23]¶	Salmeterol/fluticasone combination	92	5	0	5
	Salmeterol xinafoate	94	0	1	7
SFCT01/SCO30002 [25]¶	Fluticasone propionate	131	1	0	0
	Placebo	125	0	0	0
SZAFRANSKI [33]	Formoterol/budesonide	208	NA	NA	6
	Formoterol	201	NA	NA	6
	Budesonide	198	NA	NA	5
	Placebo	205	NA	NA	9

TABLE 3 Continued

Study [Ref.]	Intervention	Total participants	Participants		
			MI	CV death	Overall mortality
TASHKIN [34]	Budesonide/formoterol	845	1	1	7
	Formoterol	284	1	1	1
	Budesonide	275	1	1	2
	Placebo	300	0	0	1
VAN DER VALK [35]¶	Fluticasone propionate	123	0	1	4
	Placebo	121	0	0	0
VESTBO [36]	Budesonide	145	2	3	4
	Placebo	145	2	0	5
WOUTERS [37]¶	Salmeterol/fluticasone combination	189	0	0	2
	Salmeterol xinafoate	184	1	2	4

Data are presented as n. MI: myocardial infarction; NA: not available. #: reported as serious adverse event of MI or acute arrhythmia; ¶: CV adverse event data extracted from manufacturers clinical trials register; +; CV mortality data extracted from regulatory agencies as unavailable in publications.

included unpublished data from manufacturers' trial registries thus minimising the risk of publication bias.

The presence of immortal time bias may partly account for some of the mortality reduction seen in observational studies, but is not the only explanation for these divergent findings. A time-dependent analysis accounting for the period of ICS exposure *versus* control exposure (OR 1.00, 95% CI 0.79–1.26) negated the significant beneficial effect seen using a fixed time analysis (OR 0.69, 95% CI 0.55–0.86) in a study that measured 90-day mortality [49]. A significant beneficial association, albeit lower in magnitude, was seen with ICS exposure in another study that minimised the risk of immortal time bias [41]. Potential confounders, such as smoking status and lung function, and unknown residual confounding factors, such as co-existing asthma, along with the differential use of home oxygen in patients may have contributed to the perceived effect on mortality in the observational studies.

The apparent lack of CV benefit in the trials which typically exclude patients with serious comorbidities cannot conclusively rule out the potential for a CV benefit in patients with COPD seen in the observational studies. The rates of concomitant smoking in the observational studies may have been lower than that of RCTs where nearly 50% of COPD participants had 10 pack-yrs of smoking history. Factors other than smoking, such as biomass, air pollution and poor nutrition, may contribute to the burden of COPD in community patients. Certain subgroups of patients in the observational studies, especially those with severe comorbidities and a higher risk of CV events, may potentially derive a CV benefit from ICS use.

Comparisons with previous analysis

The finding of a lack of CV effect in our intention-to-treat meta-analysis of 23 published and unpublished trials involving 23,396 patients should be distinguished from other meta-analysis of ICS use limited to the published trials. Our meta-analysis had a greater ability to detect any significant difference on mortality with more precise estimates of treatment effect as shown by our relatively narrow 95% CI (0.86–1.07) for the RR of overall mortality. An earlier pooled analysis (seven published trials, n=5,085, mean duration of follow-up=26 months) reported a reduction in mortality with ICS use (adjusted hazards ratio 0.73, 95% CI 0.55–0.96) but had less than one quarter the number of patients than our analysis [50]. The effect was more pronounced in females and former smokers, and the benefits were driven by reduction in cancer deaths [50]. A subsequent Cochrane systematic review which pooled data from nine trials [51], and another recent meta-analysis of five trials found no evidence of a mortality benefit with ICS use [52].

Our failure to detect a significant effect on MI and CV death with ICS (fluticasone, budesonide and triamcinolone) use should be distinguished from a *post hoc* subgroup analysis of inhaled budesonide *versus* placebo on ischaemic cardiac events (angina pectoris, coronary artery disorder and MI) in the European Respiratory Society's study on Chronic Obstructive Pulmonary Disease (EUROSCOP) [28]. Their analysis included 1,175 participants, approximately one fifth of the number of participants in our analysis, with mild COPD (average age 52.5 yrs) and reported a significantly lower risk of ischaemic cardiac events with inhaled budesonide (RR 0.58, 95% 0.35–0.98; p=0.043). The contrasting findings could be partly explained by the inclusion by EUROSCOP of different end-points of angina, ischaemia and coronary artery disorder in patients with milder COPD. However, applying the end-points of ischaemic cardiac events of EUROSCOP to the similar 3 yr Towards a Revolution in COPD Health (TORCH) trial [18], shows no significant difference in the rate of ischaemic cardiac events in inhaled fluticasone (56 (36.%) out of 1,552) when compared to placebo (50 (3.2%) out of 1,544). We did not detect any intraclass differences in the risk of CV events between inhaled fluticasone and inhaled budesonide in our meta-analysis.

The potential mechanisms by which ICS modulate CV outcomes remain uncertain. ICS could potentially ameliorate CV disease by reducing exacerbations because acute exacerbation in COPD may precipitate CV disease [53]. The pathology of COPD includes inflammation and/or alterations in repair

Study [Ref.]	ICS Events	ICS Total	Control Events	Control Total	Weight %	Risk ratio M–H fixed (95% CI)
a) ICS-LABA *versus* LABA						
CALVERLEY [19]	3	358	2	372	1.8	1.56 (0.26–9.27)
WOUTERS [37]	0	189	1	184	1.4	0.32 (0.01–7.92)
SCO100470 [24]	0	518	1	532	1.3	0.34 (0.01–8.38)
AARON [15]	1	145	2	148	1.8	0.51 (0.05–5.57)
CALVERLEY [18]	28	1546	36	1542	32.3	0.78 (0.48–1.26)
KARDOS [27]	3	507	2	487	1.8	1.44 (0.24–8.59)
FERGUSON [20]	2	394	3	388	2.7	0.66 (0.11–3.91)
SCO40041 [23]	5	92	0	94	0.4	11.24 (0.63–200.35)
SCO100250 [22]	2	394	1	403	0.9	2.05 (0.19–22.47)
TASHKIN [34]	1	845	1	284	1.3	0.34 (0.02–5.36)
RENNARD [32]	5	988	2	494	2.4	1.25 (0.24–6.42)
Subtotal (95% CI)		5976		4928	48.1	0.92 (0.63–1.35)
Total events	50		51			
b) ICS *versus* placebo						
PAGGIARO [31]	1	142	1	139	0.9	0.98 (0.06–15.50)
VESTBO [36]	2	145	2	145	1.8	1.00 (0.14–7.00)
BURGE [16]	8	376	9	375	8.1	0.89 (0.35–2.27)
CALVERLEY [17]	1	374	1	361	0.9	0.97 (0.06–15.37)
HANANIA [26]	1	183	0	185	0.4	3.03 (0.12–73.96)
FLTA3025 [21]	1	434	1	206	1.2	0.47 (0.03–7.55)
SFCT01 [25]	1	131	0	125	0.5	2.86 (0.12–69.64)
CALVERLEY [18]	30	1552	28	1544	25.2	1.07 (0.64–1.78)
LOFDAHL [28]	9	634	14	643	12.5	0.65 (0.28–1.50)
TASHKIN [34]	1	275	0	300	0.4	3.27 (0.13–79.98)
Subtotal (95% CI)		4246		4023	51.9	0.97 (0.67–1.40)
Total events	55		56			
Total (95% CI)		10222		8951	100	0.95 (0.73–1.23)
Total events	105		107			

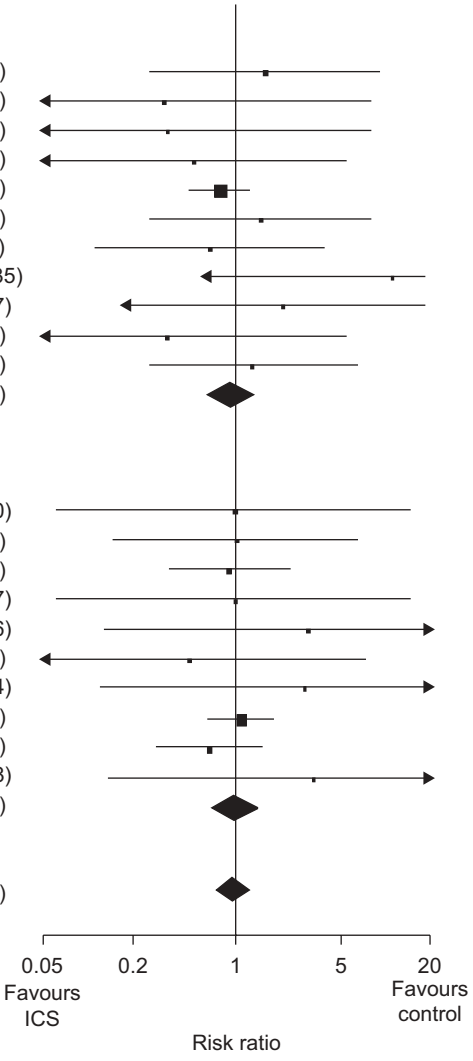

FIGURE 2. Meta-analysis of randomised controlled trials of inhaled corticosteroids (ICS) *versus* controls for myocardial infarction. a) ICS-long acting β_2-agonists (LABA) *versus* LABA and b) ICS *versus* placebo. a) Chi-squared=6.16; degrees of freedom (df)=10 (p=0.80); I^2=0%. Test for overall effect: z=0.43 (p<0.67). b) Chi-squared=2.79; df=9 (p=0.97); I^2=0%. Test for overall effect: z=0.16 (p<0.87). Overall: Chi-squared=9.06; df=20 (p=0.98); I^2=0%. Test for overall effect: z=0.41 (p<0.68). M–H: Mantel–Haenszel.

mechanisms. The ''spill-over'' of inflammatory mediators into the systemic circulation in COPD is linked to the development of CV disease [54]. However, ICS use may have limited CV benefit because ICS use does not reduce markers of systemic inflammation (serum CRP or interleukin-6 levels), with little impact on neutrophilic inflammation or matrix remodelling relevant to CV disease in COPD [54, 55].

Limitations

Our meta-analysis has several limitations, which mainly stem from the quality of reported data. The RCTs did not use specific definitions of MI or CV death, and inconsistent adverse events reporting may account for some missing outcome data. Our estimates for MI and CV death are relatively imprecise with wide CIs due to the low CV event rates in the trials. Thus, we cannot rule out the possibility of a relative reduction of 27% for MI and 20% for CV death with ICS. 14 trials in the analysis were at unclear risk of bias. The high withdrawal rates in certain trials may also mask any differences in treatment effect. There was potential clinical heterogeneity among the included trials and we cannot completely discount the possibility of statistical heterogeneity because the heterogeneity tests may be underpowered due to low event rates.

We excluded trials shorter than 6 months, but it is unlikely that a substantial CV effect would be discernible in trials of shorter duration. In the absence of patient-level data, we could not determine ICS dose–response relationships [42]. However, the exclusion of lower dose intervention arms did not change the direction or magnitude of the estimates for MI and CV death. We could not evaluate the influence of age, severity of COPD, and pre-existing CV risk factors or concomitant statin [56], or angiotensin inhibitor use on CV events associated with ICS use.

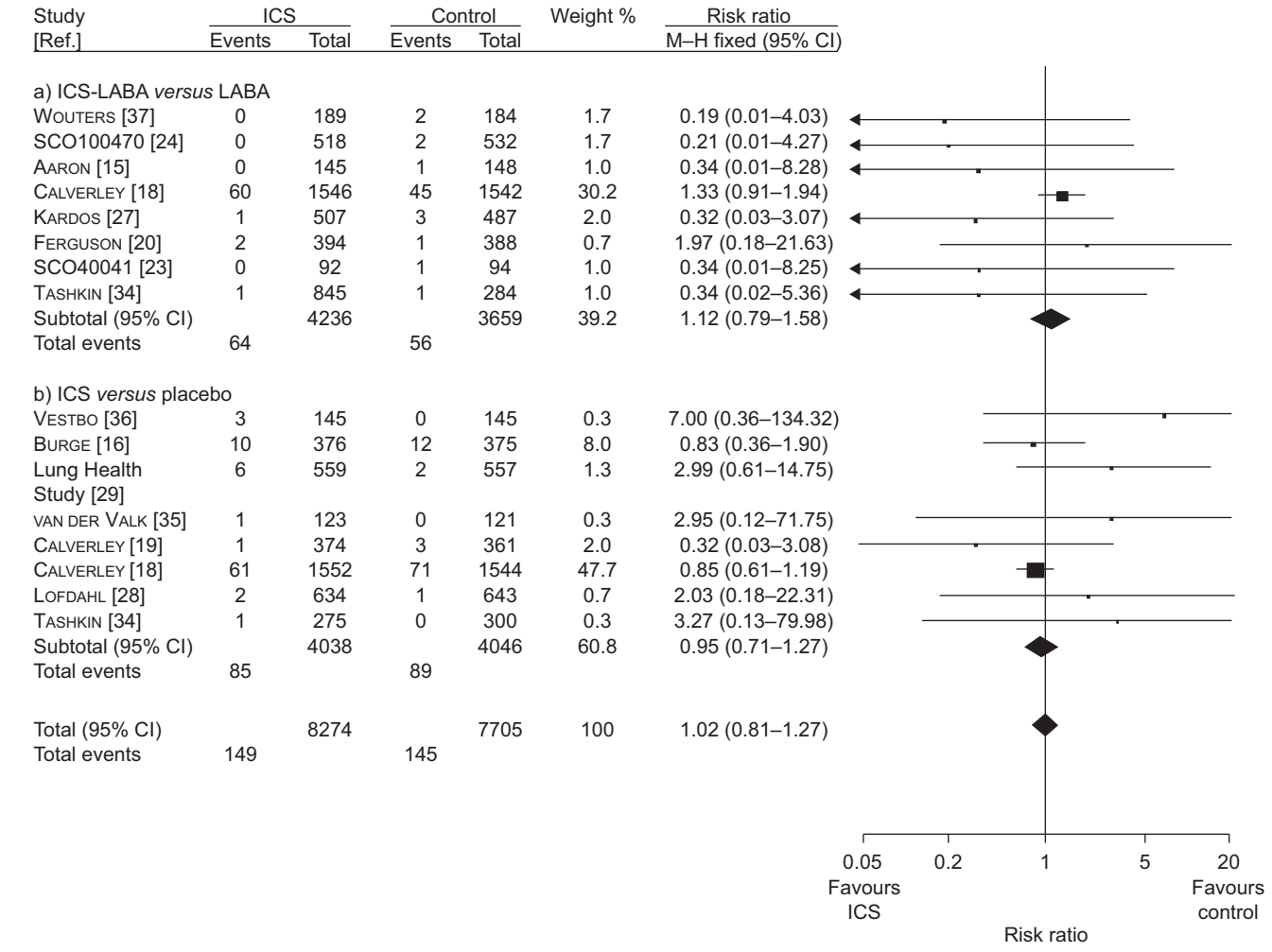

FIGURE 3. Meta-analysis of randomised controlled trials of inhaled corticosteroids (ICS) *versus* controls for cardiovascular death. a) ICS-long acting β_2-agonists (LABA) *versus* LABA and b) ICS *versus* placebo. a) Chi-squared=6.46; degrees of freedom (df)=7 (p=0.49); I^2=0%. Test for overall effect: z=0.62 (p<0.53). b) Chi-squared=6.55; df=7 (p=0.48); I^2=0%. Test for overall effect: z=0.33 (p<0.74). Overall: Chi-squared=13.85; df=15 (p=0.54); I^2=0%. Test for overall effect: z=0.14 (p<0.89). M–H: Mantel–Haenszel.

Despite these limitations, the apparent absence of improvements in CV and mortality outcomes with ICS use in the trials should be seen in the context of the potential benefit of ICS use on exacerbations, and improved quality of life in recent meta-analyses [51, 57]. Our comprehensive meta-analysis informs the recent debate on the role of ICS in COPD [58, 59]. RCTs that have reported beneficial effects on exacerbations, but only after a LABA were added to the ICS, were limited by the discontinuation of existing treatment and the absence of the fundamental ''intention-to-treat analysis'' [60]. Two recent trials [15, 18], designed for a proper intention-to-treat analysis of the primary outcomes, both found no benefit of ICS in COPD [60]. ICS do not reduce the decline in FEV1 in COPD [2, 51]. The beneficial effect of a LABA-ICS combination may possibly be attributed to the LABA component, without any additional benefit from the addition of an ICS [60].

Future research

Appropriate factorial analyses evaluating the effect of each component of the LABA-ICS combination inhaler, and re-analysis of patient level data by pre-existing ICS use in trials may clarify the optimal role of ICS use in COPD [61]. A large-scale pragmatic trial in community patients may also help to clarify the CV effects of ICS use.

The benefits of ICS in reducing exacerbations and improving symptoms should be weighed against the potential for harm, such as an increased risk of pneumonia which appears to be limited to inhaled fluticasone [7], but are uncertain for budesonide [62, 63]. Recent data suggest that fluticasone has no significant impact on bone demineralisation [64].

Clinicians will need to carefully evaluate the strengths and limitations of the current evidence concerning the effects of ICS therapy on cardiovascular events when making a treatment decision. Further research to clarify these divergent findings is clearly needed.

SUPPORT STATEMENT

The design and conduct of the study; the collection, management, analysis and interpretation of the data; and the preparation, review or approval of the manuscript was independent of any sources of

TABLE 4 Characteristics of observational studies of inhaled corticosteroids (ICS) and cardiovascular (CV) events or mortality

Study [Ref.]	Participants	Design	Data source	Duration weeks	Participants included	ICS exposure	Ascertainment of ICS exposure	Outcomes	Outcome ascertainment	Risk estimates ICS (*versus* controls) with outcomes	Bias and limitations
Fan [**38**]	2654 ICS users, 5398 non-users	PC	US VA DB	78	1. Outpatient visit or hospitalisation with ICD-9 diagnosis of COPD. 2. Using at least one pulmonary prescription during 90 days before index visit. 3. Age >45 yrs. 4. Participant in the ACQUIP RCT for ⩾1 yr.	Becl (44%), triam (45%), fluni (6%), flu (5%)	Prescription for inhalers, subdivided by 90-day exposure periods. "User" if prescription filled for >80% of each 90 days.	Death	Records date of death for veterans whose families file for the benefit.	HR of death ICS *versus* controls. Low dose (HR 0.96; 95% CI 0.69–1.33); medium/high doses (HR 0.86; 95% CI 0.67–1.10) Adjusted for distance from hospital, pulmonary prescriptions, prior hospitalisations, comorbidity.	Significant baseline differences in age, marital status, race, comorbidity, COPD clinic visits and hospitalisations, respiratory prescription use. Assumes VA system provides records on all prescriptions and patients compliant. No ascertainment of death by checking, DB known to identify 98.8% of deaths among Medicare-eligible patients.
Huiart [**39**]	371 cases, 1864 controls	Nested CC	Canadian Health Insurance DB in Saskatchewan	130	New patients with COPD. 1. At least 3 inhaler prescriptions. 2. Age >55 yrs with no previous use or ICS in 5 yrs. 3. Register in health plan for 5 yrs. 4. Entry time 3rd prescription between Jan 1990–Dec 1997. Matched for age, duration and frequency of exacerbations. Excluded lengthy hospital admissions.	Becl or bud	Exposed if recently received ICS prescription in 12 months prior to index date.	MI	Discharge diagnosis from the hospital DB, and death from vital statistics. Compared to medical charts, diagnostic agreement in hospital DB as high as 97%.	RR for AMI with ICS: crude RR 0.86 (95% CI 0.68–1.09); adjusted RR 0.83 (95% CI, 0.63–1.08), adjusted for AMI risk factors and severity of COPD: sex, HTN, DM, HLD, CV disease, number of COPD exacerbations and respiratory prescription.	Important baseline differences: sex, risk factors and history of CVD, hospitalisations in past 3 months. No dose information available; duration of exposure extrapolated from quantity dispensed, rather than compliance. Matching for COPD severity inaccurate as relied on co-prescription exposure. Limited data on smoking.
Lee [**4**]	32130 cases, 320501 controls for mortality (3159 cases, 31534 controls for CV death)	Nested CC	US VA, CMS and NDI	260	1. Age >45 yrs of US VA care for >1 yr. 2. ICD-9 diagnosis of COPD between Oct 1, 1999 and Sept. 2003 at two or more outpatient visits within 12 months or primary diagnosis of COPD.	NA	Any exposure to respiratory prescription in the 180 days before index date. No details on accuracy of pharmacy data.	Death, CVD	DB captures approximately 98% of veteran deaths. Random sample of 40% with CV death: IHD disease, cardiomyopathy, cardiac arrest, or arrhythmias.	Adjusted OR for ICS: all-cause death 0.80 (95% CI 0.78– 0.83); CVD 0.80 (95% CI 0.72–0.88), adjusted for respiratory and cardiac prescriptions, exacerbations, and presence of CV disease.	Imbalances in comorbid cardiac conditions and cardiac prescription use, and COPD exacerbations. Confounding by indication. Did not ascertain COPD severity or smoking status. Unlikely to find significant differences due to low rates of exposure.

TABLE 4 Continued

Study [Ref.]	Participants	Design	Data source	Duration weeks	Participants included	ICS exposure	Ascertainment of ICS exposure	Outcomes	Outcome ascertainment	Risk estimates ICS (*versus* controls) with outcomes	Bias and limitations
					Matched on sex, age, region, and year of diagnosis.						Immortal time bias. Uncertain accuracy of diagnosis of CVD.
MACIE [**5**]	1629 ICS users, 2393 non-users	Cohort, nested CC	Manitoba Population Health Research Repository (Canada)	39	1. Discharged from hospital with primary ICD code of COPD between Apr 1996–Mar 2000. 2. Age >35 yrs. 3. Resident of the province ⩾1 yr prior and 1 yr post-discharge until death. Patient who died within 90 days of hospital discharge excluded.	NA	Provincial retail pharmacies capture all dispensing of prescriptions except for in-patient drugs. DB has anonymous recipient IDs and information about the prescription dispensed.	Death, CVD	Death from any cause in the 275 days after hospital discharge. Analysis of death certificates for: COPD, asthma; CV and other causes.	Adjusted HR for death with ICS within 90 days of discharge. Aged >65 yrs, 0.75 (0.61–0.91). Note: absolute mortality among age >65 yrs: 11.7% in ICS users; 13.1% in non-users. ICSs reduced the risk of death by 23% (95% CI 6–37%) and CV deaths by 38% (95% CI 11–57%) compared to bronchodilators.	Significant baseline differences: age, Charlson score, respiratory prescriptions. Confounding exists. No prescription data while hospitalised so patients admitted in first 90 days of study received less ICS and likely to be high mortality group. Difficulty in judging actual drug usage, and cause of death.
MAPEL [**40**]	786 ICS users, 397 SABA users	RC	Two regional MCOs in the USA	96	1. Aged >40 yrs. 2. Had >90-day use of an ICS or SABA. 3. At least two outpatient visits or one hospital admission with relevant ICD-9 code between 1995–2000. Follow-up 1st day following 90-day period to death or disenrolment.	NA	Pharmacy claims for ⩾90-day cumulative of: 1) ICS alone, 2) LABA alone, or 3) ICS + LABA.	Death	Death obtained from state vital statistics records and matched on name, SSN and DOB.	HR for mortality: ICS *versus* SABA 0.59 (95% CI 0.46–0.78).	Significant baseline differences: age, sex, presence of asthma, disease severity. Confounding by indication. No ascertainment of exposure, compliance or use. Misclassification bias in COPD diagnosis (asthma). Uncertain risk of immortal time bias.
MAPEL [**41**]	742 ICS users, 1832 SABA users	RC, nested CC	Four US integrated HMOs	156	At least one in-patient or two outpatient visits for COPD based on ICD-9 codes from Sep 2000 to Sep 2001. Matched on sex, age, data survival follow-up.	Flu/sal, any ICS	Pharmacy records of prescriptions using National Drug Codes. Duration extrapolated from units dispensed. Prescriptions reviewed for missing data.	Death	Death during study period Sept 2000–Sept 2003 ascertained through local vital statistic registers, matched by name, sex DOB and SSN.	HR for mortality ICS *versus* SABA 0.76 (0.61–0.95). HR for mortality in propensity matched cohort: ICS *versus* SABA 0.75 (0.58–0.97). RR for death with ICS in nested CC RR 0.86 (95% CI 0.46–0.96).	Significant baseline differences: age, hospitalisation for COPD, comorbidities. Discrepancy between prescription and actual use. Duration extrapolated. Industry funded.

TABLE 4 Continued

Study [Ref.]	Participants	Design	Data source	Duration weeks	Participants included	ICS exposure	Ascertainment of ICS exposure	Outcomes	Outcome ascertainment	Risk estimates ICS (*versus* controls) with outcomes	Bias and limitations
SIN [43]	11481 ICS users, 11139 non-users	RC	CIHI hospital discharge DB in Ontario (Canada)	52	1. ICD-9 code for at least one hospitalisation with main discharge diagnosis of COPD between April 1, 1992 and March 31, 1997. 2. Aged >65 yrs. 3. Survive ⩾30 days after discharge.	Becl, bud, triam, fluni	Ontario Drug Benefit database.	Death	Captures all decedents of Ontario, including date of death.	Adjusted RR for death with ICS use (within 90 day post-discharge RR 0.71 (95% CI, 0.65 to 0.78), adjusted for age, sex, Charlson score exacerbations and co-medication. Stratified analysis on Charlson score, sex, and age did not change association.	Significant baselines differences: age, Charlson index, prescriptions and emergency visits. Confounding by indication. No verification of actual medication usage. Risk of immortal time bias.
SIN [42]	3343 ICS users, 3397 non-users	RC	CIHI hospital discharge in Alberta (Canada)	128	1. ICD-9 code for at least one hospitalisation with main discharge diagnosis of COPD between April 1, 1994 and March 31, 1998. 2. Aged >65 yrs. 3. Excluded those with primary diagnosis of asthma.	ICS	Crosschecked with Alberta Blue Cross DB with record of quantity and date dispensed. Doses imputed.	Death	Vital statistics with electronic file of all deceased persons in Alberta, including dates of death.	All cause death for ICS users *versus* non-users. Crude RR 0.61 (95% CI 0.56–0.66). Adjusted RR 0.75 (95% CI 0.68–0.82), adjustments for age, sex, comorbid conditions, ICU stay and use of other pulmonary prescription.	Significant baseline differences in age, Charlson comorbidity score and use of prescriptions. Unclear, which ICS studied, and what doses. No verification of actual use. Unclear risk of immortal time bias.
SORIANO [45]	431 ICS users, 3620 non-users	RC	UK GPRD	156	1. Newly diagnosed COPD between 1990–1999. 2. Aged >50 yrs. 3. Received ⩾3 prescriptions over 6 months. 4. Alive for 6 months after entry.	Flu	Prescriptions in 90 days post-hospital discharge.	Death	Date of death identified with Specific OMIS code.	HR for fluticasone (3 yr death). HR 0.62 (95% CI 0.45–0.85), Adjusted for age, sex, year of entry, smoking, comorbid conditions and oral steroid use.	Significant baseline differences: age, sex, prescription use, comorbidity. No verification of actual use. Risk of immortal time bias. Industry funded.
SORIANO [44]	3049 ICS users, 627 SABA users	RC	UK GPRD 1990–1999	52	1. Newly diagnosed COPD. 2. Aged >50 yrs. 3. 1st hospitalisation for COPD related condition. 4. At least 1 prescription for respiratory condition in first 90 days after discharge.	Beclo, bud, flu	Based on prescription by GP in 90 days post-discharge.	Death	NA	Death rate in 1 yr 17.1% in ICS users *versus* 24.3% in control group.	Significant baseline differences in age, smoking prescription, and hospitalisation. Confounding by indication. Ascertainment of mortality. Unclear risk of immortal time bias. Drug dosage unclear. Actual use may differ. Industry funded.

TABLE 4 Continued

Study [Ref.]	Participants	Design	Data source	Duration weeks	Participants included	ICS exposure	Ascertainment of ICS exposure	Outcomes	Outcome ascertainment	Risk estimates ICS (*versus* controls) with outcomes	Bias and limitations
					5. Excluded if died or re-admitted within 30 days.						
Tkacova [**46**]	55 ICS users, 90 non-users	RC	Slovakian university hospital	52	1. Documented outpatient clinic visit or an in-patient hospitalisation with primary diagnosis of COPD. 2. At least one bronchodilator before the index visit or hospitalisation date. 3. LTOT prescription between 1996–2002. 4. Stable condition at the time of LTOT initiation. Prescribing physician recorded details of prescription at time of initiation of O_2.	Becl (n=45), flu (n=6), bud (n=4)	Whether patients were or were not receiving ICS at time of LTOT initiation.	Death	Survival data from records of home O_2 vendors captured death.	HR for death with ICS use. HR 0.38 (95% CI 0.18–0.79). Adjusted HR 0.46 (95% CI 0.21–0.98), adjusted for age, sex, co-medication, P_{a,O_2} and P_{a,CO_2}. ICS users had significantly greater 1-yr survival (46/55 or 84%) than non-users (54/90 or 60%). (Log-rank statistics $p<0.05$).	Significant baselines differences in use of SABA, arterial hypertension and severity of COPD. Misclassification as exposure status based on single time-period, and patients may have started on ICS after that. Risk of confounding as no adjustment for risk factors.
Vollmer [**47**]	863 regular ICS users, 996 irregular ICS users, and 1043 non-users	RC	US Kaiser Permanente	208	1. Aged >50 yrs as of Jan 2000. 2. Enroled between 1998–1999. 3. Outpatient or ED visit with ICD-9 COPD code. 4. ⩾6 prescriptions of respiratory drugs, with ⩾1 prescription dispensed Sept–Dec 1999.	NA	EMR. One or more dispensing event during each of the three preceding 2 months.	Death	Vital statistics registers of Oregon and Washington. 29.5% had incomplete follow-up.	RR for death (no asthma): never smokers: 0.47 (0.19–1.16, p=0.10); ex-smokers: 0.76 (0.56–1.02, p=0.07); current smokers 1.09 (0.65–1.83, p=0.74); adjusted for age, sex, comorbidity, use of home O_2, pulmonologist, COPD hospitalisation or ED care, and propensity to use ICS.	Significant baselines differences: smoking, co-existing asthma, pulmonologist care, ED care. No verification of compliance. Incomplete follow-up. Industry funded.

PC: prospective cohort; VA: Veterans Affairs; DB: database; ICD: International Statistical Classification of Diseases and Related Health Problems; COPD: chronic obstructive pulmonary disease; ACQUIP: Ambulatory Care Quality Improvement Project; RCT: randomised controlled trial; Becl: beclometasone; triam: triamcinolone; fluni: flunisolide; flu: fluticasone; HR: hazard ratio; CC: case–control; bud: budesonide; MI: myocardial infarction; RR: relative risk; AMI: acute myocardial infarction; HTN: hypertension; DM: diabetes mellitus; HLD: hyperlipidaemia; CVD: cardiovascular disease; CMS: Center for Medicaid Services; NDI: National Death Index; NA: not available; IHD: ischaemic heart disease; ID: identification; SABA: short-acting β-agonist; MCO: managed care organisation; LABA: long-acting β-agonist; RC: retrospective cohort; SSN: social security number; DOB: date of birth; HMO: health maintenance organisation; Sal: salmeterol; CIHI: Canadian Institute of Health Information; ICU: intensive care unit; GPRD: General Practitioner Research Database; OMIS: Oxford Medical Information Systems; GP: general practitioner; LTOT: long-term oxygen therapy; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; ED: emergency department; EMR: Electronic Medical Record.

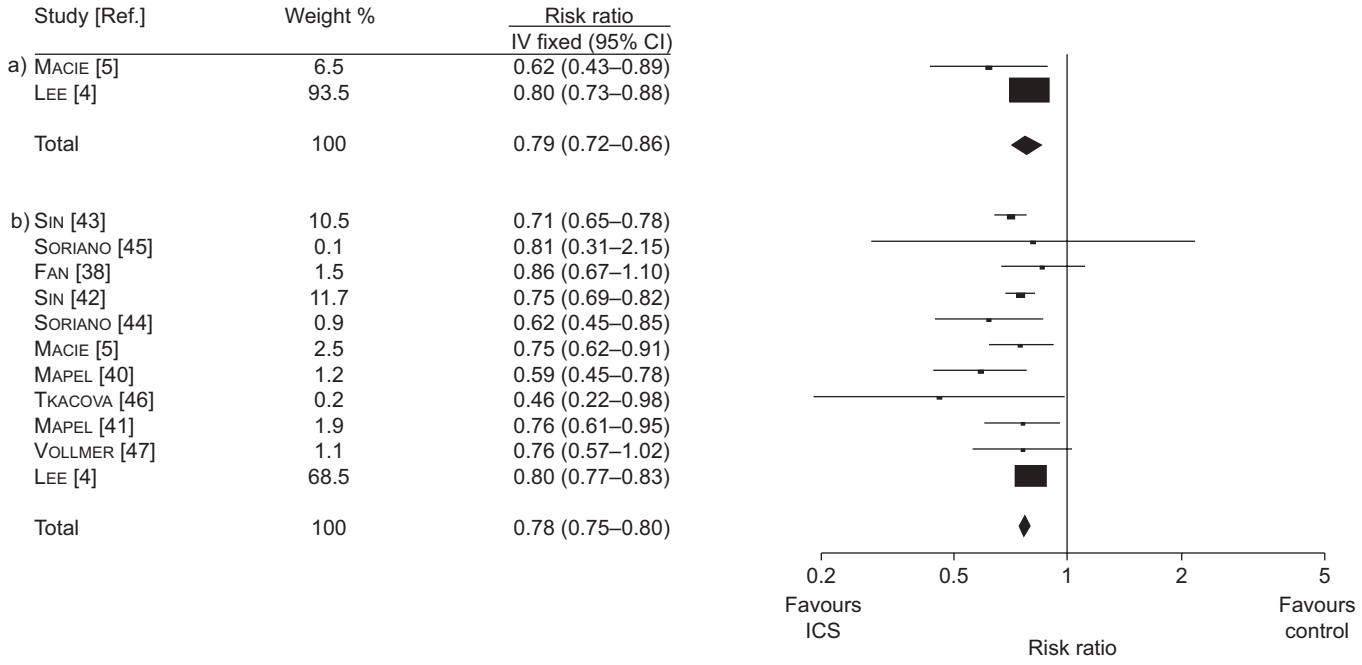

FIGURE 4. Meta-analysis of inhaled corticosteroids (ICS) *versus* controls for a) cardiovascular death and b) overall mortality in observational studies. a) Chi-squared=1.79; degrees of freedom (df)=1 (p=0.18); I^2=44%. Test for overall effect: z=5.10 (p<0.00001). b) Chi-squared=14.95; df=10 (p=0.13); I^2=33%. Test for overall effect: z=16.22 (p<0.00001). IV: inverse variance.

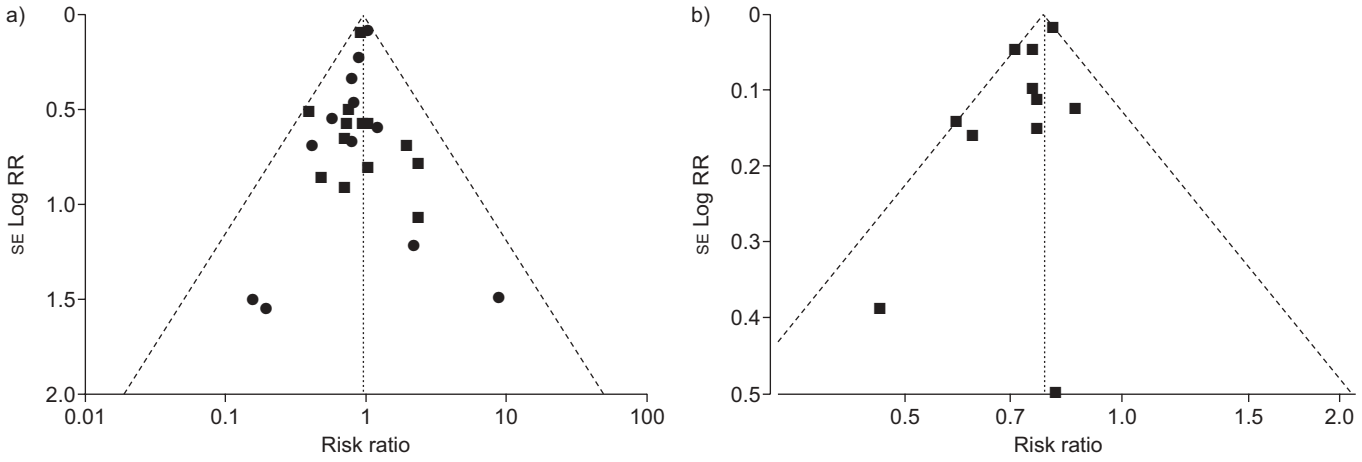

FIGURE 5. Funnel plots of risk ratios for overall mortality in the a) trials and b) observational studies. ■: inhaled corticosteroid (ICS) long acting β_2-agonists (LABA) *versus* LABA; ●: ICS *versus* placebo.

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STATEMENT OF INTEREST

None declared.

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