Effectiveness and Safety of Inhaled Corticosteroids in Older Individuals with Chronic Obstructive Pulmonary Disease and/or Asthma

A Population Study

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Abstract

Rationale: Inhaled corticosteroids (ICS) are established medications for the management of both asthma and chronic obstructive pulmonary disease (COPD), two common chronic airway diseases. However, there is still uncertainty with respect to their use in some cases, specifically in older adults with asthma, people with concurrent asthma and COPD, and some people with COPD (given the association of ICS with pneumonia).

Objectives: To compare the effectiveness and safety of ICS in older adults with asthma, COPD, or features of both in a real-word setting.

Methods: In this retrospective longitudinal population cohort study, individuals 66 years of age or older in Ontario, Canada, who met a validated case definition of physician-diagnosed COPD and/or asthma between 2003 and 2014 were followed until March 2015 through provincial health administrative data. Overlap in COPD and asthma diagnoses was permitted and stratified for in subgroup analyses. The exposure was new receipt of ICS. The primary effectiveness and safety outcomes were hospitalizations for obstructive lung disease (OLD) and hospitalizations for pneumonia, respectively. Propensity scores were used to adjust for confounders.

Results: The study included 87,690 individuals with asthma (27% with concurrent COPD) and 150,593 individuals with COPD (25% with concurrent asthma). In terms of effectiveness, controlling for confounders, ICS was associated with fewer hospitalizations for OLD (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.79–0.88) in subjects with asthma alone, with concurrent COPD attenuating the benefit. A similar association was seen in subjects with COPD and concurrent asthma (HR, 0.88; 95% CI, 0.84–0.92), but not in those with COPD alone, where ICS receipt had little impact on hospitalizations. In terms of safety, ICS receipt was associated with a marginally increased risk of pneumonia hospitalizations in people with COPD and no asthma (HR, 1.03; 95% CI, 1.00–1.06), but not in the other groups.

Conclusions: ICS was associated with fewer hospitalizations for OLD in older adults with asthma and concurrent asthma and COPD, but had little impact on OLD and pneumonia hospitalizations in those with COPD alone.

Keywords: COPD; asthma; inhaled corticosteroids; effectiveness; safety

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Inhaled corticosteroids (ICS) are established medications for the management of both asthma and chronic obstructive pulmonary disease (COPD), two common chronic airway diseases (1, 2). However, there is still uncertainty with respect to their use in some areas, specifically for asthma in older adults (3–5), for people with concurrent asthma and COPD (6), and for some people with COPD given their association with pneumonia (7).

Asthma affects up to 13% of adults 65 years of age and older (8), where it has been shown to be more severe, less likely to be associated with atopy, and more affected by comorbidity and socioeconomic factors (9, 10) than in younger people. The role of ICS in older people with asthma is unclear because they have been regularly excluded from clinical trials (3). Furthermore, studies suggest that ICS have decreased effectiveness and safety in this population (4), which is supported by findings that older individuals with asthma have a phenotype characterized by neutrophilic inflammation of the airways (11), as well as a weaker response to ICS than younger people (12). The risk of pneumonia in older adults with asthma who are taking ICS is also uncertain (5).

There are questions concerning the role of ICS (13–15) in the up to 24% of adults 65 years of age and older (1) with COPD as well. Although some randomized controlled trials (RCTs) have suggested that ICS reduce airway hyperresponsiveness, acute exacerbations, and decline in quality of life in individuals with frequent exacerbations (16–18), others have shown little benefit (7). Furthermore, real-world studies have suggested that ICS increase the risk of pneumonia, albeit not pneumonia fatality or overall mortality (15). Although it seems that certain subgroups might have better risk/benefit profiles with ICS than others (19–21), we are not aware of any studies that have directly compared the risks *and* benefits of ICS in real-world COPD populations. Such information could help inform current guidelines (22).

Finally, there is uncertainty about the role of ICS in older people with asthma who have features of COPD, and people with COPD who have features of asthma (6). Asthma guidelines are based predominantly on studies that excluded current or former smokers and individuals with minimal airway reversibility. COPD guidelines are based on studies that excluded individuals with significant bronchodilator reversibility (23). Thus, it is uncertain whether their results can be extrapolated to real-life populations with both diseases.

To address the limited knowledge and controversies regarding the use of ICS in real-life older individuals with chronic airway disease, we conducted a longitudinal population cohort study to compare the effectiveness and safety of ICS in older adults with asthma, COPD, or both in a real-world setting. Some of the results of this study were reported previously in the form of an abstract (24).

Methods

Study Design and Setting

We conducted a retrospective longitudinal population study using provincial health administrative data from over 2 million individuals 65 years of age and older living in Ontario, Canada, between 2003 and 2014 (Figure E1).

Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre. A waiver of informed consent was obtained.

Data Sources

Ontario has universal healthcare insurance, and individual-level details regarding health services provided to all residents are captured in high-quality health administrative databases. Details on these databases are available from the ICES (formerly Institute for Clinical Evaluative Sciences) Data Repository at https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx. For the current study, these databases were linked on an individual level using unique encoded identifiers. The resulting data set is held securely in coded form at the ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access (available at www.ices.on.ca/DAS). A full data set creation plan for the study is available from the authors upon request.

Study Population

We included all insured Ontario residents 66 years of age and older who met a validated case definition of physician-diagnosed COPD (COPD cohort) and/or asthma (asthma cohort) using health administrative data obtained between September 1, 2003, and March 31, 2014, and who received a medication for their disease after being identified. The subjects had to be at least 66 years old in order to have a 1-year look-back period so that we could obtain information on medication use (25).

Physician-diagnosed asthma was identified using a validated case definition of one or more asthma hospitalizations and/or three or more asthma physician visits within 2 years (89.8% [95% confidence interval (CI), 85.9–92.8] specificity and 67.9% [95% CI, 60.8–74.3] sensitivity compared with a clinical reference standard) (26).

Physician-diagnosed COPD was identified using a validated case definition of one or more COPD hospitalizations and/or three or more COPD ambulatory care visits within 2 years (95.4% specificity [95% CI, 92.6–97.4] and 57.5% sensitivity [95% CI, 47.9–66.8]) (27).

As in the real world, individuals could have both COPD and asthma features (28, 29). To further examine the impact of ICS on older people with asthma who had elements of COPD, we stratified by

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concurrent features of COPD suggested by one or more previous COPD ambulatory care visits, emergency department visits, or hospitalizations. These criteria were purposely more relaxed than the case definition described above to increase sensitivity and because codes for asthma may overshadow those for COPD in patients with both diagnoses. Likewise, we stratified our cohort of people with COPD by concurrent features of asthma suggested by one or more previous asthma ambulatory care visits, emergency department visits, or hospitalizations.

Exposure

The exposure was new receipt or use of ICS, alone or in combination with other medications, established by a preceding 1-year ICS-free period (30). The initiation date was the index date, to avoid immortal time bias.

We studied new users to prevent "prevalent user" bias, as prevalent users are more likely to adhere to, tolerate, and thus benefit from ICS treatment, resulting in improved outcomes compared with new users (31–33). Studying new users also reduces unmeasured confounding because treatments are often started at comparable times during the natural history of the disease (33). New ICS users were compared with people who received a prescription for another COPD or asthma medication who also did not use ICS in the previous year. These medications included long-acting β-agonists, short-acting β-agonists, long-acting muscarinic antagonists, and short-acting muscarinic antagonists), and their date of initiation defined the index date for these subjects.

Outcomes

Individuals were followed from their index dates to death, an outcome of interest, or March 31, 2015, whichever occurred first, at which point they were censored (Figure E1).

Primary outcomes. Because asthma and COPD can have similar presentations in the acute setting (34), the primary effectiveness outcome was hospitalization for obstructive lung disease (OLD) (COPD or asthma). The primary safety outcome was hospitalization for pneumonia.

Secondary outcomes. Secondary outcomes were hospitalizations for osteoporotic fractures, cataract surgery, incident diabetes, or cardiovascular disease (CVD), and all-cause mortality. Further details are provided in the online supplement (Table E1).

Risk Factors and Confounders

Sixty-three potential confounding variables considered at the index date were demographics, asthma and/or COPD severity (i.e., prior outpatient visits, emergency department visits, and hospitalizations related to COPD/asthma, and prior use of oral corticosteroids and respiratory antibiotics), comorbidities, treatment, and exposure for prior primary and specialist care, flu vaccination, and spirometry (Tables 1 and E1). Indicators of preventive care were used to control for a possible healthy user effect (33). The severity of comorbidities at baseline was approximated using an aggregated score, the Johns Hopkins Aggregated Diagnosis Groups categories (The Johns Hopkins ACG System, version 10). Further details are provided in Tables E1 and E2.

Analyses

Descriptive statistics characterized the study population. Unadjusted event-free survival was assessed using the Kaplan–Meier method and compared between exposed and unexposed groups with the log-rank test.

To address potential confounding, we modeled propensity scores (the probability of a patient initiating ICS given his or her unique characteristics) using the variables mentioned above. Inverse probability of exposure weighting using propensity scores was used to minimize the effect of confounding (35–37). This method allows one to estimate the marginal effect of new receipt of ICS on outcomes in the same metric that is reported in RCTs with time-to-event outcomes (35). An advantage of using inverse probability of exposure weighting is that by assigning different weights, one can estimate both the average treatment effect (ATE) and the ATE on the treated (ATT) (37). ATE estimates how outcomes would differ if everyone in the sample were exposed versus if everyone were not. ATT estimates the analogous quantity averaging only over individuals who were exposed. Because we were interested in the effect of a new receipt of ICS on adverse health consequences in older individuals with chronic airway diseases, we chose the ATT to be our primary focus (ATE was explored in a sensitivity analysis). Weighted propensity scores also often produce more precise estimates than propensity score matching (37). Balance between variables by exposure was assessed using the absolute standardized mean difference of the effect size and the Kolmogorov–Smirnov statistic (38).

The Kaplan–Meier method was used to estimate event-free survival by exposure in the propensity score–weighted sample (35). The hazard of the outcomes was regressed on subjects' ICS user status using a Cox-proportional hazards model in the weighted sample (39, 40). An intention-to-treat analysis was considered as the main approach, as even with a "new user" study design, an on-treatment analysis can bias the results if nonadherence is informative (33, 41). A time-dependent analysis (i.e., the "treatment switching" method) has not been recommended for evaluating medication effects when the same medications are added or increased at times of disease instability (41).

A priori–defined statistical interactions between receipt of ICS and the presence of asthma in patients with COPD, and vice versa, were tested. Finally, as hypothesized *a priori*, we stratified the analysis of people with asthma by features suggestive of COPD, and the analysis of people with COPD by features suggestive of asthma.

Additional Analyses

Given that some subjects with a low probability of treatment can be disqualified when a propensity scoring approach is used, to determine whether the results were generalizable to the entire study population, we used multivariable Cox-proportional hazards regressions adjusted for all covariates.

To determine whether more certainty about the diagnosis of COPD or asthma influenced the results, we tested the interaction between prior spirometry and new ICS use, and stratified by previous receipt of spirometry. Older individuals and frail individuals are usually excluded from RCTs; therefore, to assess the effects of age and frailty on the association between ICS use and our primary outcome of interest, we tested two separate interactions between age or frailty and ICS use, and stratified individuals by age groups and frailty.

We conducted a further secondary analysis in which individuals were censored at the time they stopped using ICS. Further details on the calculations for duration of

Table 1. Characteristics of older individuals with physician-diagnosed asthma (overall and by new receipt of inhaled corticosteroids)

Characteristics		New ICS Users	Non-ICS Users (Control Subjects)	Absolute Standardized Mean Difference of the Effect Size and Kolmogorov–Smirnov Statistics, *P* Value	Non-ICS Users after Propensity Score Weighting*, Mean	Absolute Standardized Mean Difference of the Effect Size and Kolmogorov–Smirnov Statistics, *P* Value
Number		42,031	45,659		31,329	
Demographics at baseline						
Age, yr, median (IQR)		70 (67–77)	71 (67–79)	0.132, 0.00	72.7 yr	0.001, 1.00
Male sex, %		33.4	37.6	0.088, 0.00	33.0	0.002, 0.82
Socioeconomic status, quintiles, %	Quintile 1 (lowest)	19.8	22.2	0.062, 0.00	20.0	0.001, 1.00
	Quintile 5 (highest)	19.4	18.0	0.039, 0.00	19.0	0.000, 1.00
Rural residence (vs. urban), %		10.4	14.6	0.137, 0.00	11.0	0.002, 0.82
Immigrant, %		7.7	4.9	0.106, 0.00	7.6	0.005, 0.56
Comorbidities, %						
Frailty		5.6	8.0	0.106, 0.00	5.7	0.007, 0.31
Cardiovascular disease		15.0	19.9	0.136, 0.00	15.0	0.001, 0.87
Hypertension		73.2	73.7	0.010, 0.14	73.3	0.001, 0.88
Diabetes		29.7	30.0	0.006, 0.34	29.7	0.002, 0.81
Gastroesophageal reflux disease		13.8	14.2	0.012, 0.07	13.8	0.002, 0.83
Atopy		78.2	74.6	0.088, 0.00	78.2	0.001, 0.91
Mental health condition		7.4	7.9	0.020, 0.00	7.6	0.008, 0.28
Dementia		7.7	11.7	0.147, 0.00	7.7	0.000, 0.97
Lung cancer		0.7	1.5	0.093, 0.00	0.8	0.004, 0.55
Osteoporotic fracture		4.7	5.5	0.038, 0.00	4.7	0.004, 0.54
Cataract		17.0	16.6	0.011, 0.09	17.2	0.003, 0.66
Healthcare exposure, %						
Primary care visits in the last yr		96.3	95.8	0.026, 0.00	96.3	0.002, 0.79
Flu vaccination in the last yr		57.7	56.0	0.035, 0.00	57.4	0.007, 0.37
Spirometry in the last 5 yr		38.7	38.3	0.009, 0.19	38.8	0.001, 0.88
Long-term care resident		2.2	6.1	0.260, 0.00	2.3	0.002, 0.75
Previous asthma- or COPD-related hospitalizations, %						
Hospitalizations for asthma, last 5 yr		3.5	4.4	0.052, 0.00	3.4	0.003, 0.69
Hospitalizations for COPD, last 5 yr		3.7	8.4	0.246, 0.00	3.8	0.006, 1.00
Medications in the last yr, %						
LABA only		0.5	2.8	0.310, 0.00	0.6	0.006, 0.30
LAMA only		1.3	5.4	0.367, 0.00	1.4	0.007, 0.25
SABA only		8.7	26.0	0.614, 0.00	8.8	0.003, 0.57
SAMA only		1.1	6.3	0.507, 0.00	1.1	0.003, 0.60
SABA and SAMA		1.1	5.8	0.459, 0.00	1.1	0.005, 0.39
Oral corticosteroids		8.7	10.5	0.063, 0.00	8.7	0.000, 0.96
Respiratory-related antibiotics	β-lactams	18.5	17.0	0.040, 0.00	18.5	0.000, 0.98
	Macrolides	23.2	21.2	0.047, 0.00	23.1	0.000, 0.96
	Cephalosporins	7.0	7.0	0.003, 0.65	7.0	0.003, 0.74
	Fluoroquinolones	16.0	17.3	0.034, 0.00	15.9	0.003, 0.67
Proton pump inhibitors		32.1	31.0	0.025, 0.00	32.0	0.002, 0.78

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; IQR = interquartile range; LABA = long-acting β-agonists; LAMA = long-acting muscarinic antagonists; SABA = short-acting β-agonists; SAMA = short-acting muscarinic antagonists.

Individuals who did not receive ICS are presented as unweighted (original) or weighted on the propensity score.

*In weight allocation using the average treatment effect on the treated approach (used in our main analysis), the exposure group has weight 1 and only the control group is weighted. In weight allocation using the average treatment effect approach (used in sensitivity analysis), both groups are weighted (for more details, *see* the online supplement). Details on all 63 variables included in the propensity score are provided in Table E2.

continuous ICS use are provided in Table E1.

Because the high number of deaths in this older population (1) could have precluded hospitalization (42), we also conducted analyses accounting for this competing risk.

We assessed the sensitivity of the results to unmeasured confounders not available in the health administrative data using the approach recommended by Lin and colleagues (43).

All statistical analyses were performed using R version 2.15.2 (https://www.r-project.org).

Results

Study Populations

The study included 87,690 individuals with physician-diagnosed asthma: 27% with concurrent COPD, median age 71 years, 36% men (Figure E2). Among these individuals, the 48% who were new ICS users were more likely to be female and live in urban (vs. rural) areas, and they were less likely to live in a long-term care institution, have prior CV comorbidity, be hospitalized for respiratory disease, or receive other inhaled medication (Table 1).

There were 150,593 individuals with physician-diagnosed COPD: 25% with concurrent asthma, median age 76 years, 52% men (Figure E3). Similarly to the asthma cohort, among these individuals, the 32% who were new ICS users were more likely to be female and live in urban areas. They were also less likely to live in a long-term care institution, have prior CV comorbidity, be hospitalized for respiratory disease, or receive other inhaled medication (Table 2).

Compared with individuals with asthma, individuals with COPD were more likely to be older, male, and have more comorbidities (results not shown).

ICS Effectiveness and Safety in People with Asthma

Among older individuals with asthma, 12% who received ICS (compared with 18% who did not receive ICS) were hospitalized with OLD over a median of 5.1 years (interquartile range: 2.3–8.7 yr). Time to first hospitalization was longer in those who received ICS ($P < 0.001$) (Figure 1).

Propensity score weighting achieved excellent balance in baseline characteristics between people who did and did not receive ICS (Table 1; Figure E4). Among the balanced individuals, the absolute reduction in hospitalizations for OLD with receipt of ICS at 5 years was a modest 1.3% (95% CI, 0.7–2.1%). The relative reduction in hazard was 12% (Tables 3 and E3). However, having features of COPD significantly modified the association (P value for the interaction <0.01). A greater benefit was observed in individuals *without* features of COPD, and receipt of ICS was associated with a 16% decreased hazard of hospitalization (Table 3).

In terms of safety, new users of ICS had fewer hospitalizations for pneumonia or CVD and less all-cause mortality than those who did not receive ICS. They also did not appear to have an increased risk of cataract surgery, hospitalization for fractures related to osteoporosis, or incident diabetes (Table 3).

Effectiveness and Safety of ICS in People with COPD

Among older individuals with COPD, 27.1% who received ICS (compared with 29.7% who did not receive ICS) were hospitalized with OLD over a median of 3.5 years (interquartile range: 1.4–6.6 yr). Time to first hospitalization was longer in those who received ICS (log-rank test: $P < 0.0001$) (Figure 2).

Propensity score weighting again achieved excellent balance in baseline characteristics between individuals with COPD who did and did not receive ICS (Tables 2 and E2; Figure E5). Among the balanced individuals, ICS was not associated with a decrease in absolute or relative risk of hospitalizations for OLD (Tables 3 and E3). However, this was modified if asthma features were present (P value for the interaction <0.01). People with COPD and features of asthma who received ICS had a 12% reduced hazard of hospitalization for OLD, and those with no indications of asthma had a small but statistically significant increase in OLD hospitalizations of questionable clinical significance (Table 3).

In terms of safety, new users of ICS with COPD had no increase in hospitalizations for pneumonia, but those with asthma features had a reduction in pneumonia hospitalizations and those without trended toward higher risk (Table 3). Hazards associated with ICS were not increased for cataract surgery, hospitalizations for CVD, or fractures related to osteoporosis or diabetes development. There was a small but statistically significant improvement in survival in people with ICS (Table 3).

Secondary Analyses

The results obtained using multivariable Cox-proportional hazards regressions adjusted for all covariates were similar to those obtained from the primary analysis (Table E4). Our findings were robust when analyses were repeated in individuals with prior spirometry (Tables E5 and E6), when ICS users were censored at the time they stopped using ICS (Table E7), and in sensitivity analyses considering potential unmeasured confounding (Figures E6–E10).

We found statistically significant interactions between age/frailty and the association between ICS use and OLD hospitalizations in both the asthma and COPD cohorts (Tables E8 and E9). In the COPD cohort, subjects who were older than 75 years and those who were frail and receiving ICS had a higher risk of hospitalization. In individuals who were 75 years old and younger, we found a small but statistically significant protective effect of new ICS use on OLD hospitalizations (Table E8). In patients with asthma, we found a greater protective effect of ICS in nonfrail individuals 71 years of age and younger (Table E9).

Competing Risk Analyses

Among 27,310 individuals with asthma who died during follow-up (31.1%), 18,946 died (a competing event) without being hospitalized with OLD and 19,047 died without being hospitalized with pneumonia. Among 83,254 (55.3%) individuals with COPD who died during follow-up, 51,839 died without being hospitalized with OLD and 56,731 died without being hospitalized with pneumonia.

Similar results were obtained for our primary outcomes adjusting for competing risk of death (Table E10).

Discussion

We conducted a large, real-life, retrospective, longitudinal population study of older individuals with physician-diagnosed asthma and COPD, and found that among older adults with asthma and concurrent asthma and COPD, but not with COPD alone, new use of ICS was associated with a lower risk of OLD hospitalizations and a favorable safety profile. Among

Table 2. Characteristics of older individuals with physician-diagnosed chronic obstructive pulmonary disease (overall and by new receipt of inhaled corticosteroids)

Characteristics		New ICS Users	Non-ICS Users (Control Subjects)	Absolute Standardized Mean Difference of the Effect Size and Kolmogorov–Smirnov Statistics, *P* Value	Non-ICS Users after Propensity Score Weighting*, Mean	Absolute Standardized Mean Difference of the Effect Size and Kolmogorov–Smirnov Statistics, *P* Value
Number		47,557	103,036			
Demographics at baseline						
Age, median (IQR), yr		75 (70–82)	76 (70–82)	0.048, 1.00	76.2	0.005, 1.00
Male sex, %		49.6	52.9	0.066, 0.00	49.9	0.006, 0.30
Socioeconomic status, quintiles, %	Quintile 1 (lowest)	24.4	25.2	0.019, 0.00	24.3	0.000, 0.97
	Quintile 5 (highest)	16.0	15.4	0.013, 0.00	15.8	0.003, 0.97
Rural residence (vs. urban), %		16	19	0.068, 0.00	16.3	0.003, 0.83
Immigrant, %		3.6	2.6	0.051, 0.00	3.5	0.005, 0.38
Comorbidities, %						
Cardiovascular disease		28.1	31.0	0.063, 0.00	28.3	0.004, 0.51
Hypertension		76.6	74.6	0.046, 0.00	76.5	0.001, 0.83
Diabetes		32.0	29.9	0.045, 0.00	31.9	0.003, 0.64
Gastroesophageal reflux disease		13.5	13.5	0.001, 0.80	13.6	0.001, 0.88
Atopic conditions		65.8	63.0	0.059, 0.00	65.6	0.003, 0.63
Mental health condition		7.6	7.7	0.005, 0.42	7.8	0.005, 0.36
Dementia		14.7	17.9	0.089, 0.00	14.9	0.004, 0.48
Lung cancer		2.9	3.8	0.053, 0.00	3.0	0.004, 0.44
Osteoporosis		7.3	8.0	0.023, 0.00	7.5	0.006, 0.30
Cataract		23.5	21.9	0.039, 0.00	23.6	0.001, 0.83
Healthcare exposure, %						
Primary care visits in the last yr		94.8	95.3	0.021, 0.00	94.8	0.001, 0.93
Flu vaccination in the last yr		54.1	53.5	0.012, 0.03	54.0	0.003, 0.61
Spirometry in the last 5 yr		42.9	43.9	0.020, 0.00	42.9	0.002, 0.79
Being in long term care		5.2	9.8	0.206, 0.00	5.3	0.003, 0.58
Previous asthma- or COPD-related hospitalizations, %						
Hospitalizations for asthma, last 5 yr		1.3	1.1	0.012, 0.02	1.2	0.005, 0.40
Hospitalizations for COPD, last 5 yr		17.8	20.6	0.074, 0.00	18.0	0.004, 0.46
Medications, in the last yr, %						
LABA only		0.8	2.9	0.235, 0.00	0.8	0.006, 0.23
LAMA only		7.0	16.2	0.357, 0.00	7.2	0.006, 0.22
SABA only		11.8	24.2	0.383, 0.00	12.0	0.006, 0.24
SAMA only		2.6	9.2	0.416, 0.00	2.7	0.006, 0.27
SABA and SAMA		2.8	9.0	0.371, 0.00	2.9	0.005, 0.33
Oral corticosteroids		10.0	11.0	0.033, 0.00	10.1	0.003, 0.64
Respiratory-related antibiotics	β-lactams	15.9	15.0	0.025, 0.00	15.8	0.004, 0.49
	Macrolides	22.2	20.7	0.036, 0.00	22.0	0.003, 0.61
	Cephalosporins	8.0	7.8	0.008, 0.16	8.0	0.001, 0.81
	Fluoroquinolones	22.0	23.1	0.027, 0.00	22.0	0.000, 0.97
Proton pump inhibitors		33.8	32.5	0.029, 0.00	33.7	0.002, 0.71

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; IQR = interquartile range; LABA = long-acting β-agonists; LAMA = long-acting muscarinic antagonists; SABA = short-acting β-agonists; SAMA = short-acting muscarinic antagonists.

Individuals who did not receive ICS are presented as unweighted (original) or weighted on the propensity score.

*In weight allocation using the average treatment effect on the treated approach (used in our main analysis), exposure group has weight 1 and only controlled group is weighted. In weight allocation using the average treatment effect approach (used in sensitivity analysis), both groups are weighted (for more details, *see* the online supplement). Details on all 63 variables included in the propensity score are provided in Table E2.

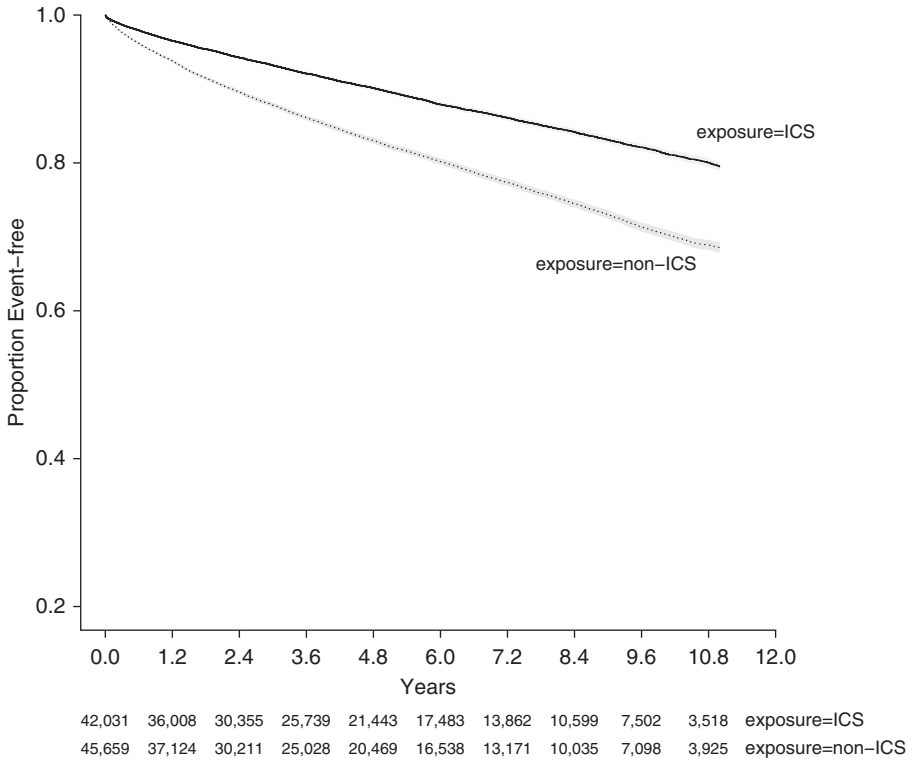

Figure 1. Unadjusted Kaplan–Meier survival curves for hospitalization due to obstructive lung disease (chronic obstructive pulmonary disease or asthma) in older individuals with asthma by receipt of inhaled corticosteroids (ICS). The numbers at risk are presented above the *x*-axis.

individuals with COPD and no concurrent asthma, there was no evidence that ICS prevented OLD hospitalizations and there was a trend toward increased risk of hospitalizations for pneumonia. To the best of our knowledge, this is the first large-scale, real-world population study to comprehensively examine the effectiveness and safety of ICS in people with asthma, COPD, and, particularly, both diseases together—an area for which there is little guiding evidence (22, 44). By allowing the magnitudes of risks and benefits to be directly compared, our study provides practical real-world findings that can be used by affected patients and their physicians to optimize care and health outcomes.

Our findings confirm previous studies that supported the use of ICS in older individuals with asthma (45, 46) and in individuals with COPD and concurrent asthma (21, 47–49). The results of our study are also consistent with previous studies that examined the role of ICS in people with COPD for severe exacerbations requiring hospitalization as an outcome (50–54). Although earlier RCTs demonstrated modestly improved outcomes in patients with COPD using ICS, more recent studies have cast doubt on the exact role of ICS by highlighting their risks—specifically, pneumonia (55). In this study, we extended these findings by examining the risks/benefits of ICS in a large, real-world COPD population without asthma, and found a negative risk/benefit profile. This suggests that ICS prescribed for the wrong patients with COPD might cause harm. One limitation of our study is that we included all individuals with COPD in the COPD cohort instead of focusing on those with frequent exacerbations, for whom ICS are recommended. This would be an important area of future study.

We did not find a clearly increased risk of pneumonia in people with COPD, which seems inconsistent with some previous studies (54, 56). However, it is consistent with a meta-analysis by Festic and colleagues, who found that although ICS use was associated with a significantly increased unadjusted risk of pneumonia, it was not associated with an increased risk of pneumonia fatality in RCTs (15). The authors suggested that although ICS might predispose to increased risk of pneumonia in people with COPD, their antiinflammatory effect counterbalances pneumonia, resulting in similar or improved mortality (15). In support of this hypothesis, other studies have suggested that ICS decrease the risk of pneumonia (57–59). Numerous RCTs that reported an increased risk of pneumonia have also been criticized for focusing mainly on ambulatory events that were not radiologically confirmed and/or for not uniformly adjusting for potential confounders.

Our findings are also consistent with studies showing that, despite an improvement in respiratory outcomes, ICS do not significantly decrease the risk of CVD (60). The exception in our study was people with asthma but no COPD, who might have gained a modest benefit, perhaps through reductions in serum C-reactive protein levels (61, 62). Our study was also consistent with other studies showing an association between ICS and significantly lower all-cause mortality (15, 61, 63, 64), which has been explained by the immunosuppressive and antiinflammatory effects of ICS treatment (14, 65), and the potentially protective effect of ICS on death due to nonrespiratory causes (64). Future studies will need to rigorously test this hypothesis.

Our study has several limitations. First, there are limitations associated with the "new users" design, as this design may give excessive weight to short-term users (31) and those starting new courses of therapy (31, 32). To address this, we adjusted for concurrent medication use, markers of disease severity, and factors associated with medication adherence.

Selection bias is a concern with observational research studies, and in this study, patients who received ICS for the first time—in comparison with our control group, who were users of other medications—were more likely to have been prescribed them for more severe or unstable disease. To avoid this, we considered many potential confounders and were successful in achieving an excellent balance between our groups. Furthermore, this phenomenon would bias our results toward finding ICS to be ineffective in reducing asthma and COPD hospitalizations. Thus, the positive results we obtained in people with asthma and concurrent asthma and COPD are likely underestimated. Although this bias could, at

Table 3. Adjusted association between receipt of inhaled corticosteroids and the primary and secondary outcomes in older individuals with chronic airway disease*

Outcomes	Individuals with Asthma Hazard Ratio (95% Confidence Interval), *P* Value				Individuals with Chronic Obstructive Pulmonary Disease Hazard Ratio (95% Confidence Interval), *P* Value			
		History of Chronic Obstructive Pulmonary Disease				History of Asthma		
Number	All 87,690	Yes 23,799		No 63,891	All 150,593	Yes 37,319		No 113,274
Primary Outcomes								
Obstructive lung disease hospitalization	**0.88 (0.85–0.92)** <0.0001	0.95 (0.89–1.00), 0.07		**0.84 (0.79–0.88)** <0.0001	1.00 (0.98–1.02) 0.81	**0.88 (0.84–0.92)** <0.0001		**1.06 (1.03–1.08)** <0.0001
Pneumonia hospitalization	**0.89 (0.86–0.93)** <0.0001	**0.90 (0.84–0.96)** 0.001		**0.89 (0.85–0.94)** <0.0001	0.99 (0.96–1.01) 0.25	**0.90 (0.86–0.95)** <0.0001		**1.03 (1.00–1.06)** 0.03
Secondary Outcomes								
All-cause mortality	**0.88 (0.86–0.91)** <0.0001	**0.91 (0.87–0.96)** <0.001		**0.87 (0.84–0.90)** <0.0001	**0.92 (0.91–0.94)** <0.0001	**0.90 (0.87–0.93)** <0.0001		**0.95 (0.93–0.96)** <0.0001
Cardiovascular disease hospitalization	**0.91 (0.88–0.94)** <0.0001	**0.96 (0.91–1.02)** 0.22		**0.89 (0.85–0.92)** <0.0001	0.98 (0.96–1.00) 0.07	**0.94 (0.90–0.98)** <0.01		1.01 (0.98–1.04) 0.48
Cataract surgery	0.95 (0.89–1.03) 0.23	0.97 (0.85–1.11) 0.64		0.95 (0.87–1.04) 0.28	**0.93 (0.88–0.98)** <0.01	0.96 (0.86–1.06) 0.39		**0.93 (0.87– 0.99)** 0.02
Hospitalization for fractures related to osteoporosis	1.00 (0.97–1.04) 0.85	0.98 (0.92–1.05) 0.59		1.01 (0.97–1.05) 0.61	1.00 (0.97–1.02) 0.76	**0.94 (0.89–0.99)** 0.02		1.02 (0.99–1.06) 0.18
Incident diabetes†	1.01 (0.97–1.06) 0.58	1.00 (0.91–1.10), 0.97		1.02 (0.96–1.08) 0.50	1.02 (0.98–1.07) 0.30	1.00 (0.93–1.08) 0.99		1.03 (0.98–1.08) 0.21

Reference group: nonusers of inhaled corticosteroids at index date.
Items in bold indicate a statistically significant effect.
*Estimates of the average treatment effect on the treated.
†Among subjects who were free of diabetes at baseline (n = 61,545).

least in part, explain the decreased effectiveness of ICS in people with COPD, we believe it is unlikely that we failed to successfully balance confounders in the COPD-only group and not the others. Furthermore, any bias would shift both effectiveness and safety outcomes, likely in opposite directions, maintaining the same or similar ICS risk/benefit profiles.

To ensure that we sufficiently addressed selection bias, we conducted further analyses to determine the likelihood that unmeasured confounding could explain our results. According to our sensitivity analyses (Figures E6–E10), an unmeasured confounder, such as active smoking, would have to be twice as prevalent in non-new ICS users than in new ICS users, and have no correlation with any of the variables that were already adjusted for (e.g., the presence of CVD) for it to explain away the findings in individuals with concurrent COPD and asthma—a situation that is unlikely. Furthermore, we found that although it was plausible to find an unmeasured confounder that would cause the observed adjusted hazard ratio of 1.06 (95% CI, 1.03–1.08) in the COPD without a history of asthma group to become nonsignificant (i.e., be entirely due to residual confounding), it was unlikely that a confounder existed that would cause the same hazard ratio to become protective.

Misclassification is another common limitation of studies using health administrative data, which could create bias if it introduced a second condition that would be more likely to respond to ICS than the one being studied. For example, if people with asthma were mistakenly included in our COPD ICS group, this could bias results in the COPD group to favor ICS. Although such misclassification could have occurred in our study that might have caused some overlap between the groups (as occurs in real life), the asthma group contained mostly people with asthma and the COPD group contained mostly people with COPD, as evident by the significantly different characteristics, notably with respect to age and mortality. Furthermore, we found a positive effect of ICS only in the asthma and concurrent asthma/COPD cohorts, and not in patients with COPD. In a second scenario, if the misclassified condition being introduced was less likely to respond to ICS than the one being studied (for example, if heart failure was mistaken for COPD), it would likely attenuate the effectiveness of

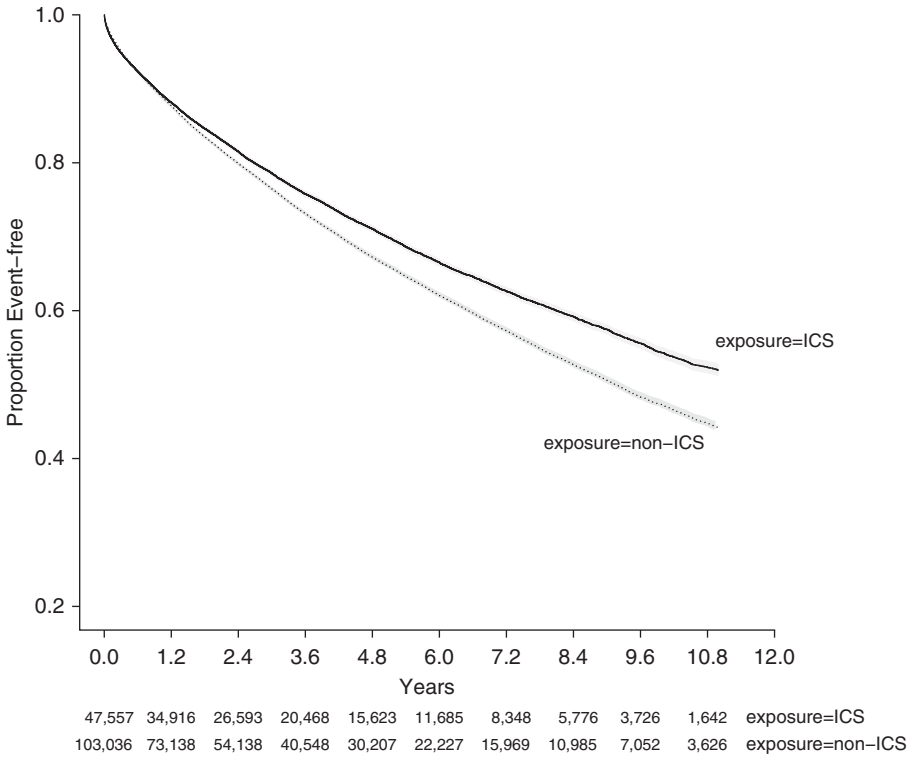

Figure 2. Unadjusted Kaplan–Meier survival curves for hospitalization due to obstructive lung disease (chronic obstructive pulmonary disease or asthma) in older individuals with chronic obstructive pulmonary disease by receipt of inhaled corticosteroids (ICS). The numbers at risk are presented above the *x*-axis.

ICS, but not bias it in one direction or another.

To address any residual concerns that misclassification played a role, we conducted further analyses. A limitation of our study is that, as occurs in the real world, not all people received spirometry to confirm their COPD diagnoses, and furthermore, there were no spirometry results for those who did. Previous studies have shown that only 40% of people with COPD undergo pulmonary function testing around the time of diagnosis (66, 67), only half (52.5%) of all asthma diagnoses are confirmed by spirometry, and only 19.1% of patients with asthma are monitored annually with spirometry (68). This is consistent with our findings. We used multiple approaches to address this limitation and confirm the robustness of our results: *1*) we included prior spirometry in the propensity score and multivariable Cox regressions; *2*) we included potential predictors of receiving spirometry, such as sex, age, income status, and prior comorbidities (66, 69) in our statistical model; and *3*) we performed an additional analysis and did not find that our results changed among people who had received prior spirometry.

We did not adjust for temporal trends in treatment of asthma and/or COPD in our study. However, we believe that temporal trends did not bias our results significantly because the time frame was relatively short, temporal trends would affect both groups, and the comparison groups in our study were balanced by age, baseline comorbidities, treatment, and prior healthcare exposure.

Finally, two real-world factors likely caused us to underestimate the incremental benefit of new ICS use: *1*) the "intention to treat" study design, as among people with asthma, 57% of individuals in the non-ICS group initiated ICS in the follow-up period, and among people with COPD, 49% of the non-ICS group initiated ICS in the follow-up period; and *2*) low adherence to inhaled medications, as has been well documented in the literature (70).

The strengths of our study are its real-world relevance and comprehensive examination of both the effectiveness and safety of ICS in elderly people with physician-diagnosed asthma, COPD, and both at the same time, so that risks and benefits could be reliably compared. Although other studies have focused on the impact of ICS on COPD and asthma hospitalizations and safety separately, by studying both in one study we were able to provide a more practical, complete picture of ICS use. Although RCTs might be considered the gold standard for producing reliable evidence, only a highly exceptional RCT or series of RCTs could replicate our approach, and even then would lack the real-world nature of our findings.

Conclusions

Among older adults with asthma and concurrent asthma and COPD, but not COPD alone, newly prescribed ICS were associated with a lower risk of OLD hospitalizations and showed a favorable safety profile. Older adults with asthma but no history of COPD benefited the most from ICS use, and those with COPD and no features of asthma had the highest risk of respiratory hospitalizations and pneumonia. ■

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