Effect of type and dosage of newly prescribed inhaled corticosteroids on obstructive lung disease and pneumonia hospitalisations in older individuals with asthma, COPD or both: a retrospective study of health administrative data

To the Editor:

The safety and risk–benefit profiles associated with different types and dosages of inhaled corticosteroids (ICS) in older individuals with asthma and COPD remain unknown [1, 2]. Limited evidence suggests that adults with asthma prescribed medium or high ICS doses are at risk of clinically important systemic side-effects that do not plateau with higher doses as efficacy outcomes do [3]. Older patients with COPD have been shown to have increased risk of pneumonia with both budesonide and fluticasone [4]; however, the risk seems greater with the latter [2, 4–6].

Our objective was to determine whether specific types or dosages of ICS were differentially associated with rates of hospitalisation for obstructive lung disease and pneumonia in older new users of ICS with asthma or COPD.

For this retrospective longitudinal population study we utilised provincial health administrative data from all insured individuals aged 66 years and older living in Ontario, Canada between 2003 and 2014 who met a validated case definition of physician-diagnosed COPD (COPD cohort) and/or asthma (asthma cohort) and were new ICS users (as determined by a preceding 1-year ICS-free period) [7]. Full definitions of the population of interest, exposure and covariates are reported elsewhere [8]. Overlap in COPD and asthma was examined by stratifying individuals with each (COPD or asthma) by a history of the other defined as one or more previous ambulatory care visits, emergency department visits or hospitalisations. Ethics approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Canada. A waiver of informed consent was obtained.

The ICS receipt date was the index date. ICS types were categorised as: 1) budesonide, 2) fluticasone and 3) other (beclomethasone, ciclesonide or mometasone). Initial ICS daily dosages were converted to their equivalent fluticasone dosage [9, 10]; for descriptive purposes, they were categorised as low (⩽250 µg), moderate (251–500 µg), and high (>500 µg) [11].

We followed included individuals from their index dates to death, an outcome of interest or 31 March, 2015, at which point they were censored. The primary outcome was hospitalisation for pneumonia; secondary outcome was hospitalisation for asthma or COPD.

We considered important covariates [8], including individual demographics, comorbidities, disease severity, medications, oxygen, long-term positive airway pressure treatment, primary and specialist care, flu vaccination, and spirometry (table 1).

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This study suggested a less favourable safety-effectiveness profile for fluticasone compared to budesonide and other ICS in elderly individuals with asthma, COPD or both. Higher ICS dose was not associated with improved effectiveness in these populations. https://bit.ly/3iNdjkQ

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TABLE 1 The effect of inhaled corticosteroids (ICS) dosages/type on the outcomes, obstructive lung disease and pneumonia hospitalisations, adjusted for baseline differences, including the type/dosage of the ICS and year of the ICS prescription[#]

Initial ICS dosages and type	Adjusted HR (95% CI)	
	Obstructive lung disease hospitalisations	Pneumonia hospitalisations
Physician-diagnosed asthma		
ICS dosages		
1000 *versus* 500 µg[¶] of fluticasone equivalent dosage	1.05 (0.99–1.11)	1.04 (0.98–1.09).
ICS types		
Budesonide *versus* fluticasone	**0.79 (0.74–0.85)**	**0.88 (0.82–0.94)**
Other ICS *versus* fluticasone	**0.71 (0.60–0.85)**	0.90 (0.77–1.06)
Physician-diagnosed COPD		
ICS dosages		
1000 *versus* 500 µg[¶] of fluticasone equivalent dosage	1.04 (1.00–1.07)	**1.06 (1.02–1.10)**
ICS types		
Budesonide *versus* fluticasone	**0.80 (0.77–0.84)**	**0.88 (0.83–0.92)**
Other ICS *versus* fluticasone	**0.71 (0.63–0.79)**	**0.77 (0.69–0.87)**

Bold font indicates a statistically significant effect. [#]: variables included in the statistical model were demographics at baseline (age, sex, socioeconomic, rural and immigrant status, being in long-term care), prior comorbidities (frailty, cardiovascular (CV) hospitalisations, hypertension, diabetes, gastro-oesophageal reflux disease, atopy, mental health condition, dementia, cancer, osteoporosis, cataracts), prior disease severity (asthma and COPD hospitalisations in the past 5 years), medications in the past year prior to the index date (long-acting beta-agonists, long-acting anticholinergics, short-acting beta-agonists, short-acting anticholinergics, oral corticosteroids, respiratory-related antibiotics, proton pump inhibitors, CV medications), ICS dosages/type at the index date, ICS coverage in follow-up, prior utilisation of supplemental oxygen, long-term positive airway pressure treatment, primary and specialist care, flu vaccination, and spirometry. [¶]: comparing 75th to 25th percentile.

To investigate the relationship between ICS type and dosages and the outcomes of interest, we used multivariable Cox-proportional hazards regressions adjusted for all covariates including ICS type or dosage at the index date, as applicable, and the ICS coverage in follow-up. We modelled the fluticasone-equivalent daily ICS dose continuously using restricted cubic spline transformation. As hypothesised *a priori,* we stratified the asthma population by a history of COPD and the COPD population by a history of asthma [8]. Statistical analyses were performed using R version 2.15.2 (The R Project for Statistical Computing; www.r-project.org).

Of 87 690 individuals with physician-diagnosed asthma (27% with concurrent COPD), 42 031 (48%) were new ICS users: median age of 70 years (interquartile range (IQR): 67–77 years), 33% men. Of 150 593 individuals with physician-diagnosed COPD (25% with a history of asthma), 47 557 (32%) were new ICS users: median age of 75 years (IQR: 70–82 years), 50% men.

Over a median follow-up of 5.4 years (IQR: 2.5–8.9 years), of 42 031 asthma patients who were ICS new users, 4854 (12%) were hospitalised at least once for asthma or COPD, and 4990 (12%) were hospitalised at least once for pneumonia. Over a median follow-up of 3.7 years (IQR: 1.6–6.8 years), of 47 557 COPD patients who were ICS new users, 12 905 (27%) were hospitalised for asthma or COPD, and 10 872 (23%) were hospitalised for pneumonia.

Asthma ICS new users received a median of 750 µg of fluticasone equivalents per day (IQR: 500–1000 µg), with 59% using >500 µg and 41% using ⩾1000 µg daily. ICS treatment was initiated with budesonide in 29% of patients, with fluticasone in 65%, and with another ICS in 6%. In adjusted analyses, higher ICS dose (1000 µg *versus* 500 µg) was not associated with a higher risk of pneumonia hospitalisations (HR 1.04, 95% CI 0.98–1.09) and did not reduce asthma or COPD hospitalisation (HR 1.05, 95% CI 0.99–1.11) (table 1). Compared to fluticasone, budesonide was associated with fewer pneumonia hospitalisations (adjusted HR 0.88, 95% CI 0.82–0.94) and with fewer asthma or COPD hospitalisations (HR 0.79, 95% CI 0.74–0.85). Receipt of other ICS was also associated with fewer asthma or COPD hospitalisations (HR 0.71, 95% CI 0.60–0.85).

COPD ICS users received a median of 750 µg fluticasone equivalents per day (IQR 500–1000 µg), with 60% using >500 µg and with 45% using ⩾1000 µg. ICS treatment was initiated with budesonide in 22% of

patients, with fluticasone in 74% and another ICS in 4%. In adjusted analyses, a higher ICS dose (1000 µg *versus* 500 µg) was associated with a higher risk for pneumonia hospitalisation (HR 1.06, 95% CI 1.02–1.10) but not a reduction in asthma or COPD hospitalisations (HR 1.04, 95% CI 1.00–1.07) (table 1). Compared to fluticasone, budesonide (HR 0.88, 95% CI 0.83–0.92) and other ICS (HR 0.77, 95% CI 0.69–0.87) were associated with fewer pneumonia hospitalisations. Budesonide (HR 0.80, 95% CI 0.77–0.84) and other ICS (HR 0.71, 95% CI 0.63–0.79) were also associated with fewer asthma or COPD hospitalisations than fluticasone.

Results in individuals with concurrent COPD and asthma were similar to those in subjects with COPD or asthma alone in both populations, this was also confirmed by nonsignificant interactions terms (p-values>0.1).

Our findings are consistent with previous studies showing a higher risk of pneumonia associated with an increased daily ICS dose in individuals with COPD [6, 12]. They are also consistent with other studies showing more favourable safety-effectiveness profiles for budesonide and other ICS compared to fluticasone [2, 13]. This may be explained by differences in pharmacology and pharmacokinetics between medications [14]. It has been suggested that fluticasone may increase risk of pneumonia because of higher lipophilicity and slower dissolution rate [13]. Despite plausible mechanisms and adjustment for dosage, however, we cannot exclude confounding due to fluticasone being more likely to be prescribed in higher dosages in individuals with more severe disease.

Our study has several limitations. First, individuals with poor adherence or poor control on existing medications may be overrepresented among new users, and the 'new users' study design may give excessive weight to short-term users [15]. Further, early symptoms of pneumonia could be misclassified as a COPD exacerbation prompting the use of ICS, incorrectly attributing them to pneumonia; however, this bias would apply to all groups, and we did not see an increase in pneumonia in all groups. Unmeasurable variables could also confound study results such a symptom severity, lung function, smoking and blood eosinophil levels. Further, there was a possibility of confounding by indication if clinicians were more likely to prescribe fluticasone to sicker patients than other ICS. To minimise this, we employed a new users design and adjusted for multiple factors that were proxies of COPD or asthma severity.

Among older adults with physician-diagnosed COPD who were new users of ICS, higher ICS dose was associated with increased risk of pneumonia hospitalisations, but not with reduced risk of obstructive lung disease hospitalisations. Fluticasone appears to have a less favourable safety-effectiveness profile compared to other ICS in older individuals with asthma, COPD, or both. Our study adds important findings to the growing body of evidence on the relative magnitudes of risks and benefits according to ICS type and dose. This practical knowledge can be used by health professionals to optimise safe medication use and health outcomes in individuals with obstructive lung disease receiving ICS for the first time in later life.

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Data availability: In Ontario (Canada), details on virtually all physician and hospital services are captured in health administrative databases housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). For the current study, these databases were linked on an individual level using unique encoded identifiers. The resulting dataset is held securely in coded form at the ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified 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.

Author contributions: All co-authors were involved in the following: study conception and design, interpretation of data, revising the manuscript critically for the accuracy and important intellectual content, and final approval of the version to be published. T. Kendzerska additionally was involved in the following: literature search, obtaining administrative data, analyses of data and drafting of the manuscript. A.S. Gershon additionally was involved in ethics board application, obtaining administrative data, analyses of data and drafting of the manuscript. A.S. Gershon and T. Kendzerska had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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