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ORIGINAL RESEARCH

Inhaled Corticosteroids Particle Size and Risk of Hospitalization Due to Exacerbations and All-Cause Mortality in Patients with Chronic Obstructive Pulmonary Disease. A Nationwide Cohort Study

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Background: Extra-fine particle inhaled corticosteroids (ICS) improve peripheral airway distribution, but their effect on risk of exacerbations and all-cause mortality in patients with chronic obstructive pulmonary disease (COPD) is unclear.

Methods: This observational cohort study compares patients with COPD who received extra-fine particle ICS to those who received standard particle size ICS from 2010 to 2017 while followed in outpatient clinics. The primary outcome was the time to a COPD exacerbation that required hospitalization, with all-cause mortality as a secondary outcome. Data were analyzed using an adjusted Cox proportional hazards model and a competing risk analysis. Two predefined subgroup analyses of patients treated with pressurised metered dose inhalers (pMDIs) and patients with a previous exacerbation history, was carried out. Lastly, we created a propensity score matched cohort as a sensitivity analysis.

Results: Of the 40,489 patients included, 38,802 (95.8%) received stand particle size ICS and 1,687 (4.2%) received extra-fine particle ICS. In total 7,058 were hospitalized with a COPD exacerbation, and 4,346 died. No significant protective effect of extra-fine particle ICS against hospitalization due to COPD exacerbations (HR 0.93, 95% CI 0.82–1.05, p=0.23) or all-cause mortality (HR 1.00, 95% CI 0.85–1.17, p=0.99) was found when compared to standard particle size ICS. However, in the subgroup analysis of patients treated with pMDIs, extra-fine particle ICS was associated with reduction in risk of exacerbations (HR 0.72, 95% CI 0.63–0.82, p<0.001) and all-cause mortality (HR 0.72, 95% CI 0.61–0.86, p<0.001).

Conclusion: The administration of extra-fine particle ICS was not associated with reduced risk of exacerbations or all-cause mortality in our primary analysis. A subgroup consisting of patients treated with pMDIs suggested potential protective benefits.

Keywords: COPD, Inhaled Corticosteroids, Particle size, COPD exacerbations

Introduction

Inhaled corticosteroids (ICS) are commonly used for treatment of Chronic Obstructive Pulmonary Disease (COPD) in combination with bronchodilators.[1,2] ICS therapy has been shown to effectively prevent exacerbations in COPD patients

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with a history of frequent exacerbations and evidence of eosinophilic inflammation.[3–5] The impact of ICS on mortality in these patients is still somewhat uncertain.[2,6] The ETHOS and IMPACT trials suggest beneficial effects on all-cause mortality, although in milder COPD populations compared to our cohort.[7,8]

ICS particle size affects the distribution within the lungs.[9,10] The median mass aerodynamic diameter (MMAD) is the measure of particle size for ICS, which typically ranges from 1–5 µm in commonly used devices.[11] Extra-fine ICS particles, with a MMAD of less than 2 µm, are more likely to reach the peripheral airways.[9,12] The increased distribution of ICS in the peripheral airways may potentially reduce the risk of exacerbations and thereby mortality since exacerbations are one of the drivers of mortality risk.[13] Currently, two types of ICS with extra-fine particles are available: beclomethasone dipropionate hydrofluoroalkane inhaler (HFA) and extra-fine particle ciclesonide HFA.[14] The indication for extra-fine particle ICS for patients with COPD lacks consensus and receives minimal attention in the GOLD guideline.[13] Notably, no studies have elucidated a systematic algorithm for patient selection in this context. Given its typically elevated cost relative to alternative therapies, one might conjecture that its administration pertains to individuals exhibiting inadequate responses to prior treatment regimens.

Despite the potential benefits of extra-fine particle ICS in COPD management, there is limited evidence supporting their effectiveness on exacerbations and all-cause mortality in patients with COPD. Therefore, the clinical importance remains unclear. Thus, the aim of this study is to investigate whether the use of extra-fine particle ICS, as compared to standard particle size ICS, is associated with lower risk of exacerbations and all-cause mortality in patients with COPD.

Methods

Study Population and Design

This nationwide cohort study included patients with COPD followed in Danish outpatient clinics from January 2010 to December 2017. Patients with no redeemed prescriptions of ICS the year prior to cohort entry were excluded. The eligibility process is summarized in Figure 1. The primary outcome was hospitalization due to a COPD exacerbation, defined using

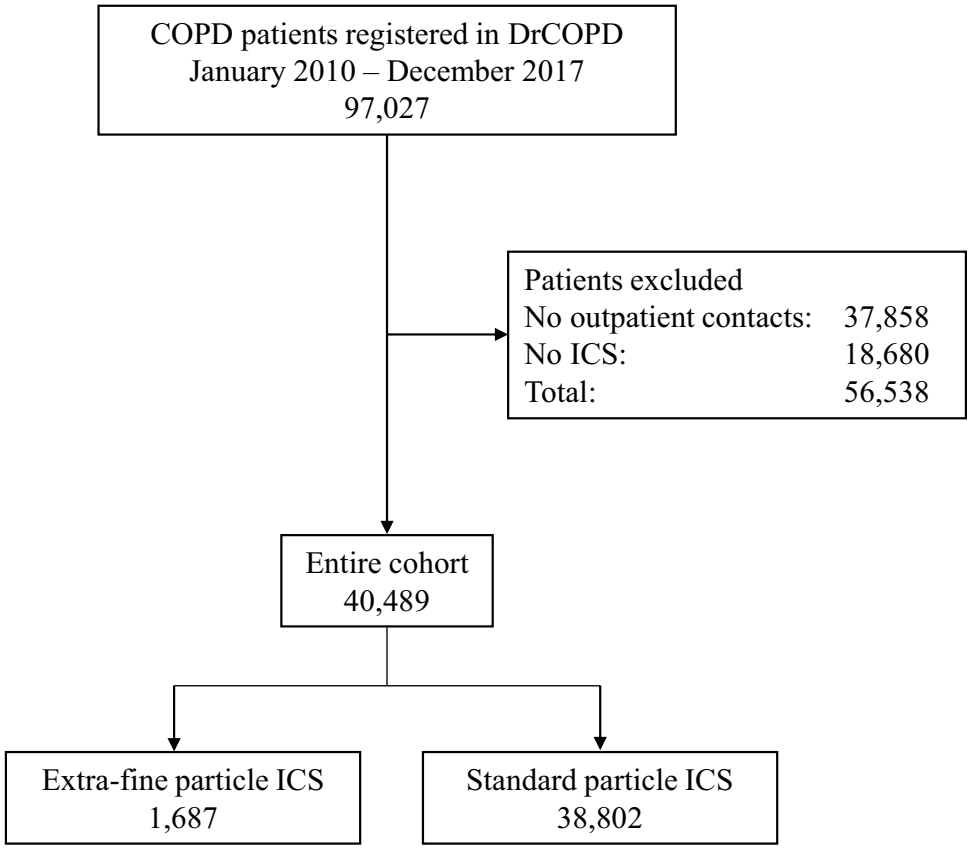

Figure 1 Study flowchart. Patients with no outpatient contacts and not in ICS treatment the year prior to cohort entry were excluded from the study.
Abbreviations: ICS, Inhaled Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; DrCOPD, Danish Registry of Chronic Obstructive Pulmonary Disease.

WHO ICD-10 diagnosis codes.[15] For the principal diagnosis, a broad definition of COPD (DJ41-44.9) was used, while for the secondary diagnosis only patients included with the exact diagnosis code of acute exacerbations (DJ44.1) was included. This ensured that patients admitted to the hospital for planned activities, such as minor "daytime surgeries" who also had stable COPD as a secondary diagnosis, were not considered as an outcome. The secondary outcome was all-cause mortality. Cohort entry was defined as the date of the first outpatient visit. The follow-up time was 365 days, or whichever occurred first: a hospitalization due to a COPD exacerbation or death. Data were obtained from multiple nationwide Danish registers and merged using the Danish CPR number system, a unique identification number assigned to all residents in Denmark. The following registers were used: (1) The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD), a nationwide database that includes individual patient data such as the severity of airflow obstruction, body mass index (BMI), and smoking status for all outpatient visits and hospitalizations due to exacerbations of COPD.[16] (2) The Danish National Patient Registry, which contains data on hospital admissions and outpatient visits. This database was used to identify severe COPD exacerbation and to categorize comorbidities in the study population.[17] (3) The Danish National Database of Reimbursed Prescriptions (DNDRP) was used to identify redeemed medication to characterize ICS consumption. The DNDRP is a database that includes data on all collected prescriptions handed out at Danish pharmacies.[18] (4) The Danish Register of Causes of Death, which covers all deaths among citizens dying in Denmark since 1970.[19]

Demographic and clinical data including age, BMI, smoking status, and FEV_1 in % of predicted normal at the initial outpatient visit registered in DrCOPD were used for clinical characterization. If a value was missing, the first non-missing value from a later outpatient session was utilized. Data on patients' medication were derived from dispensed prescriptions in the year prior to enrollment. A predefined analysis plan was made, and the study protocol can be found online.[20]

ICS Particle Size and Exposure

ICS were categorized into two groups based on particle size: extra-fine particle ICS and standard particle size ICS. Among the ICS types examined, only beclomethasone HFA and ciclesonide HFA fell into the extra-fine particle category, while the remaining ICS types were categorized as standard particle size ICS.[14] Participants who were administered multiple types of ICS were categorized based on the type to which they had the highest cumulative exposure. The categorization of particle size into two broad categories was chosen to align with the common terminology used in the literature on ICS particle size,[21] and to ensure adequate group sizes for our statistical analyses, which involved multiple adjustments.

Exposure to ICS was determined by analyzing redeemed prescriptions from the year prior to cohort entry. To calculate the budesonide equivalent dose, we used the following conversion ratios: mometasone and beclomethasone at 1:1, beclomethasone HFA and fluticasone propionate at 1:2, ciclesonide at 1:2.5, and fluticasone furoate at 1:10.[22] The conversion ratios are summarized in Supplementary Table 1.

Statistical Analysis

Cox proportional hazard regression models were utilized to estimate the association between extra-fine particle ICS and the risk of hospitalization due to COPD exacerbation and all-cause mortality. Additionally, we conducted Fine and Gray competing risk regression models that accounted for the competing risk of death.

All adjusted models incorporated the following variables: extra-fine particle ICS (categorical), age (continuous), sex (categorical), smoking status (categorical), BMI (modeled using splines), FEV_1% (modeled using splines), ICS equivalent dose in the year prior to cohort entry (modeled using splines), and asthma (categorical). Information regarding WHO ICD-10 codes used for comorbidities is detailed in Supplementary Table 2, and Anatomical Therapeutic Chemical (ATC) codes used for medications are provided in Supplementary Table 3.Continuous variables were checked for linearity and modeled using restricted cubic splines with 5 knots when linearity was not met.[23] All variables were tested for the proportional hazard assumption. Complete case analysis was utilized to handle missing data. Cumulative incidence curves are presented for graphical presentation.

Predefined subgroup analyses included patients with ≥2 moderate exacerbations (identified using prescription data on oral corticosteroids) or ≥1 exacerbation requiring hospitalization, in the year prior to cohort entry, as well as a subgroup of patients treated with pressurised metered dose inhaler (pMDI), since all extra-fine particle ICS are delivered via

pMDIs, but non-extra-fine particle ICS can also be dispensed via dry powder inhalers DPIs. Additionally, a propensity score matched cohort was created with the greedy match method, with up to 5 controls per case, using a logistic propensity score caliper of 0.25.[24] Matching was based on age, sex, smoking status, FEV_1%, BMI, ICS equivalent dose in the year prior to cohort entry, long-acting beta-agonist and long-acting muscarinic antagonist treatment, exacerbation history, and co-diagnosis with asthma.

The merging of registers and preparation of datasets, as well as the propensity score matched cohort, were created using SAS 9.4 statistical software. Statistical analysis and graphical presentation were performed using R version 4.1.4.

Results

This observational cohort study included 40,489 COPD patients treated with ICS in outpatient clinics, of whom 1,687 (4.2%) received extra-fine particle ICS. Patients treated with extra-fine particle ICS had baseline characteristics similar to those treated with standard particle size ICS, including age, BMI, sex, and FEV_1%. However, differences were observed for daily ICS dosage, LABA and/or LAMA treatments, two or more OCS courses, hospitalizations, and a co-diagnosis with asthma or congestive heart failure, as summarized in Table 1. Our cohort of outpatient COPD patients had an average age of 70, a median FEV_1% of 45%, and 44% had ≥2 exacerbations treated with oral corticosteroids or ≥1 exacerbation leading to a hospital admission.

Table 1 The Baseline Characteristics for the Cohort and the Propensity Score Matched Population

	Cohort (n=40,489)		**Propensity score matched population* (n=9,149)**	
	Standard particle size ICS• (n=38,802)	**Extra-fine particles ICS• (n=1,687)**	**Standard particles size ICS• (n=7,624)**	**Extra-fine particles ICS• (n=1,525)**
Characteristics at cohort entry				
Age, years, Median (IQR)	70.9 (63.3–77.9)	69.5 (61.8–76.5)	69.7 (62.0–76.8)	69.5 (61.8–76.3)
Male, n (%)	17,701 (45.6)	744 (44.1)	3,363 (44.1)	673 (44.1)
BMI, kg/m,^{2} Median (IQR)	25.0 (21.0–29.0)	25.0 (21.4–29.0)	25.0 (21.0–29.0)	25.0 (21.4–29.0)
BMI unknown, n (%)	2,843 (7.3)	102 (6.0)	–	–
Smoking status, n (%)				
Active	12,054 (31.1)	450 (26.7)	2,216 (29.1)	437 (28.7)
Former	22,770 (58.7)	1,025 (60.8)	4,917 (64.5)	996 (65.3)
Never	1,216 (3.1)	95 (5.6)	491 (6.4)	92 (6.0)
Unknown	2,762 (7.1)	117 (6.9)	–	–
FEV_1%, Median (IQR)	45.0 (33.0–59.0)	46.0 (34.0–60.0)	45.0 (33.0–59.0)	45.0 (33.0–60.0)
GOLD stage 1–4 according to FEV_1%, n (%)				
≥ 80	1,636 (4.2)	80 (4.7)	350 (4.6)	71 (4.7)
79–50	13,222 (34.1)	590 (35.0)	2,867 (37.6)	569 (37.3)
49–30	13,795 (35.6)	599 (35.5)	2,883 (37.8)	586 (38.4)
<30	7,135 (18.4)	308 (18.3)	1,524 (20.0)	299 (19.6)
Unknown	3,014 (7.8)	110 (6.5)	–	–
GOLD E†, n (%)	16,875 (43.5)	739 (43.8)	3,369 (44.2)	678 (44.5)

(*Continued*)

Table 1 (Continued).

	Cohort (n=40,489)		Propensity score matched population* (n=9,149)	
	Standard particle size ICS˙ (n=38,802)	Extra-fine particles ICS˙ (n=1,687)	Standard particles size ICS˙ (n=7,624)	Extra-fine particles ICS˙ (n=1,525)
COPD treatment based on redeemed prescriptions 365 days prior to cohort entry				
Daily ICS dose⊦, µg, median (IQR)	658 (316–1315)	671 (329–1151)	658 (316–1263)	690 (329–1151)
LABA or LAMA, n (%)	24,112 (62.1)	694 (41.1)	3,146 (41.3))	634 (41.6)
LABA + LAMA, n (%)	6,986 (18.0)	737 (43.7)	3,473 (45.6)	686 (45.0)
≥2 OCS treatments, n (%)	8,390 (21.6)	480 (28.5)	1,822 (23.9)	441 (28.9)
Hospitalization 365 days prior to cohort entry				
≥1 AECOPD-Hosp, n (%)	15,220 (39.2)	579 (34.3)	2,945 (38.6)	525 (34.4)
≥1 All-Cause-Hosp, n (%)	25,145 (64.8)	985 (58.4)	4,823 (63.3)	890 (58.4)
Comorbidities‡, n *(%)*				
Asthma	10,342 (26.7)	627 (37.2)	2,692 (35.3)	556 (36.5)
CHF	10,096 (26.0)	321 (19.0)	1,830 (24.0)	287 (18.8)
Myocardial infarction	5,170 (13.3)	178 (10.6)	989 (13.0)	157 (10.3)
Renal failure	3,673 (9.5)	129 (7.6)	703 (9.2)	122 (8.0)

Notes: *A greedy match algorithm was used for propensity score matching, comparing up to five controls receiving ICS with standard particle size to each case getting extra-fine particles. The following variables were used for matching age, sex, smoking status, FEV_1%, BMI, daily usage of ICS in budesonide equivalent dosage, number of OCS, treatment with LABA or LAMA, exacerbation history, and co-existing asthma. ˙Devices using ciclesonide or beclomethasone hydrofluoroalkane solutions were classified as extra-fine particles, whereas all other ICS devices were classified as standard particle size. †GOLD E: ≥2 exacerbations treated with oral corticosteroids or ≥1 exacerbation leading to a hospital admission. ⊦Calculation of budesonide equivalent dose was based on the cumulative amount of ICS taken in the year before joining the cohort. Supplementary Table 1 provided the ratios used to determine the budesonide equivalent dose. ATC codes are summarized in Supplementary Table 3. ‡The registered comorbidities were based on the ICD-10 codes summarized in Supplementary Table 2, and were determined using data from the five years preceding the first outpatient visit.
Abbreviations: ICS: Inhaled Corticosteroids. IQR: Interquartile Range. BMI: Body Mass Index. FEV_1%: Forced Expiratory Volume in the first second in % of predicted normal. GOLD: Global Initiative for Chronic Obstructive Lung Disease. COPD: Chronic Obstructive Lung Disease. LABA: Long-Acting Beta-Agonist. LAMA: Long-Acting Muscarinic Antagonist. OCS: Oral Corticosteroids. AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Hosp: Hospitalization. CHF: Congestive Heart Failure.

The propensity score matched cohort resulted in 1,525 patients treated with extra-fine particle ICS and 7,625 controls treated with standard particle size ICS. In the propensity score matched cohort, baseline characteristics of patients treated with extra-fine particle ICS and standard particle size ICS were comparable to those in the original cohort, particularly concerning age, BMI, sex, and FEV1%. Furthermore, disparities noted in the original cohort were mitigated. The results of the matching are summarized in Table 1. The baseline characteristics of the subgroups are reported in Supplementary Table 4.

Our primary fully adjusted analysis showed no protective effect of extra-fine particle ICS regarding hospitalization due to COPD exacerbations (HR 0.93, 95% CI 0.82–1.05, p=0.23). Furthermore, all-cause mortality was not affected (HR 1.00, 95% CI 0.85–1.17, p=0.99). The analysis including death as a competing risk showed similar results as the primary analysis. The unadjusted analysis showed a decreased risk of hospitalization due to COPD exacerbation for patients treated with extra-fine particle ICS. However, no association was found for all-cause mortality (see Table 2). Furthermore, the propensity score matched analysis showed similar results with no impact on hospitalization due to COPD exacerbations or all-cause mortality. A predefined adjusted subgroup analysis of patients with a history of exacerbations showed no effect of extra-fine particle ICS compared to standard particle size ICS on risk of either hospitalization or all-cause mortality. The predefined adjusted subgroup analysis of patients treated with pMDIs showed that extra-fine particle ICS was associated with a decreased risk of hospitalization due to COPD exacerbations (HR 0.72,

Table 2 Risk of Severe COPD Exacerbation and All-Cause Mortality Based on the Use of Extra-Fine Particle ICS Compared to Standard Particle Size ICS. Fine and Gray's Subdistribution Hazard Ratios Were Calculated Using Exacerbation Requiring Hospitalization as the Event and All-Cause Mortality as a Competing Risk. The Hazard Ratios for All Adjusted Variables Can Be Found in the Supplementary Table 5

	Course specific hazards Event: exacerbation requiring hospitalization		Competing risk analysis Fine and Gray		Course specific hazards Event: all-cause mortality	
	Event (n)	ICS EF HR(95% CI)	Event (n)	ICS EF sHR(95% CI)	Event (n)	ICS EF HR(95% CI)
Unadjusted (n=36,531)	7,058	0.87(0.77–0.98)*	7,058	0.87(0.77–0.99)*	4,346	0.87(0.74–1.02)
Adjusted[•] (n=35,531)	7,058	0.93(0.82–1.05)	7,058	0.92(0.81–1.05)	4,346	1.00(0.85–1.17)
Propensity score matched[†] (n=7,986)	1,524	0.88(0.77–1.00)	1,524	0.88 (0.77–1.00)	782	0.96(0.81–1.13)
Adjusted[•]**subgroup Exacerbators**[⊦] (n=15,886)	4,679	0.88(0.76–1.03)	4,679	0.89 (0.77–1.04)	2,601	0.95(0.77–1.16)
Adjusted[•]**subgroup pMDI devices**[‡] (n=8,264)	2,162	0.72(0.63–0.82)*	2,162	0.74(0.64–0.85)*	1,534	0.72(0.61–0.86)*

Notes: *Statically significant at a significance level of 0.05. [•]The model was adjusted for the following variables: age (continuous variable), BMI (modeled using a spline function), sexr (categorical), smoking status (categorical), FEV_1% (modeled using a spline function), and ICS consumption in budesonide equivalent doses the year prior to cohort entry (modeled using a spline function), and co-diagnosis with asthma (categorical). [†]Propensity score matching was conducted on age, sex, smoking status, FEV_1%, BMI, ICS consumption in budesonide equivalent doses in the year prior to cohort entry, LABA/LAMA treatment, exacerbation history, and co-diagnosis with asthma. [⊦]A history of ≥2 moderate COPD exacerbations treated with oral corticosteroids or ≥1 severe COPD exacerbation requiring hospitalization the year prior to cohort entry. [‡]In this subgroup analysis, all patients treated with dry powder devices were excluded since extra-fine ICS formulations are exclusively as pMDI.

Abbreviations: COPD, Chronic Obstructive Lung Disease; Confidence Interval; SHR, Subdistribution Hazard Ratio; pMDI, pressurised metered dose inhaler.

95% CI 0.63–0.82, p-value <0.001) and for all-cause mortality (HR 0.72 95% CI 0.61–0.86, p-value <0.001) as compared to standard particle size ICS delivered as pMDI. Complete results of all analyses with hazard ratios, confidence intervals, and p-values for all the factors adjusted for can be found in Supplementary Table 5.

Cumulative incidence curves for hospitalization due to COPD exacerbations according to extra-fine particle ICS treatment are shown in Figure 2 and for all-cause mortality in Figure 3. The unadjusted curves consistently demonstrate a lower incidence of exacerbations and all-cause mortality in patients treated with extra-fine particle ICS. The difference in cumulative incidence is most pronounced in the subgroup of patients treated with pMDIs. However, the differential in cumulative incidence for either exacerbations or all-cause mortality was not evident in the analysis conducted on the propensity score matched cohort.

The average daily budesonide equivalent dose was 657.5 µg for standard particle size ICS and 670.7 µg for the extra-fine particle ICS group. Budesonide and fluticasone propionate were the most prescribed types of ICS for standard particle size ICS, while beclomethasone HFA was the most prescribed ICS type for extra-fine particle ICS. ICS consumption is summarized in Table 3.

Discussion

In this large nationwide cohort, no protective effects of extra-fine particle ICS compared to standard particle size ICS against exacerbations or all-cause mortality were observed. This held true across both the primary adjusted analysis and in the propensity score matched population. Extra-fine particle ICS role in COPD management have previously received limited attention regarding pertinent clinical outcomes such as exacerbations and all-cause mortality. A predefined subgroup analysis of patients with a previous history of exacerbations did not show any benefit from extra-fine particle

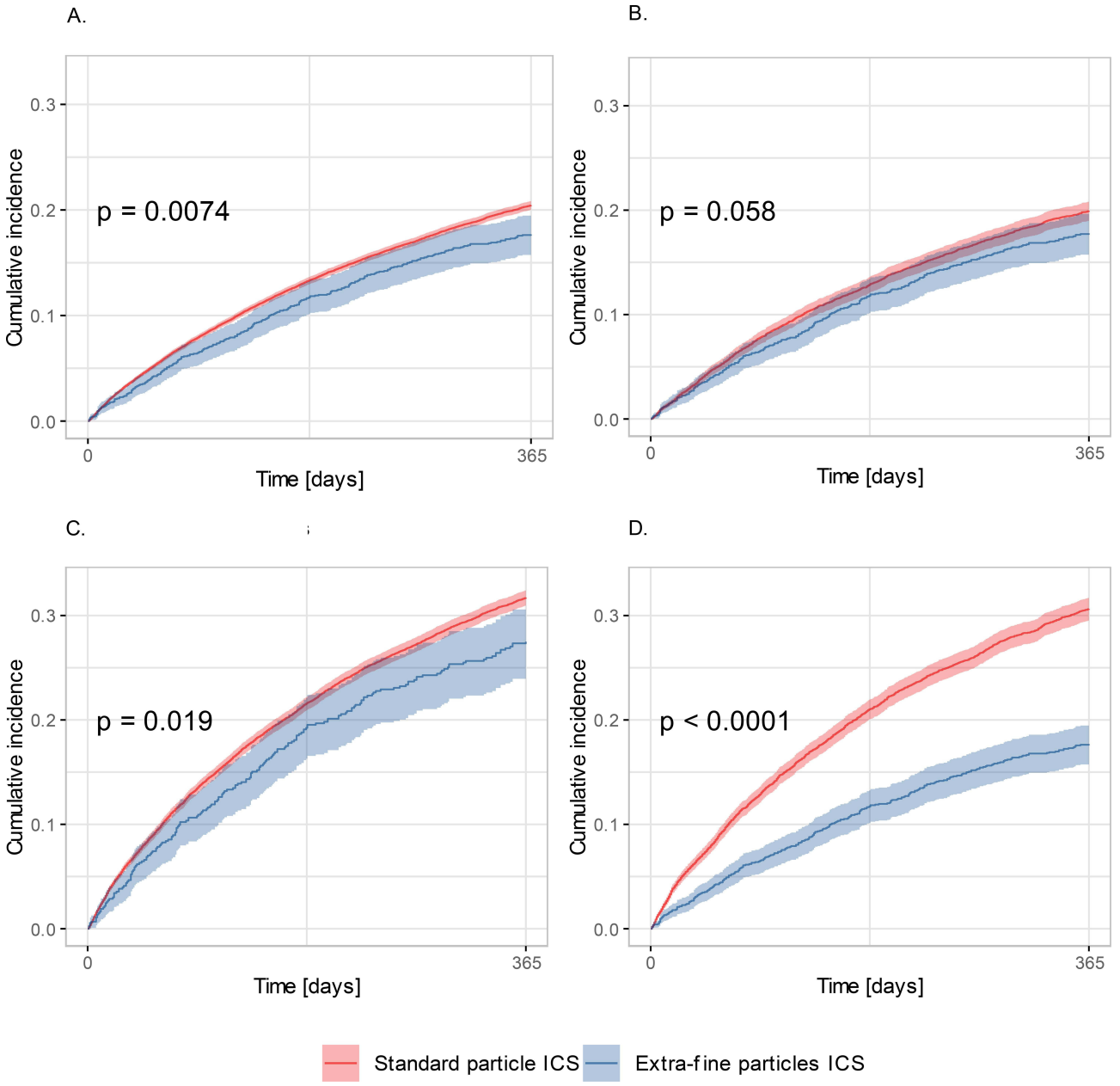

Figure 2 Cumulative incidence curves for severe chronic obstructive pulmonary disease (COPD) exacerbations for patients treated with extra-fine particle inhaled corticosteroids (ICS) compared to standard particle size ICS. P-values generated using Log rank test. Graph (**A**) (Entire cohort), graph (**B**) (Propensity score matched population), graph (**C**) (Subgroup exacerbators), and graph (**D**) (Subgroup Spray inhaler). Graphs (**A**, **C**, and **D**) are unadjusted curves, whereas graph (**B**) is based on the propensity score matched population.

ICS treatment either. Despite conducting this subgroup analysis with the purpose of maximizing the likelihood of observing a potential effect of extra-fine particle ICS, we found no significant effect in this specific population. In contrast, our analysis deviates when considering patients treated with pMDIs. In this context, we observed that the use of extra-fine particle ICS appeared to have significant protective effects on severe COPD exacerbations and all-cause mortality. This subgroup was chosen in an attempt to establish a more directly comparable group, given that all extra-fine particle ICS are formulated as pMDIs.

The adjusted subgroup analysis consisting of patients treated with pMDIs suggests a nearly 30% reduction in all-cause mortality for patients treated with extra-fine particle ICS compared to standard particle size ICS. Considering the challenges of establishing a certain effect of ICS on all-cause mortality, a reduction solely based on particle size of that

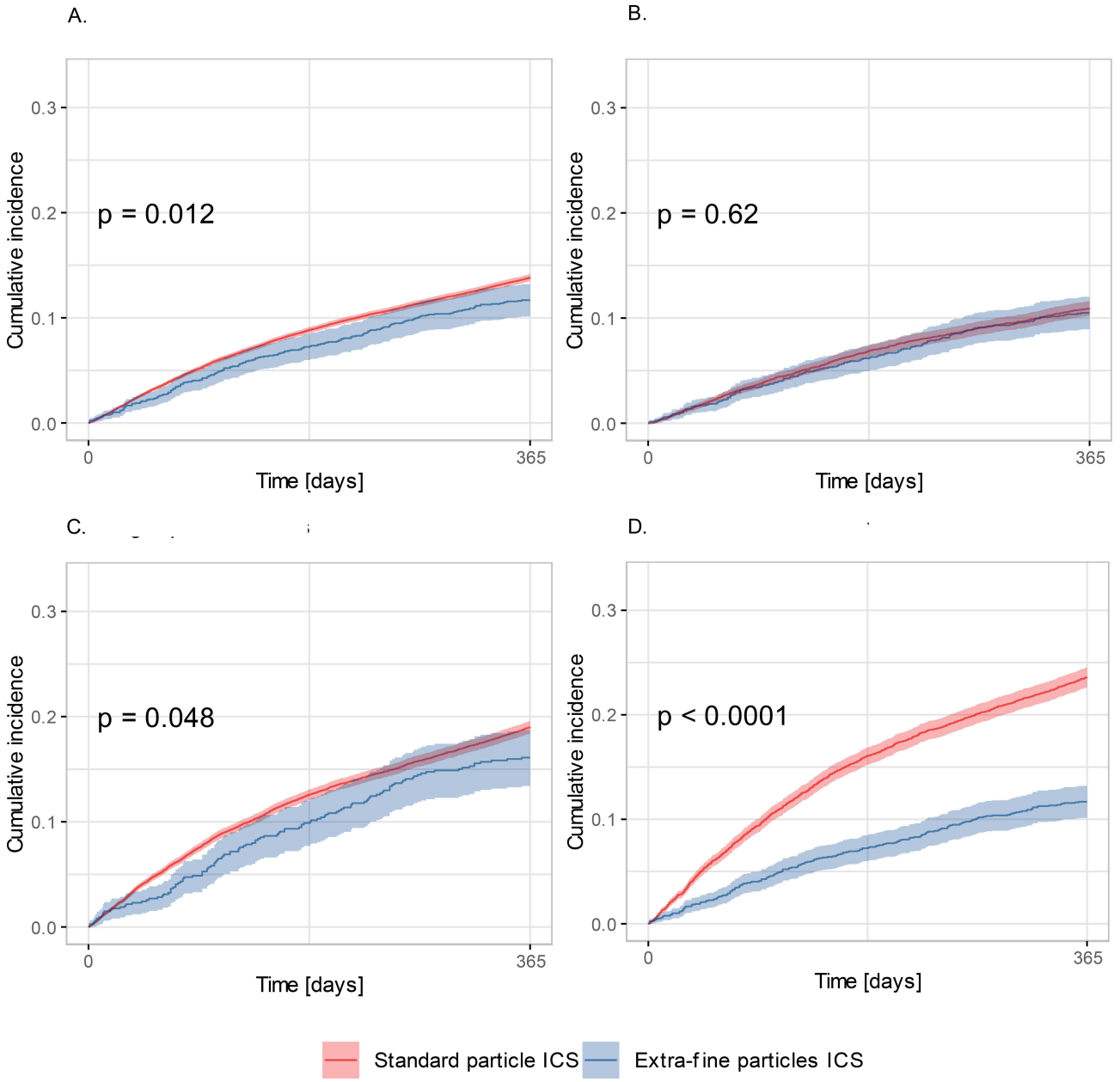

Figure 3 Cumulative incidence curves for all-cause mortality for patients treated with extra-fine particle inhaled corticosteroids (ICS) compared to standard particle size ICS. P-values generated using Log rank test. Graph (**A**) (Entire cohort), graph (**B**) (Propensity score matched population), graph (**C**) (Subgroup exacerbators), and graph (**D**) (Subgroup Spray inhaler). Graphs (**A**, **C**, and **D**) are unadjusted curves, whereas graph (**B**) is based on the propensity score matched population.

scale is not expected.[2,6] An important note is that patients treated with standard particle size ICS pMDIs presented baseline characteristics that were not analogous to those treated with extra-fine particle ICS. Notably, they were older, had a lower FEV_1%, and used higher doses of ICS (See Supplementary Table 4). Therefore, the results observed might be influenced by confounding by indication. Residual confounding may persist due to unaccounted variables, and the observed results could potentially be influenced by prescription patterns or other unmeasured factors inherent to retrospective analyses. Although our findings provide an intriguing direction for future research, the evidence to support a clear protective effect of extra-fine particle ICS in this subgroup remains inconclusive. A randomized clinical trial comparing the same dose of ICS dispensed via pMDI but with different particle sizes would be preferable.

To our knowledge, this study is the first to investigate the effects of extra-fine particle ICS on COPD exacerbations leading to hospitalization and all-cause mortality in a large and well-characterized real-life cohort. A smaller

Table 3 ICS Usage Characteristics the Year Before Cohort Entry Based on Redeemed Prescriptions

	Standard particle size ICS *, (n=38,802)	**ICS extra-fine particles*, (n=1,687)**
Daily ICS dose[•], µg, median (IQR)	657.5 (315.6–1,315.1)	670.7 (328.8–1,150.7)
ICS exposure groups[†,] n (%)		
Low (<500 µg/day)	15,851 (40.9)	620 (36.8)
Moderate (500–899 µg/day)	8,414 (21.7)	467(27.7)
High (≥900 µg/day)	14,537(37.5)	600 (35.6)
Number of prescriptions, median (IQR)	5 (3–9)	6 (3–10)
ICS type users[ŀ], n (%)		
Beclomethasone	38 (0.1)	0
Beclomethasone HFA	0	1,358 (81.4)
Budesonide	20,372 (52.5)	0
Fluticasone propionate	17,895 (46.1)	0
Fluticasone furoate	444 (1.1)	0
Ciclesonide	0	329 (18.6)
Mometasone	53 (0.1)	0

Notes: *Devices containing beclomethasone HFA solutions or ciclesonide are categorized as extra-fine particles, all other ICS devices are categorized as standard particle size ICS. •Based on ICS accumulated budesonide equivalent dose one year prior to cohort entry. Budesonide equivalent dose were calculated using ratios summarized in Supplementary Table 1. †ICS Exposure groups based of NICE's guidelines.[22] ŀPatients treated with multiple ICS types were categorized based on the type they received the highest accumulated budesonide equivalent dose of.

Abbreviations: ICS: Inhaled Corticosteroids. IQR: Interquartile Range. HFA: Hydrofluoroalkane inhaler.

retrospective study matched extra-fine beclomethasone dipropionate to fluticasone propionate (n=189 for each group) for patients with COPD and showed no difference in exacerbation rates consistent with our findings.[25]

There are numerous studies available on the use of extra-fine particle ICS in patients with asthma. In a recent randomized controlled trial, no significant difference was observed between extra-fine beclomethasone and an active comparator with standard particle size beclomethasone.[26] However, a meta-analysis of real-life studies investigating the effectiveness of extra-fine particle ICS for asthma treatment reported potential benefits. The analysis showed improved odds of asthma control at lower prescribed doses of ICS.[27] The potential difference in effectiveness between asthma and COPD patients can be explained by the less prominent effect of ICS in COPD management.

The present study has several strengths, including a large dataset of more than 40,000 patients with COPD who were followed in outpatient clinics. Approximately 1,700 of these patients received extra-fine particle ICS. We had complete data on redeemed prescriptions, the primary outcome and mortality. The study had a high level of completeness, with low amounts of missing data across all adjusted variables. The missing data was generally observed in patients who missed all of the adjusted variables simultaneously. The patients with missing data had similar ages as those with complete data, suggesting that most missing data were likely due to registration issues. This indicates that the missing data were likely to be missing completely at random.

Although the study had several strengths, some limitations should be considered when interpreting the results. First, the diagnosis of exacerbation was based on hospitalization records, and clinicians may have misclassified this condition. Correct diagnosis of acute dyspnea in COPD patients may be challenging, particularly in differentiating exacerbations from respiratory infections. However, this possible misclassification is unlikely to introduce a biased effect, as the ICS

particle size is unlikely to affect the accuracy of the exacerbation diagnosis, ie, non-discriminative bias. Our cohort consists of patients followed in outpatient clinics, with a relatively advanced disease as outlined by the baseline characteristics. It remains uncertain whether our results can be generalized to COPD patients not followed in outpatient clinics. Furthermore, baseline eosinophil levels were unavailable for this study. Nevertheless, subgroup analysis focusing on patients with elevated eosinophil levels is of considerable interest, as it may unveil potential improvements in outcomes related to exacerbations and all-cause mortality. The study used data on redeemed prescriptions rather than actual medication intake, which may result in overestimating ICS consumption. Since the data were gathered from multiple prescriptions over a one-year period, any resulting error is expected to be minor and unlikely to have a significant impact on the primary outcome. The comparison between the two groups was not solely based on ICS particle size but also on the type of ICS used. We accounted for this by adjusting for dose equivalency. It is important to note that there is currently no evidence suggesting that one type of ICS is better than others in preventing exacerbations or all-cause mortality. Patients using multiple types of ICS, were categorized by the type with the highest cumulative exposure, could lead to potential bias. While this method captures real-world clinical scenarios, it may introduce confounding effects, albeit to a minimal extent, given that this subset represents a small portion of our study population.

In conclusion, the predominant adjusted analyses revealed no significant difference between extra-fine particle ICS compared to standard particle size ICS in preventing exacerbations or all-cause mortality. However, a subgroup analysis excluding patients treated with DPIs, suggested potential protective benefits. The results from this subgroup analysis should be interpreted with caution.

Ethics

In Denmark, ethics approval or patient consent is not required for the retrospective use of register data.[28] All data accessed and analyzed in this study were stored on an encrypted service and comply with Danish data protection and privacy regulations.

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