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Use of aclidinium did not increase the risk of death in a noninterventional cohort study in the Clinical Practice Research Datalink (CPRD), United Kingdom

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ABSTRACT

Background: Aclidinium bromide is an inhaled long-acting muscarinic antagonist (LAMA). Although the initial potential increased cardiovascular and mortality risk among users of tiotropium has been ruled out by several observational studies, and clinical trials, there are still concerns related to the use of newer LAMA medications. The current study aimed to evaluate the risk of death among users of aclidinium and other LAMAs.

Methods: We conducted a cohort and nested case-control study among patients with COPD aged 40 years or older to compare the risk of all-cause mortality among users of aclidinium and other COPD medications with the risk among users of long-acting β2 agonists (LABA), in the Clinical Practice Research Datalink (CPRD) in the United Kingdom (2012–2017).

Results: Mortality rates per 1,000 person-years were 32.9 for aclidinium, 43.8 for tiotropium, 38.0 for other LAMA, 47.1 for LABA/ICS, and 38.1 for LABA. The RR of death compared with current use of LABA was 0.54 (confidence interval [95% CI], 0.40–0.72) for aclidinium, 0.96 (95% CI, 0.76–1.21) for tiotropium, 0.76 (95% CI, 0.58–0.99) for other LAMA, and 1.08 (95% CI, 0.90–1.31) for LABA/ICS. Decreased risk for death observed among users of aclidinium was driven by overall current single use (RR = 0.41; 95% CI, 0.22–0.79), which corresponded to 26% of the aclidinium users (< 15 cases) and not by multiple use (RR = 1.02; 95% CI, 0.71–1.48).

Conclusion: Use of aclidinium, tiotropium, other LAMA, or LABA/ICS was not associated with an increased risk of all-cause mortality as compared with the use of LABAs.

1. Introduction

Long-acting muscarinic antagonists (LAMAs) are widely used among patients with chronic obstructive pulmonary disease (COPD). As many as 35% of patients with COPD in the United Kingdom (UK) in 2013 had used LAMAs in the previous year [1]. LAMAs are recommended as first-line therapy and at the same level as long-acting beta agonists (LABAs) in patients with COPD severity B and are preferable over LABA among patients classified under COPD severity C and D (Global Initiative for Chronic Obstructive Lung Disease [2]. Cardiovascular and mortality safety concerns for tiotropium, the first LAMA approved in Europe, were not confirmed in large long-term clinical trials (UPLIFT and TIOSPIR) [3,4]. However, cardiovascular safety and mortality remains as a potential risk for other LAMAs, including aclidinium [5,6,7,8].

This is the first of a series of observational post-authorisation safety studies (PASS) performed in the routine clinical practice to evaluate the

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; FEV1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HES, Hospital Episode Statistics database; ICD, International Classification of Diseases; ICS, inhaled corticosteroids; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonists; LRTA, leukotriene receptor antagonists; mMRC, modified Medical Research Council; ONS, Office for National Statistics; PASS, post-authorisation safety study; ppFEV1, percent predicted forced expiratory volume in 1 s; RR, relative risks; SABA, short-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation

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cardiovascular safety of aclidinium, a LAMA approved in the European Union in 2012. To put the results of this study in the context of a population that frequently use multiple medications, this study compared aclidinium with LABAs as well as with other COPD medications. The studies are being performed sequentially as the number of users of aclidinium are accrued in the UK, the country where the study is being performed. This first study aimed to compare all-cause mortality in patients with COPD initiating treatment with aclidinium bromide and other selected COPD medications with all-cause mortality in patients with COPD initiating treatment with LABAs. Cardiovascular mortality and other major cardiovascular events (stroke and acute myocardial infarction) will be evaluated in future studies when a higher number of users of aclidinium has been accrued in the UK.

2. Materials and methods

This is a case-control study nested in a population-based cohort of adult patients aged 40 years or older with a recorded diagnosis of COPD initiating treatment with aclidinium, tiotropium, other LAMA (glycopyrronium and umeclidinium), LABA/inhaled corticosteroids (LABA/ICS), or LABA identified in the Clinical Practice Research Datalink (CPRD) in the UK from 01 September 2012 through 01 March 2017. For a subset of practices where linkage data was available, the study also included information from the Office for National Statistics (ONS) and the Hospital Episode Statistics database (HES). COPD diagnoses were identified through outpatient diagnosis recorded in CPRD GOLD or inpatient diagnosis recorded in HES (ICD-10 codes J40-J44) at any time before the cohort entry date or up to 30 days after the cohort entry date. Patients with COPD with or without prior history of asthma could enter the study, and asthma history was evaluated as a potential confounder in the analysis. Patients were included if they were new users of the study medications, defined as having a prescription of the study medication within the study period and no prescription of this medication in the last 6 months, and if they had at least 1 year of prior enrollment in the CPRD before cohort entry date. Patients with life-threatening conditions (cancer, HIV, respiratory failure, end-stage renal disease, organ transplant, drug or alcohol abuse, coma, or congenital anomalies) at baseline were excluded from the study. New users were followed from the cohort entry date (i.e., the day of the first prescription within the study period) until the earliest of the following dates: death (index date), disenrollment from the practice, date the practice stops contributing data, or end of the study period.

All patients included in the cohort that had a confirmed death event and death date, either through an electronic algorithm or review of patient profiles [9], were considered cases. Evaluation of cause of death was not performed because of low availability among those in non-linkable practices. Up to four controls were selected for each case from the risk set of patients alive at the time of the case and matched by age, sex, and year of cohort entry, using risk-set density sampling. The index date of the case was assigned to their matched controls.

Time at risk for the effects of each study medication was ascertained according to the days' supply of each prescription. Episodes of current use of each study medication were defined by consecutive prescriptions with a maximum gap of 7 days between the end of the days' supply of one prescription and the start of the next prescription. For each study medication in the cohort study, we accumulated the time risk for all episodes of current use. In the nested case-control analysis, exposure to each study medication was evaluated at the index date. Although the effect was hypothesised to be acute, i.e. during exposure or shortly after, because the etiological exposure window is unknown [10], exposure was classified into one of the following mutually exclusive categories based on the end of the days' supply of the most recent episode: 1) current use if overlapped or ended within 7 days before the index date, 2) recent use if ended between 7 days and 60 days before the index date, and 3) past use if ended beyond the 60 days period. In addition, sensitivity analyses for alternative definitions of duration of exposure were also performed to evaluate different exposure windows and differences in adherence and compliance that would lead to modification of the estimated duration of use. Current use was classified into current single or multiple use depending on whether patients were concurrently treated with other study medications at the index date. Current single use was further subclassified as switching if patients had recent use of other study medications at the index date.

Sociodemographic and clinical characteristics such as age, sex, obesity, smoking, comorbidities, and comedications were ascertained based on information before the cohort entry date. COPD severity was defined according to the GOLD classification categories A, B, C, or D (Tables S–1) based on the percent predicted forced expiratory volume in 1 s [FEV_1], symptoms (modified Medical Research Council grade, COPD assessment test score, or breathlessness), and exacerbation history [11] both before or at the cohort entry date and before or at the index date. When no data on expected FEV_1 were recorded, the percent predicted FEV_1 was calculated by applying formulas from the Global Lung Function Initiative (European Respiratory Society Task Force TF 2009-03) to establish improved lung function reference values [12].

Crude and age- and sex-standardised mortality rates and 95% confidence intervals (CIs) were estimated for current use of each study medication using the age and sex distribution of person-time in current users of aclidinium bromide as the standard population. Conditional logistic regression was used to estimate crude and adjusted relative risks (RRs) and 95% CIs of all-cause mortality for the risk factors and all medication-use comparisons of interest. Crude RRs obtained from the matched sample were adjusted by the matching factors by design (i.e., age, sex and year of cohort entry). The final multivariable regression models included variables considered clinically relevant, those that changed the coefficient by approximately 5% from the models comparing current single use and current use of aclidinium bromide, and the variables with a relative risk of 2 or more or 0.5 or less in the univariate analysis.

3. Results

The study included 3,555 new users of aclidinium, 19,413 new users of tiotropium, 5,308 new users of other LAMA, 21,718 new users of LABA/ICS, and 4,797 new users of LABA (Fig. 1). The percentage of eligible patients was approximately 82% among users of aclidinium and users of other LAMA and was much lower among users of the rest of the study medications, particularly among users of LABA/ICS (14.4%). The main reason for exclusion was not being a new user during the study period.

Assessment of the new users in the study cohorts at baseline (before cohort entry date) showed that the mean age was 68 years, approximately half of new users were women, one-third were current smokers, and one-third were obese. In general, new users of aclidinium and, to a lesser extent, new users of other LAMA had more severe COPD than new users of the other study medications, with 57.2% of the aclidinium users, 53.5% of the other LAMA users, 50.8% of the tiotropium users, 50.1% of the LABA/ICS users, and 41.5% of the LABA users classified under categories C or D of the [11] COPD severity classification. Having a recorded diagnosis of asthma prior to start date (compatible with Asthma-COPD Overlap Syndrome) was more frequent among new users of LABA/ICS (38.8%), and prior use of ICS in the 6 months prior to start date was more frequent among new users of LABA/ICS (17.7%) and LABA (20.8%) than among users of other study medications. There were no major differences in the distribution of cardiovascular comorbidities and comedications and on the Charlson Comorbidity Index score categories between study cohorts (Tables S–2).

A total of 3,822 deaths were identified in CPRD GOLD, HES, and ONS. Overall, 3,819 (99.9%) of the identified cases of death were confirmed. Mortality rates per 1,000 person-years of current use were lowest for new users of aclidinium (32.91). The highest mortality rates were for new users of LABA/ICS (47.14) and new users of tiotropium

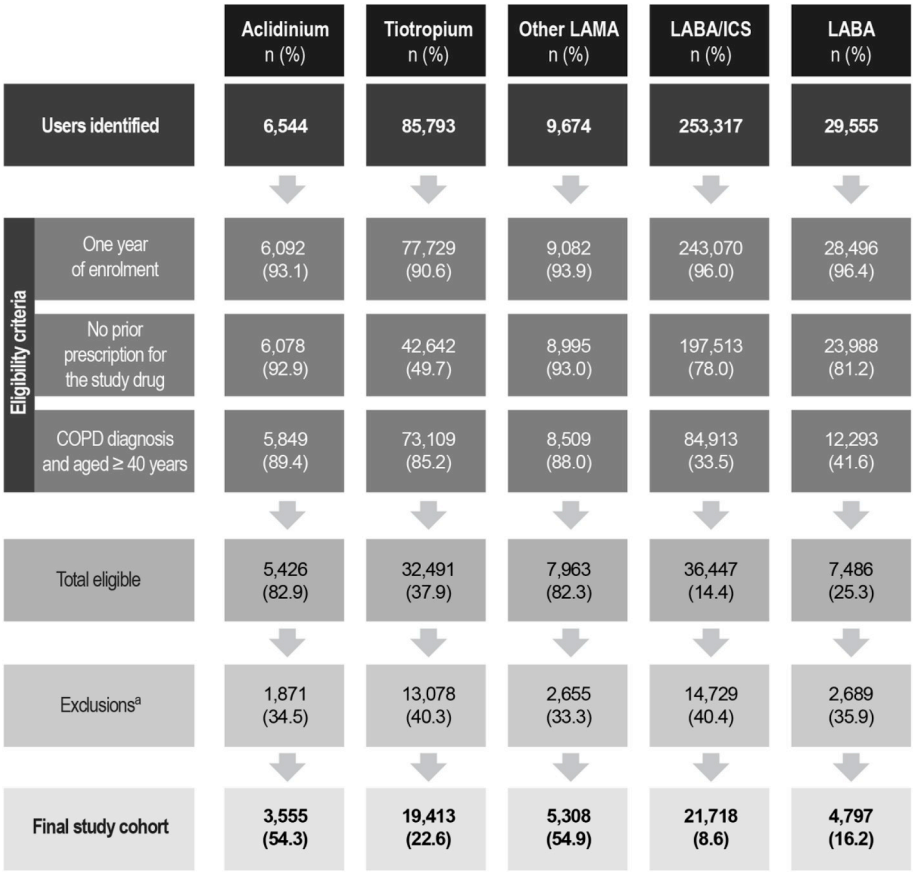

Fig. 1. Cohort Attrition for Users of Aclidinium and Other Study Medications. BMI = body mass index, COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LAMA = long-acting anticholinergic. [a] Percentage excluded is of the total eligible users. Exclusion criteria: malignancy, noncardiovascular life-threatening conditions, and missing data on smoking and BMI (2.6% of users).

Table 1
Crude and age- and sex-standardised mortality rates during current use of the study medications by study cohort.

	Person-Years of Current Use	Number of Cases	Crude Mortality Rate per 1,000 Person-Years (95% CI)	Age- and Sex-Standardised Mortality Rate[a] per 1,000 Person-Years (95% CI)
Aclidinium	3, 008	99	32.91 (26.75–40.07)	32.91 (26.43–39.40)
Tiotropium	20, 509	925	45.10 (42.24–48.11)	43.76 (40.92–46.61)
Other LAMA	3, 592	141	39.26 (33.04–46.30)	37.97 (31.64–44.29)
LABA/ICS	24, 577	1,184	48.17 (45.47–51.00)	47.14 (44.43–49.86)
LABA	3, 732	149	39.93 (33.78–46.88)	38.12 (31.91–44.33)

CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LAMA = long-acting muscarinic anticholinergic.
Note: Analysis was restricted to new users of each study medication.
[a] Age- and sex-standardised to the distribution of person-time in current users of aclidinium.

(43.76) (Table 1).

Of the 3,819 confirmed deaths (cases), 3,808 were matched to 15,207 controls on age, sex, and year of cohort entry; 11 confirmed deaths could not be matched to controls because of very old age and were excluded from the nested case-control analysis. The distribution of cases and controls across risk factors and univariate RRs and 95% CIs are presented in Table 2. The risk factors more strongly associated with an increase in the risk of death ([RR] ≈ or ≥ 2) and included as covariables in the regression model were prior use of nebulisers, COPD severity, smoking status, underweight, pneumonia, heart failure; higher Charlson Comorbidity Index; prior use of short-acting anticholinergics, mucolytics, cough and cold preparations, xanthines, oral glucocorticosteroids, and antiarrhythmics; number of previous hospitalisations, outpatient visits, and number of previous prescriptions for non-respiratory medications.

Current use of aclidinium and current use of other LAMA were associated with a decreased risk of death compared with current use of LABA (RR = 0.54; 95% CI, 0.40–0.72; and RR = 0.76, 95% CI, 0.58–0.99, respectively). No association was observed for current use of tiotropium or LABA/ICS. Relative risks for recent and past use of all study medications were higher than 1 compared with RRs for current use of LABA (Fig. 2).

The reduced risk of death observed among users of aclidinium was driven by current single users (RR = 0.41; 95% CI, 0.22–0.79), while no decreased risk was observed among multiple users (RR = 1.02; 95% CI, 0.71–1.48). Effect estimates among current single users of aclidinium were based on a low number of cases, i.e., between 10 and 15 current single users of aclidinium without switching and fewer than five current single users of aclidinium with switching. Current use of the study drug after switching from another COPD study medication was associated with a higher risk of death, except for switchers to aclidinium. Among current single users, RRs comparing current use of each medication switchers from other study medication to current use of LABA without switching were 1.84 (95% CI, 0.89–3.81) for LABA, 0.30 (95% CI, 0.07–1.36) for aclidinium, 1.50 (95% CI, 1.05–2.13) for tiotropium, 1.54 (95% CI, 0.68–3.50) for other LAMA, and 1.59 (95% CI, 1.14–2.21) for LABA/ICS. Except for aclidinium (RR = 1.02, 95% CI, 0.71–1.48), multiple use of the study medications was also associated

Table 2
Distribution of cases and controls by risk factors and relative risk (95% CI) in Univariate analysis.

Risk factor	Cases (%) (N = 3,808) n (%)	Controls (%) (N = 15,207) n (%)	Relative risk[a] (95% CI)
Demographic and lifestyle habits at the start date			
Age (years)			
40-69	886 (23.3)	3, 513 (23.1)	Ref
70 +	2,933 (76.7)	11, 694 (76.9)	0.88 (0.66–1.17)
Current smoking[b] (ref is never)	1,279 (33.6)	3, 975 (26.1)	2.21 (1.91–2.55)
Obesity[c] (ref is normal weight)	951 (24.9)	4, 523 (29.7)	0.77 (0.70–0.85)
Underweight[c] (ref is normal weight)	703 (18.5)	1,319 (8.7)	1.97 (1.76–2.21)
COPD severity			
COPD severity at the start date			
A, low risk, fewer symptoms	788 (20.6)	5, 012 (33.0)	Ref
B, low risk, more symptoms	626 (16.4)	2, 787 (18.3)	1.43 (1.28–1.61)
C, high risk, fewer symptoms	890 (23.3)	3, 532 (23.2)	1.61 (1.44–1.79)
D, high risk, more symptoms	1,515 (39.7)	3, 876 (25.5)	2.47 (2.24–2.72)
COPD severity at the index date			
A, low risk, fewer symptoms	631 (16.5)	5, 392 (35.5)	Ref
B, low risk, more symptoms	412 (10.8)	2, 421 (15.9)	1.46 (1.28–1.67)
C, high risk, fewer symptoms	1,116 (29.3)	3, 591 (23.6)	2.69 (2.42–3.00)
D, high risk, more symptoms	1,660 (43.5)	3, 803 (25.0)	3.77 (3.41–4.18)
Medical history[c]			
Asthma within 5 years of start date (ref is no asthma)	1,035 (27.1)	5, 292 (34.8)	0.71 (0.65–0.77)
Emphysema	415 (10.9)	1, 041 (6.8)	1.67 (1.48–1.88)
Pneumonia in the year before start date	232 (6.1)	346 (2.3)	2.81 (2.37–3.34)
Hypertension	2,244 (58.7)	8, 643 (56.8)	1.09 (1.01–1.17)
Depressive disorders	1,246 (32.6)	4, 605 (30.3)	1.13 (1.04–1.22)
Diabetes treatment (ref is no diabetes)	655 (17.1)	2, 023 (13.3)	1.37 (1.24–1.51)
Hyperlipidaemia	1,241 (32.6)	4, 776 (31.4)	1.06 (0.98–1.14)
History of cardiovascular disease	1,858 (48.8)	6,057 (39.8)	1.48 (1.37–1.59)
Ischaemic heart disease	1,249 (32.8)	4, 166 (27.4)	1.30 (1.21–1.41)
Acute myocardial infarction	545 (14.3)	1, 461 (9.6)	1.58 (1.42–1.76)
Angina	787 (20.7)	2, 703 (17.8)	1.21 (1.10–1.32)
Coronary angioplasty	252 (6.6)	871 (5.7)	1.17 (1.01–1.35)
Aortocoronary bypass graft	182 (4.8)	662 (4.4)	1.11 (0.93–1.31)
Cerebrovascular diseases	738 (19.3)	2, 215 (14.6)	1.41 (1.29–1.55)
Heart failure	690 (18.1)	1, 520 (10.0)	2.04 (1.85–2.26)
Arrhythmias	960 (25.1)	2, 578 (17.0)	1.69 (1.54–1.84)
Peripheral vascular disease	569 (14.9)	1, 513 (9.9)	1.59 (1.43–1.76)
Renal disease	1,253 (32.8)	4, 054 (26.7)	1.38 (1.27–1.50)
Urinary tract infection	1,120 (29.3)	4, 258 (28.0)	1.07 (0.99–1.16)
Liver disorders	99 (2.6)	267 (1.8)	1.49 (1.18–1.89)
Pulmonary embolism	154 (4.0)	376 (2.5)	1.67 (1.38–2.02)
Osteoporosis	822 (21.5)	2, 623 (17.2)	1.35 (1.23–1.48)
Charlson Comorbidity Index at the start date 3 or more (ref is 0)	769 (20.1)	1, 750 (11.5)	2.49 (2.24–2.78)
Use of medications			
Respiratory medications[d]			
Aclidinium/formoterol	9 (0.2)	34 (0.2)	1.06 (0.51–2.21)
Other LAMA/LABA	51 (1.3)	140 (0.9)	1.47 (1.06–2.03)
Short-acting anticholinergic	260 (6.7)	476 (3.1)	2.26 (1.93–2.64)
Short-acting beta2-agonist	2,628 (68.8)	9, 409 (61.9)	1.36 (1.26–1.47)
Inhaled corticosteroids	162 (4.3)	830 (5.5)	0.77 (0.65–0.91)
Xanthines	217 (5.7)	430 (2.8)	2.09 (1.77–2.47)
LRTA and omalizumab	61 (1.6)	377 (2.5)	0.64 (0.49–0.84)
Mucolytics	687 (18.0)	1, 373 (9.0)	2.21 (2.00–2.44)
Antihistamines for systemic use	424 (11.1)	1, 107 (7.3)	1.60 (1.42–1.80)
Oral glucocorticoids	1,302 (34.1)	3, 166 (20.8)	1.97 (1.82–2.13)
Cough and cold preparations	270 (7.1)	512 (3.4)	2.20 (1.89–2.56)
Nebulisers	583 (15.2)	658 (4.3)	4.05 (3.59–4.57)
Other medications[e]			
Antibiotics	2,012 (52.6)	7, 029 (46.2)	1.30 (1.21–1.39)
Vaccines	3,017 (79.0)	12, 614 (82.9)	0.77 (0.70–0.84)
Cardiovascular medications	3,005 (78.7)	11, 270 (74.1)	1.31 (1.20–1.43)
Lipid-lowering drugs	1,900 (49.9)	7, 479 (49.2)	1.03 (0.96–1.11)
Agents acting on rennin-angiotensin system	1,547 (40.5)	6, 269 (41.2)	0.97 (0.90–1.04)
Beta-blockers	846 (22.2)	2, 774 (18.2)	1.28 (1.18–1.40)
Calcium channel blockers	1,033 (27.0)	4, 359 (28.7)	0.92 (0.85–1.00)
Diuretics	1,629 (42.6)	4, 968 (32.7)	1.56 (1.45–1.68)
Antiarrhythmics	59 (1.5)	122 (0.8)	1.95 (1.43–2.67)
Nitrates	509 (13.4)	1, 520 (10.0)	1.39 (1.25–1.55)
Antidepressants	1,067 (27.9)	3, 176 (20.9)	1.49 (1.38–1.62)
Insulins	187 (4.9)	448 (2.9)	1.70 (1.43–2.02)
Blood glucose–lowering drugs	567 (14.8)	1, 843 (12.1)	1.26 (1.14–1.40)
Health care resource utilisation[e]			
Number of outpatient visits			
0-15	2,066 (54.1)	9, 735 (64.0)	Ref
16-25	1,017 (26.6)	3, 677 (24.2)	1.31 (1.20–1.43)

(*continued on next page*)

Table 2 (*continued*)

Risk factor	Cases (%) (N = 3,808) n (%)	Controls (%) (N = 15,207) n (%)	Relative risk[a] (95% CI)
26 or more	736 (19.3)	1, 795 (11.8)	1.96 (1.77–2.16)
Number of referrals to respiratory specialist			
0	3,586 (93.9)	14, 487 (95.3)	Ref
1 or more	233 (6.1)	720 (4.7)	1.31 (1.13–1.53)
Number of hospitalisations			
0	2,083 (54.5)	10, 240 (67.3)	Ref
1	699 (18.3)	2, 610 (17.2)	1.33 (1.20–1.46)
2 or more	1,037 (27.2)	2, 357 (15.5)	2.19 (2.01–2.39)
Number of prescriptions for respiratory medications			
0-10	1,510 (39.5)	7, 510 (49.4)	Ref
11-20	1,082 (28.4)	4, 242 (27.9)	1.27 (1.17–1.39)
21 or more	1,227 (32.1)	3, 455 (22.7)	1.77 (1.62–1.93)
Number of prescriptions to nonrespiratory specialists, n (%)			
0-40	1,077 (28.3)	6,058 (39.8)	Ref
41-80	1,161 (30.5)	4,847 (31.9)	1.37 (1.25–1.51)
81 or more	1,570 (41.2)	4,302 (28.3)	2.11 (1.93–2.31)

BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic anticholinergic; LRTA = leukotriene receptor antagonists; Ref = reference.
Note: Risk factors are measured at the start date unless otherwise specified.
[a] Relative risk matched on year of birth, sex, and year of start date.
[b] Based on the latest available information during the 10 years before or at the start date.
[c] Based on the latest available information during the 3 years before or at the start date. Categories: underweight (BMI $< 20\,kg/m^2$), normal weight (BMI 20 to $< 25\,kg/m^2$), overweight (BMI 25 to $< 30\,kg/m^2$), obese ($\geq 30\,kg/m^2$).
[c] Any time before the start date, unless otherwise specified.
[d] Within 3 months before the index date.
[e] Within 12 months before the index date.

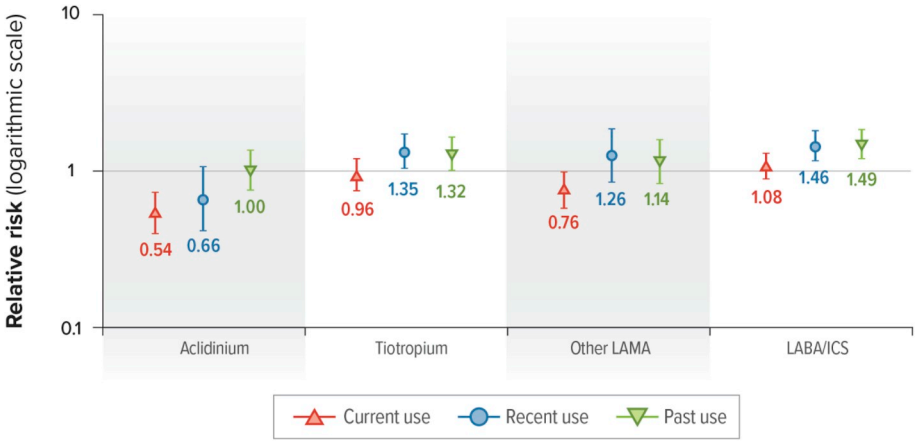

Fig. 2. Adjusted Relative Risk of Mortality Death for Current, Recent, and Past Use of the Study Medications Versus Current Use of LABA.
ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LAMA = long-acting muscarinic antagonists.
Note: The number of cases and controls for current use of LABA (reference category) differed across the study medications. Current users of both LABA and the specific study medication of interest were excluded from each corresponding analysis. Exposure for each study medication was evaluated at the index date and classified in the following 3 mutually exclusive categories: 1) current use: when the days' supply of the most recent prescription overlapped or ended within 7 days before the index date, 2) recent use: when the days' supply of the most recent prescription ended more than 7 days but 60 days or less before the current use period, and 3) past use: when the days' supply of the most recent prescription ended before the recent use period.
This multivariable conditional regression analysis was adjusted by age; sex; severity of chronic obstructive pulmonary disease at start date; smoking status; obesity; Charlson Index; pneumonia; asthma; heart failure; use of short-acting muscarinic antagonists, oral glucocorticosteroids, mucolytics, and nebulisers; hospitalisations; and number of prescriptions for respiratory medications and nonrespiratory medication.

with an increased risk of death, although RRs were lower than those for switchers (Fig. 3). The magnitude of all crude RRs of mortality decreased further away from 1 when they were adjusted for COPD severity and other confounders. The risk of death was higher at the start of treatment with LABA than at the start of treatment with the rest of COPD medications or with longer treatment. Compared with short duration of current use of LABA, RRs for short duration of use (< 30 days) were 0.46 (95% CI, 0.26–0.76) for aclidinium, 0.65 (95% CI, 0.43–0.98) for tiotropium, 0.70 (95% CI, 0.43–1.13) for other LAMA, and 0.87 (95% CI, 0.61–1.24) for LABA/ICS. Compared with short duration of current use of LABA, RRs for long duration of use (≥30 days) were 0.54 (95% CI, 0.36–0.83) for aclidinium, 0.79 (95% CI, 0.53–1.19) for tiotropium, 0.70 (95% CI, 0.47–1.05) for other LAMA, and 1.16 (95% CI, 0.73–1.85) for LABA/ICS.

Results for current use of the study medications were similar in the analysis stratified by categories of COPD severity, measures of airflow limitation, age, and history of asthma. Among patients with a history of cardiovascular disease, the risk of death was lower in users of each study medication than in users of LABA, although precision was low. The study results were consistent across sensitivity analyses for alternative definitions of duration of exposure and COPD severity and patient subgroups (Figure S-1).

4. Discussion

This is the first observational study on all-cause mortality in users of aclidinium and new LAMA medications. Compared with LABA, use of aclidinium and other LAMAs did not increase the risk of death. The reduced risk of death among aclidinium users was driven by the current single-use category (patients not using other COPD study medications), which comprises around 26% of the new users of aclidinium and had a low number of exposed cases, i.e., less than 15 cases. There was no difference in mortality among aclidinium users in the multiple use category (those patients using other COPD study medications in addition

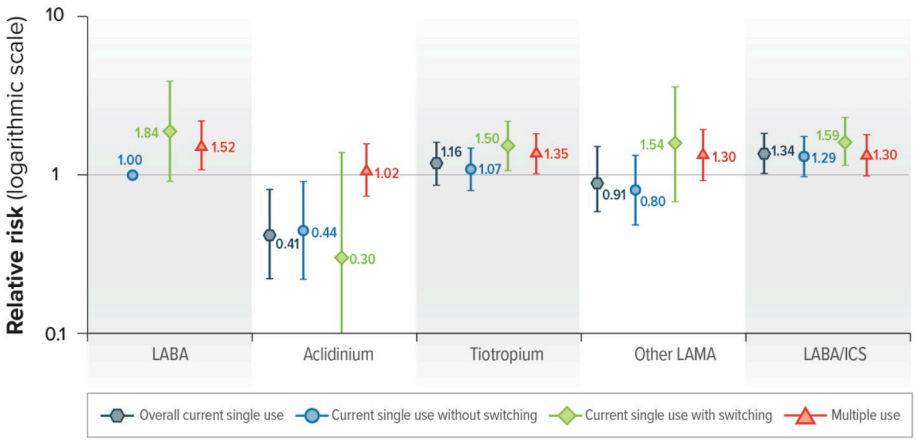

Fig. 3. Adjusted Relative Risk of Mortality Death for Current Single and Current Multiple Use Versus Current Single Use of LABA[a].
ICS = inhaled corticosteroid; LABA = long-acting β2 agonist; LAMA = long-acting muscarinic antagonists.
Note: Current use was classified into current single ("overall current single use") or multiple use, depending on whether patients were concurrently treated with other study medications at the index date. Current single use was further subclassified as switching if patients had recent use of other study medications at the index date. "Overall current single use" refers to current use with and without switching. This multivariable conditional regression analysis was adjusted by age; sex; severity of chronic obstructive pulmonary disease at start date; smoking status; obesity; Charlson Index; pneumonia; asthma; heart failure; use of short-acting muscarinic antagonists, oral glucocorticosteroids, mucolytics, and nebulisers; hospitalisations; and number of prescriptions for respiratory medications and nonrespiratory medication
[a] Reference is current single use of LABA without switching (no recent use of other study medications).

to aclidinium), which comprised approximately 74% of the aclidinium study cohort.

A 60% reduction of the risk of death among overall current single users is so large that an alternative explanation should be ruled out. Immortal time bias could occur because current users of aclidinium are more likely to have received LABA in the past than the opposite. Patients must have survived the prior use of LABA to be in the aclidinium or the other LAMA cohort, thus this time is immortal. This would be supported by the finding that RRs for recent and past use of all study medications were higher than RRs for current use of LABA. Immortal time bias due to inappropriate classification of exposure should be ruled out because risk-set sampling was applied to the selection of controls [13,14]. Another possibility could be that there is a time window bias resulting from different time-window lengths between cases and controls; however, this was avoided in the study design by matching by year of cohort entry and assigning the same index date to controls as the index date of their matched pair, thus accounting for duration of opportunity of exposure [15]. Alternatively, channelling bias may have played a role so that LABA and aclidinium—despite having similar indications—are preferentially prescribed to groups of patients with varying baseline prognoses (e.g., the physician may try to avoid prescribing beta-blockers and beta agonists among patients with cardiovascular disease, as shown by differences in the severity of the disease. However, results from analyses stratified by COPD severity and airflow limitation and from sensitivity analyses measuring COPD severity before the index date instead of before the start date were consistent with the overall results. Similarly, adjustment by comorbidities, including history of cardiovascular disease, did not change the study results. Nonetheless, ultimately it cannot be ruled out that some of these differences between patients have not been controlled in the analysis.

Based on the descriptive analysis, new users of aclidinium were more likely to have severe COPD than new users of LABA; this is in line with what is reported in the literature [16]). Therefore, one would expect that new users of aclidinium would have a higher risk of death and not the contrary. When looking at current single users of LABA, we found that these patients were more likely to be on palliative care or to be classified as fragile prior to index date (i.e., that LABA is more frequently prescribed as current single medication among patients with a higher risk of death), and this channelling bias may explain—at least in part—the reduced risk of death when comparing current single use of aclidinium to current single use of LABA [17]. If channelling bias is related to single use of LABA, then a risk reduction should have been seen when comparing any single use of the study medications to single use of LABA. This was not observed. An alternative hypothesis is again channelling bias related to selective prescription of newer medications as monotherapy—including aclidinium and the other LAMA—to a different set of patients who have a special good prognosis, or that the physicians perceive these patients as being able to "resist" the initiation of a newer medication.

The highest risk of death in patients switching or concurrently treated with multiple COPD medications could be compatible with residual confounding from the inability to adequately control for worsening of COPD symptoms or exacerbations leading to death. A causal effect, with combinations of these medications increasing the risk of conditions such as tachyarrhythmia cannot be ruled out, although the main effect was observed among current single users of aclidinium.

Another potential explanation of a lower risk among current users of aclidinium could be depletion of susceptible patients, if aclidinium tends to follow the use of the other agents rather than vice versa. This may be further supported by the finding that new users of aclidinium and other LAMA with a history of cardiovascular disease showed lower RR of death when compared with current users of LABA with a prior history of cardiovascular disease.

Another interesting finding was that the risk of death was higher at the start of treatment with LABA than at the start of treatment with the rest of COPD medications or with longer treatment. This is in line with a recent observational study comparing use of LABA and LAMA versus no use, where the increased risk observed among users of both medications was limited to the first 30 days after initiation [18]. In an attempt to have a more similar population between the comparator groups and mitigate selection bias in our study, the comparison was done between LAMA and LABAs. Therefore, it cannot be discarded that if compared with COPD patients without treatment, new use of LAMA would be associated with an increased risk of death.

Finally, outcome misclassification is unlikely as deaths were identified mainly through hospitalisation and death registry records, and deaths with inconsistent information about occurrence and date of death were confirmed through a review of the recorded clinical information. One of the strengths of the study is that we adjusted effect estimates by COPD severity according to the [11] classification, which uses data on symptoms, exacerbations, hospitalisations, and airflow limitation. In addition, misclassification of COPD and asthma, and potential increased risk of death in patients with both conditions, did not affect the study results, as indicated in the stratified analysis by history of asthma.

Overall, results from this study indicate that the use of aclidinium, tiotropium, other LAMA, or LABA/ICS is not associated with an increased risk of all-cause mortality as compared with the use of LABAs. Although this study was performed in the UK, the medication effects should be applicable to other patient populations with similar health

care systems and patterns of use. Results of this study are also consistent withthose reported in the ASCENT clinical trial performed in the United States and Canada [19], which was designed to evaluate the cardiovascular safety of aclidinium among patients with high cardiovascular risk (history of cerebrovascular, coronary, or peripheral artery disease, or presence of at least two cardiovascular risk factors), and did not find an increased risk of death when compared with placebo [20]. Results are also consistent with the phase 3 clinical trials for tiotropium (UPLIFT and TIOSPIR) and most observational studies of tiotropium, which did not find an increased risk of death [3,4]. Results from the aclidinium cardiovascular PASS programme on heart failure, stroke, acute myocardial infarction, and arrhythmias will provide more information on the cardiovascular safety of aclidinium and other COPD medications.

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Conflicts of interest

Cristina Rebordosa, Estel Plana, Jaume Aguado, Jordi Castellsague, and Susana Perez-Gutthann, are salaried employees of RTI Health Solutions and work on projects funded by pharmaceutical companies. As salaried employees of RTI Health Solutions, Susana Perez-Gutthann also participates in scientific advisory boards (for studies and medications) that are funded by pharmaceutical companies.

Ana Frances, Alejhandra Lei, Esther García-Gil, and Javier Nuevo are employees of AstraZeneca.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.04.018.

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