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Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease
A Nested Case-Control Study

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IMPORTANCE The associations between cardiovascular disease (CVD) and inhaled long-acting β_2-agonists (LABAs) or long-acting antimuscarinic antagonists (LAMAs) in chronic obstructive pulmonary disease (COPD) are greatly debated. Pivotal and relevant randomized clinical trials included prior LABA or LAMA users and excluded patients with baseline CVD; therefore, cardiovascular events arising from first-time LABA or LAMA use, if any, could not be observed. There is an urgent need to examine whether new use of and duration since initiating LABAs and LAMAs could act as important determinants of cardiovascular events.

OBJECTIVE To investigate risk of CVD associated with LABAs and LAMAs, focusing on the initiation and duration of LABA and LAMA therapies.

DESIGN, SETTING, AND PARTICIPANTS This nested case-control study included 284 220 LABA-LAMA–naïve patients with COPD at least 40 years old (mean age, 71.4 years; 68.9% men), retrieved from the Taiwan National Health Insurance Research Database for health care claims from 2007 to 2011.

EXPOSURE LABA or LAMA use was measured in the year preceding the event or index date, stratified by duration since initiation of LABA or LAMA treatment, new and prevalent users, concomitant COPD medications, and individual agents.

MAIN OUTCOMES AND MEASURES Cases with inpatient or emergency care visits for coronary artery disease, heart failure, ischemic stroke, or arrhythmia were identified and individually matched to 4 randomly selected controls. Conditional logistic regressions were performed to estimate odds ratios of CVD from LABA and LAMA treatment.

RESULTS During a mean follow-up of 2.0 years, 37 719 patients with CVD (mean age, 75.6 years; 71.6% men) and 146 139 matched controls (mean age, 75.2 years; 70.1% men) were identified. New LABA and LAMA use in COPD was associated with a 1.50-fold (95% CI, 1.35-1.67; $P < .001$) and a 1.52-fold (95% CI, 1.28-1.80; $P < .001$) increased cardiovascular risk within 30 days of initiation, respectively, whereas the risk was absent, or even reduced with prevalent use. Individual LABA agents, LAMA dosage forms, and concomitant COPD regimens did not differ in the CVD risks. The risk persisted in an alternative case-crossover study and remained across subgroups without CVD history or prior exacerbations.

CONCLUSIONS AND RELEVANCE New initiation of LABAs or LAMAs in patients with COPD is associated with an approximate 1.5-fold increased severe cardiovascular risk, irrespective of prior CVD status and history of exacerbations.

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Chronic obstructive pulmonary disease (COPD) is a chronic and irreversible inflammatory lung disease, presently posing a significant burden to health care systems across the world.[1-6] Long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the mainstay therapies for COPD[7,8]; however, these agents were found to increase the risk of cardiovascular disease (CVD), although the findings varied, concluding that there was no increased risk[9-14] or that there was a 1.1- to 4.5-fold increased cardiovascular risk.[15-18] These studies, even a large randomized clinical trial (RCT),[9] generally observed few cardiovascular events, excluded patients with severe illness,[9-11] and obtained incomplete medication records[17,18] as well as dropped more than 50% of eligible patients.[15] All of these limitations could potentially weaken the causality or generalizability of the association.

Notably, inclusion of patients with tolerability to the risk of CVD receiving LABA or LAMA therapy is probably a major drawback in previous large RCTs. The 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial[10] and the 3-year Toward a Revolution in COPD Health (TORCH) trial,[9] which observed a reduced or no increase in CVD risk, included more than 45% and 35% of participants who had received inhaled cholinergics and LABAs, respectively, and the 2 trials excluded patients with a history of recent CVD and life-threatening cardiovascular events. Accordingly, patients who had developed severe CVD with new use of LABAs or LAMAs could have been excluded, and only those LABA or LAMA prevalent users who had probably developed tolerance to the cardiovascular risk were included in the trials. Accordingly, we suspect that new use of and duration since initiating LABAs and LAMAs could act as important determinants of CVD risk, which to date have not been examined in details in previous studies.

The present study investigated use of LABAs and LAMAs associated with the risk of CVD in a nationwide population of patients with COPD, focusing on new use and duration of therapy, individual agents, dosage forms, and concomitant COPD regimens.

Key Points

Question Does the duration since initial use and new use of inhaled long-acting β_2-agonists (LABAs) or antimuscarinic antagonists (LAMAs) for the treatment of chronic obstructive pulmonary disease (COPD) act as important determinants of the risk of cardiovascular disease?

Findings In this nested case-control study of more than 280 000 patients with COPD, new use of LABAs or LAMAs is associated with an approximate 1.5-fold increased cardiovascular risk within 30 days of initiation therapy.

Meaning Health care professionals need to be very vigilant with regard to any cardiovascular symptoms within 30 days of initiating LABA or LAMA treatment for COPD.

Methods

Study Design and Data Source

We performed a nested case-control study of a nationwide COPD population 40 years or older with the data retrieved from the Taiwan National Health Insurance Research Database (NHIRD) from January 1, 2007, to December 31, 2011, as depicted in eFigure 1 in the Supplement. The NHIRD contains all medical and pharmacy claims records from all medical care settings for more than 99% of the 23 million Taiwanese inhabitants covered under a compulsory and universal national health insurance. The claims are audited quarterly by the National Health Insurance Administration,[19] and multiple disease diagnosis codes in the database have been validated, including several CVD diagnoses.[20-22] The study was exempt from a full review by the institutional review board of Tri-Service General Hospital, National Defense Medical Center.

Identification of Study Cohort

We identified patients with COPD 40 years or older who had made 2 outpatient visits or an inpatient visit for COPD (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 491.xx, 492.xx, and 496.xx) in a single year from January 1, 2008, to June 30, 2011, accompanied by a record of filling at least 1 COPD medication at each visit. The cohort entry date was set as the date of the first COPD outpatient visit or the discharge date from a COPD hospitalization. We excluded patients who had received any LABA-LAMA therapy or who lacked continuous health insurance coverage for 1 year preceding cohort entry. We followed-up the remaining patients until the earliest of CVD outcome (defined in the outcome measurement), National Health Insurance program withdrawal, death, or the end of the study period (December 31, 2011). We determined mortality from the NHIRD based on a previously reported approach.[23]

Case Identification

We identified CVD cases as patients who had made an inpatient or emergency department (ER) visit with a primary diagnosis of coronary heart disease (*International Classification of Diseases, 9th Revision, Clinical Modification* [*ICD-9-CM*], codes 410-414), cardiac arrhythmia (code 427), heart failure (code 428), or ischemic stroke (codes 433-434). The adopted coding system for acute myocardial infarction, heart failure, and ischemic stroke has been validated with high accuracy.[20,21,24] We set the first CVD event as the index date.

Each case was matched to 4 randomly selected controls from risk set samples by cohort entry date (±180 days) and disease risk score (DRS) (±0.01) of predicting the occurrence of a cardiovascular outcome during follow-up. Use of the DRS to match cases with controls yields better statistical precision than does exact matching on multiple discrete factors in a nested case-control setting.[25] Estimation of the DRS is detailed in eMethods 1 in the Supplement.

Exposure Measurement

We examined all LABA and LAMA prescription records in the year before the index date for both cases and controls. Specifically, drug use was classified into current (≤30 days),

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recent (31-90 days), past (91-180 days), and remote (>180 days) use based on the most recent prescription date preceding the index date. Current users were further classified as new users if they had no other dispensing records in the 31 to 365 days before the index date and prevalent users otherwise. We also used restricted cubic spline models to analyze the duration of new LABA and new LAMA therapy (as detailed in eMethods 2 in the Supplement). New use of LABAs and LAMAs was also categorized according to various combinations with COPD medication agents, individual LABAs, and different drug-containing devices of LAMAs. Individual agents of LABAs and LAMAs comprised salmeterol, formoterol, and tiotropium. Nonusers of LABAs-LAMAs and new theophylline users were set as the reference group in the main analyses and sensitivity analyses, respectively.

Measurement of Covariates

Important determinants of CVD were considered, such as prior CVDs, hypertension, diabetes, hyperlipidemia, use of CVD medications, and agents related to cardiotoxicity. We also considered proxy indicators of COPD severity, including the number of COPD-related outpatient visits accompanied by oral corticosteroids or respiratory antibiotic prescription records (referred to as moderate exacerbation) and the number of severe exacerbation events (defined as any inpatient or ER admission for COPD), as well as the presence of incident or prevalent COPD. Other factors related to LABA-LAMA use or CVD were considered (as detailed in eTable 1 in the Supplement). We first measured these factors in the year preceding cohort entry, and included them in a logistic regression model to estimate the DRS of encountering a CVD outcome during follow-up (eMethods 1 in the Supplement). Second, we treated these confounders as time-varying effects by also assessing concomitant medications and the remaining factors during the 6 months and in the year prior to the index date, respectively.

Statistical Analysis

The covariate balance before and after DRS matching was assessed using the standardized difference, and meaningful imbalances between groups were determined when the standardized difference was greater than 0.1.[26] We used conditional logistic regressions to estimate the odds ratio (OR) of CVD with LABA or LAMA use. We expressed the absolute risk of CVD arising from LABA and LAMA treatment as the number needed to harm (NNTH)[27] according to a previously reported formula.

Data sets were constructed and analyzed by using SAS (version 9.3; SAS Institute Inc) and STATA (version 13; StataCorp) statistical software, respectively. We defined tests with 2-sided $P < .05$ as significant.

Sensitivity and Subgroup Analysis

Multiple additional analyses were performed. First, we adopted a case-crossover study to avoid selection bias and minimize time-invariant confounding (eMethods 3 and eFigure 2 in the Supplement). Second, to mitigate confounding by indication bias, we repeated the analyses by treating patients who began new treatment with theophyllines, another class of bronchodilators used for COPD therapy, in the 30 days before the index date as the reference group. Third, to address protopathic bias, we used a lag-time approach[28] that disregarded any prescription records of LABAs and LAMAs in the 7 days before the index date and restricted new LABA and LAMA users to those who received spirometry testing within 30 days before or on the date of initiating these medications to justify respiratory medication use. We also excluded patients who started any cardiovascular medications in the 30 days before the index date and those with any chest pain (*ICD-9* code 786.5) or dyspnea/breathing difficulty diagnoses (code 786.0) as possible presymptoms of CVD. Fourth, events of heart failure were excluded from the CVD outcome. Fifth, we also performed stratified analyses by CVD care type, baseline CVD status, CVD severity (fatal vs nonfatal), COPD severity, asthma comorbidity, use of theophyllines, and use of systemic short-acting β_2-agonists. Sixth, we adjusted for all covariates that were measured preceding the index date in **Table 1** and evaluated the impact of unmeasured confounding using a rule-out approach,[29] as detailed in eFigure 3 in the Supplement.

Results

The study cohort consisted of 284 220 LABA-LAMA-naive patients with COPD with a mean age of 71.4 years, 68.9% of whom were male. During a mean follow-up of 2.0 years, we identified 37 719 patients with severe CVD requiring hospitalization or emergency care, at a rate of 6.6 per 100 person-years, and included 146 139 matched controls (eFigure 4 in the Supplement).

All characteristics were balanced prior to cohort entry between cases and controls (Table 1). During follow-up, most of the covariates remained balanced between the 2 groups, and only a few factors differed significantly higher between cases and controls, for which statistical adjustment was performed.

As indicated in **Table 2**, overall use of inhaled long-acting bronchodilators was not associated with an increased risk of CVD across different recency of therapy, although a 10% decrease in cardiovascular risk was observed with past LABA use. Among current users, new initiation of LABA and LAMA treatment was associated with a 1.50-fold (95% CI, 1.35-1.67; $P < .001$) and a 1.52-fold (95% CI, 1.28-1.80; $P < .001$) increased cardiovascular risk, respectively, while prevalent LABA or LAMA use yielded a 9% to 12% reduction in risk. In addition, new LABA use vs new LAMA use yielded no difference in the risk of CVDs ($P = .93$) (eTable 2 in the Supplement).

Various clinical usages of LABAs and LAMAs within 30 days of therapy initiation were scrutinized (**Table 3**). The adjusted ORs ranged minimally from 1.42 to 1.51 across the various LABA medication regimens. Salmeterol and formoterol were found to present similar CVD risks. Different LAMA regimens, including use of tiotropium only, carried similar risks, ranging from 1.39-fold to 1.58-fold increases. Analyses of individual CVD outcomes revealed increased risks of coronary artery disease and heart failure with LABA and LAMA treatment, and an increased risk for cardiac arrhythmias with LAMA therapy (eTable 3 in the Supplement).

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Table 1. Clinical Characteristics Between Cases and Matched Controls[a]

Characteristic	At Baseline, No. (%)[a]			During Follow-up, No. (%)[b]		
	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]
Age, mean (SD), y	75.6 (10.3)	75.2 (10.2)	0.042	75.6 (10.3)	75.2 (10.2)	0.042
Sex, male No. (%)	27 019 (71.6)	102 404 (70.1)	0.034	27 019 (71.6)	102 404 (70.1)	0.034
Prior CVD[d]						
CAD						
None	21 304 (56.5)	86 351 (59.1)		22 565 (59.8)	92 072 (63.0)	
Hospitalization or ER visits	3687 (9.8)	7795 (5.3)	0.008	0	0	0.065
History of CAD	12 728 (33.7)	51 993 (35.6)		15 154 (40.2)	54 067 (37.0)	
Heart failure						
None	27 958 (74.1)	115 949 (79.3)		28 674 (76.0)	117 107 (80.1)	
Hospitalization or ER visits	2912 (7.7)	4877 (3.3)	0.078	0	0	0.100
History of heart failure	6849 (18.2)	25 313 (17.3)		9045 (24.0)	29 032 (19.9)	
Ischemic stroke						
None	32 072 (85.0)	126 408 (86.5)		33 282 (88.2)	129 718 (88.8)	
Hospitalization or ER visits	1903 (5.1)	5610 (3.8)	0.028	0	0	0.017
History of ischemic stroke	3744 (9.9)	14 121 (9.7)		4437 (11.8)	16 421 (11.2)	
Cardiac arrhythmia						
None	29 143 (77.3)	116 390 (79.6)		30 034 (79.6)	118 225 (80.9)	
Hospitalization or ER visits	902 (2.4)	1917 (1.3)	0.046	0	0	0.032
History of arrhythmia	7674 (20.4)	27 832 (19.0)		7685 (20.4)	27 914 (19.1)	
Hypertension	26 501 (70.3)	103 676 (70.9)	0.015	24 136 (64.0)	92 373 (63.2)	0.016
Diabetes	11 482 (30.4)	43 119 (29.5)	0.020	10 977 (29.1)	39 884 (27.3)	0.040
Asthma	7979 (21.2)	29 743 (20.4)	0.020	8087 (21.4)	27 889 (19.8)	0.059
Newly diagnosed COPD	16 030 (42.5)	58 272 (39.9)	0.053	16 030 (42.5)	58 272 (39.9)	0.053
Severe COPD exacerbations. No.[e]						
0	33 081 (87.7)	131 099 (89.7)		33 592 (89.1)	136 272 (93.3)	
1	3778 (10.0)	12 563 (8.6)	0.066	3404 (9.0)	8452 (5.8)	0.148
≥2	860 (2.3)	2477 (1.7)		723 (1.9)	1415 (1.0)	
COPD Severity Indicators, No. (%)						
Moderate COPD exacerbations, No.[f]						
0	33 281 (88.2)	128 393 (87.9)		33 418 (88.6)	132 875 (90.9)	
1	2938 (7.8)	11 627 (8.0)	0.013	3353 (8.9)	10 295 (7.0)	0.071
≥2	1500 (4.0)	6119 (4.2)		948 (2.5)	2969 (2.0)	
Type of COPD medications, No.						
0	16 003 (42.4)	63 413 (43.4)		16 137 (42.8)	65 959 (45.1)	
1	14 755 (39.1)	57 933 (39.6)	0.033	15 221 (40.4)	62 961 (43.1)	0.106
≥2	6961 (18.5)	24 793 (17.0)		6361 (16.9)	17 219 (11.8)	
Site of the initial diagnosis of COPD						
Outpatient	35 618 (94.4)	139 686 (95.6)	0.053	35 618 (94.4)	139 686 (95.6)	0.053
Inpatient	2101 (5.6)	6453 (4.4)		2101 (5.6)	6453 (4.4)	
Health Care Use, No. (%)						
Outpatient visits, No.						
≤16	8717 (23.1)	31 972 (21.9)		16 789 (44.5)	67 789 (46.4)	
12-31	11 915 (31.6)	47 272 (32.4)	0.022	8582 (22.8)	33 452 (22.9)	0.045
≥32	17 087 (45.3)	66 895 (45.8)		12 348 (32.7)	44 898 (30.7)	
Comorbidities, No. (%)						
Pulmonary disease						
Acute bronchitis	14 137 (37.5)	55 088 (37.7)	0.004	10 155 (26.9)	38 019 (26.0)	0.021
Pneumonia	9379 (24.9)	30 843 (21.1)	0.089	8782 (23.3)	29 493 (20.2)	0.075
Influenza	1978 (5.2)	7782 (5.3)	0.004	1412 (3.7)	5256 (3.6)	0.008
Pulmonary embolism	136 (0.4)	479 (0.3)	0.006	153 (0.4)	389 (0.3)	0.024

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Table 1. Clinical Characteristics Between Cases and Matched Controls[a] (continued)

Characteristic	At Baseline, No. (%)[a]			During Follow-up, No. (%)[b]		
	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]
CVD						
Peripheral vascular disease	2585 (6.9)	9357 (6.4)	0.018	2141 (5.7)	6908 (4.7)	0.043
Rheumatic heart disease	1432 (3.8)	3512 (2.4)	0.080	1008 (2.7)	2192 (1.5)	0.082
Hemorrhagic stroke	860 (2.3)	3146 (2.2)	0.009	672 (1.8)	2333 (1.6)	0.014
Hyperlipidemia	8245 (21.9)	32 994 (22.6)	0.017	6483 (17.2)	25 480 (17.4)	0.007
Cancer	5394 (14.3)	18 644 (12.8)	0.045	4987 (13.2)	18 843 (12.9)	0.010
Renal failure	3971 (10.5)	12 882 (8.8)	0.058	4063 (10.8)	11 536 (7.9)	0.099
Dementia	3472 (9.2)	11 904 (8.2)	0.038	3594 (9.5)	11 892 (8.1)	0.049
Chronic liver disease	3498 (9.3)	13 466 (9.2)	0.002	2707 (7.2)	10 187 (7.0)	0.008
Parkinsonism	1806 (4.8)	6668 (4.6)	0.011	1688 (4.5)	5971 (4.1)	0.019
Comedication, No. (%)						
CV medication						
Antiplatelets	23 272 (61.7)	89 672 (61.4)	0.007	18 967 (50.3)	65 648 (44.9)	0.108
Calcium channel blockers	23 836 (63.2)	92 158 (63.1)	0.003	18 595 (49.3)	69 021 (47.2)	0.041
Diuretics	22 495 (59.6)	84 070 (57.5)	0.043	18 420 (48.8)	63 820 (43.7)	0.104
Angiotensin receptor blockers	14 032 (37.2)	52 040 (35.6)	0.033	11 716 (31.1)	41 621 (28.5)	0.056
Angiotensin-converting enzyme inhibitor	11 149 (29.6)	41 967 (28.7)	0.019	6241 (16.6)	19 453 (13.3)	0.091
β-Blockers						
CV-selective	7762 (20.6)	29 760 (20.4)	0.005	4998 (13.3)	16 740 (11.5)	0.055
Non-CV-selective	10 520 (27.9)	39 172 (26.8)	0.024	5945 (15.8)	19 300 (13.2)	0.073
Digoxin	5346 (14.2)	17 067 (11.7)	0.074	4261 (11.3)	12 811 (8.8)	0.084
Antiarrhythmic agents	4972 (13.2)	15 769 (10.8)	0.074	3525 (9.4)	10 835 (7.4)	0.070
Nitrates	5459 (14.5)	17 746 (12.1)	0.069	3032 (8.0)	9129 (6.3)	0.070
Anticoagulants	4701 (12.5)	15 263 (10.4)	0.063	2280 (6.0)	6338 (4.3)	0.077
Lipid-lowering agents						
Statins	7323 (19.4)	27 768 (19.0)	0.010	5114 (13.6)	18 485 (12.7)	0.027
Others	152 (0.4)	546 (0.4)	0.005	70 (0.2)	254 (0.2)	0.003
COPD medications						
Methylxanthines	14 037 (37.2)	59 209 (40.5)	0.068	16 726 (44.3)	65 386 (44.7)	0.008
Short-acting β_2-agonists						
Oral/injection	17 027 (45.1)	64 531 (44.2)	0.020	17 027 (45.1)	64 531 (44.2)	0.020
Nebulized	3749 (9.9)	12 077 (8.3)	0.058	2398 (6.4)	6246 (4.3)	0.093
Inhaled						
0 Canister	25 096 (66.5)	104 088 (71.2)		28 153 (74.6)	119 237 (81.6)	
≤6 Canisters	10 717 (28.4)	36 068 (24.7)	0.100	8441 (22.4)	23 890 (16.4)	0.163
>6 Canisters	1906 (5.1)	5983 (4.1)		1125 (3.0)	3012 (2.1)	
Short-acting muscarinic antagonists						
Nebulized	8788 (23.3)	28 177 (19.3)	0.098	5320 (14.1)	12 953 (8.9)	0.165
Inhaled						
0 Canister	31 267 (82.9)	125 117 (85.6)		32 428 (86.0)	131 247 (89.8)	
≤6 Canisters	5652 (15.0)	18 413 (12.6)	0.071	4891 (13.0)	13 776 (9.4)	0.114
>6 Canisters	800 (2.1)	2609 (1.8)		400 (1.1)	1116 (0.8)	
Inhaled corticosteroids	1662 (4.4)	5734 (3.9)	0.024	3972 (10.5)	13 785 (9.4)	0.037
Oral long-acting β_2-agonists	2 (0.01)	13 (0.01)	0.004	546 (1.5)	1766 (1.2)	0.021
Systemic anticholinergic						
Antihistamine	24 062 (63.8)	92 993 (63.6)	0.003	13 218 (35.0)	47 868 (32.8)	0.048
Gastrointestinal antispasmodics	8299 (22.0)	31 814 (21.8)	0.006	3460 (9.2)	12 304 (8.4)	0.027
Bladder antimuscarinics	3036 (8.1)	11 780 (8.1)	<0.001	1521 (4.0)	5614 (3.8)	0.010
Others	4622 (12.3)	18 105 (12.4)	0.004	2086 (5.5)	7439 (5.1)	0.020
NSAIDs	31 105 (82.5)	120 663 (82.6)	0.003	19 788 (52.5)	75 109 (51.4)	0.021

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Table 1. Clinical Characteristics Between Cases and Matched Controls[a] (continued)

Characteristic	At Baseline, No. (%)[a]			During Follow-up, No. (%)[b]		
	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]	Cases (n = 37 719)	Controls (n = 146 139)	SDiff[c]
Systematic corticosteroids	20 149 (53.4)	73 517 (50.3)	0.062	13 606 (36.1)	44 309 (30.3)	0.122
Antipsychotic	9396 (24.9)	34 394 (23.5)	0.032	5432 (14.4)	17 237 (11.8)	0.077
Antidepressant	7373 (19.6)	28 311 (19.4)	0.004	4326 (11.5)	15 345 (10.5)	0.031
Vaccine	13 330 (35.3)	54 564 (37.3)	0.042	12 997 (34.5)	54 170 (37.1)	0.054

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; ER, emergency department; DRS, disease risk score; NSAIDs, nonsteroidal anti-inflammatory drugs; SDiff, standardized difference.

[a] All comorbidities and comedications were measured in the year preceding entry date.

[b] All comorbidities were measured in the year, and comedications in the 6 months before index date.

[c] Covariates with SDiff> 0.1 represent meaningful differences between groups.

[d] Prior CVDs were measured in 3 severity levels.

[e] Severe COPD exacerbation was defined as patients requiring hospital or ER visits for COPD.

[f] Moderate COPD exacerbation included patients who were prescribed with either an antibiotics or oral corticosteroid in an outpatient COPD visit.

Table 2. Risk of CVD With Prior Use of LABA and LAMA Compared With Nonuse, Stratified by Recency[a]

Bronchodilator	Cases[b] (n = 37 719)	Controls[b] (n = 146 139)	Crude OR (95% CI)	*P* Value	Adjusted OR[c] (95% CI)	*P* Value
Nonuse of LABA or LAMA, No. (%)	31 732 (84.1)	124 943 (85.5)	1 [Reference]		1 [Reference]	
Current bronchodilator use (≤30 d)						
LABA	1482 (3.9)	4981 (3.4)	1.18 (1.12-1.26)	<.001	1.06 (0.99-1.12)	.08
New use	520 (1.4)	1186 (0.8)	1.74 (1.57-1.93)	<.001	1.50 (1.35-1.67)	<.001
Prevalent use	962 (2.6)	3795 (2.6)	1.01 (0.94-1.08)	.81	0.91 (0.85-0.98)	.02
LAMA	648 (1.7)	2440 (1.7)	1.05 (0.96-1.15)	.26	1.00 (0.92-1.10)	.97
New use	190 (0.5)	463 (0.3)	1.62 (1.37-1.92)	<.001	1.52 (1.28-1.80)	<.001
Prevalent use	458 (1.2)	1977 (1.4)	0.92 (0.83-1.02)	.11	0.88 (0.79-0.98)	.02
LABA and LAMA	581 (1.5)	1706 (1.2)	1.37 (1.24-1.50)	<.001	1.16 (1.05-1.28)	.003
New use	50 (0.1)	84 (0.1)	2.38 (1.68-3.38)	<.001	2.03 (1.42-2.91)	<.001
Prevalent use	531 (1.4)	1622 (1.1)	1.31 (1.19-1.45)	<.001	1.11 (1.00-1.23)	.04
Recent bronchodilator use (31-90 d)						
LABA	787 (2.1)	2770 (1.9)	1.13 (1.04-1.22)	.004	0.97 (0.89-1.05)	.47
LAMA	304 (0.8)	1129 (0.8)	1.07 (0.94-1.22)	.28	1.00 (0.88-1.14)	.98
LABA and LAMA	192 (0.5)	604 (0.4)	1.28 (1.09-1.51)	.003	1.09 (0.92-1.29)	.31
Past bronchodilator use (91-180 d)						
LABA	621 (1.7)	2384 (1.6)	1.03 (0.95-1.13)	.46	0.90 (0.83-0.99)	.03
LAMA	205 (0.5)	875 (0.6)	0.93 (0.80-1.08)	.36	0.86 (0.74-1.00)	.06
LABA and LAMA	98 (0.3)	338 (0.2)	1.14 (0.91-1.43)	.26	0.95 (0.76-1.20)	.69
Remote bronchodilator use (>180 d)						
LABA	738 (2.0)	2643 (1.7)	1.11 (1.02-1.21)	.01	1.04 (0.96-1.13)	.33
LAMA	259 (0.7)	1046 (0.7)	0.98 (0.86-1.13)	.82	0.96 (0.84-1.10)	.55
LABA and LAMA	72 (0.2)	280 (0.2)	1.03 (0.80-1.34)	.82	0.95 (0.73-1.24)	.71

Abbreviations: CVD, cardiovascular disease; LABA, inhaled long-acting β_2-agonist; LAMA, inhaled antimuscarinic antagonist; OR, odds ratio.

[a] Recency was defined from the first supply date of the most recent prescription until the index date.

[b] Data are given as number (percentage).

[c] Adjusted for all covariates with standardized difference > 0.1 in Table 1.

Figure 1 presents the results of duration-response analysis, which indicated that the cardiovascular risks peaked at around the 30th day after new initiation of LABA or LAMA therapy; waned from 31 to 60 days of therapies, and reduced to a level even lower than the baseline risk from 71 to 240 days.

Our main findings remained robust in most of the sensitivity analyses (**Figure 2**, eTables 4 and 5, eFigures 2 and 3 in the Supplement). The increased risk of CVD with new LABA and new LAMA use persisted in a case-crossover analysis (eTables 4-5, eFigure 2 in the Supplement) and in comparison with new use of theophyllines. The results of the analyses performed to address protopathic bias corresponded closely to the main findings. The LABA- or LAMA-associated risk of CVDs remained significant regardless of patients' CVD history and COPD exacerbations. In addition, an unmeasured confounder could fully account for our findings only if the confounder increased the CVD risk by 4-fold

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Table 3. Risk of CVD With New Use of LABAs and LAMAs, Stratified by Characteristics of Therapy

Bronchodilator	Cases (n = 37 719)[a]	Controls (n = 146 139)[a]	Crude OR (95% CI)	P Value	Adjusted OR (95% CI)[b]	P Value
Nonuse of LABA or LAMA, No. (%)	31 732 (84.1)	124 943 (85.5)	1 [Reference]		1 [Reference]	
New LABA Use, No. (%)						
Regimen[c]						
LABA + ICS	517 (1.4)	1173 (0.8)	1.75 (1.57-1.94)	<.001	1.51 (1.36-1.68)	<.001
LABA + SABA	230 (0.6)	448 (0.3)	2.02 (1.72-2.37)	<.001	1.42 (1.21-1.68)	<.001
LABA + ipratropium	199 (0.5)	371 (0.3)	2.11 (1.78-2.51)	<.001	1.42 (1.19-1.70)	<.001
LABA + methylxanthines	231 (0.6)	514 (0.4)	1.80 (1.54-2.10)	<.001	1.50 (1.28-1.76)	<.001
Individual drugs[c]						
Salmeterol	368 (1.0)	828 (0.6)	1.76 (1.56-1.99)	<.001	1.49 (1.31-1.69)	<.001
Formoterol	149 (0.4)	353 (0.2)	1.67 (1.38-2.02)	<.001	1.52 (1.25-1.85)	<.001
New LAMA Use, No. (%)						
Regimen[d]						
LAMA only	66 (0.2)	170 (0.1)	1.52 (1.14-2.03)	.004	1.58 (1.19-2.11)	.002
LAMA + SABA	68 (0.2)	150 (0.1)	1.78 (1.33-2.37)	<.001	1.39 (1.04-1.87)	.03
LAMA + ipratropium	52 (0.1)	94 (0.1)	2.17 (1.54-3.05)	<.001	1.47 (1.04-2.08)	.03
LAMA + methylxanthines	101 (0.3)	247 (0.2)	1.62 (1.29-2.05)	<.001	1.47 (1.16-1.86)	.001
Route						
DPI only	176 (0.5)	425 (0.3)	1.63 (1.37-1.95)	<.001	1.53 (1.28-1.83)	<.001
Mist	14 (0.04)	38 (0.03)	1.48 (0.80-2.73)	.21	1.37 (0.74-2.55)	.32

Abbreviations: CVD, cardiovascular disease; DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LAMA, inhaled antimuscarinic antagonist; OR, odds ratio; SABA, short-acting β_2-agonist.

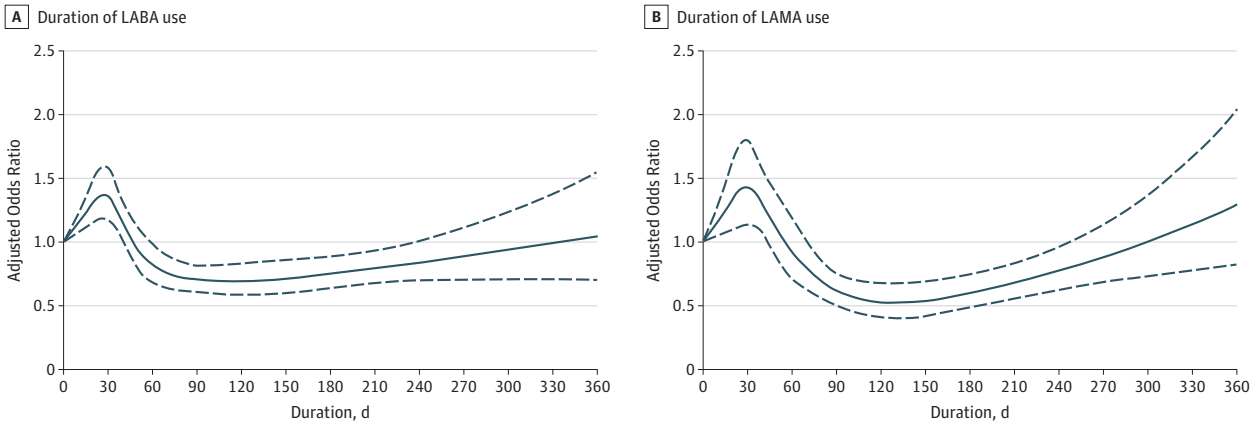
[a] Data are given as number (percentage).

[b] Adjusted for all covariates with standardized difference > 0.1 in Table 1.

[c] Patients using LABA only and LAMA plus ICS regimens were not shown owing to small sample sizes.

[d] Excluding analysis for combination of salmeterol and formoterol owing to few exposures.

Figure 1. Duration-Response Curves for the Adjusted Odds Ratios (95% CIs) of the Cardiovascular Risk as a Function of Duration of New LABA and New LAMA Therapy



Duration-response curves for the adjusted odds ratios (solid line) and 95% CIs (dashed line) of the cardiovascular risk as a function of duration of new inhaled long-acting β_2-agonists (LABAs) therapy (A) and duration of new inhaled antimuscarinic antagonists (LAMAs) therapy (B) by using a restricted cubic splines function in multiple conditional logistic regressions.

and was more prevalent in new LABA and LAMA users by 3.5 and 3.6 times, respectively, than in nonusers (eFigure 3 in the Supplement).

One severe CVD event requiring hospitalization or ER care occurred for every 406 (95% CI, 303-580) new LABA users and 391 (95% CI, 254-725) new LAMA users during the first 30 days of therapy (eTable 6 in the Supplement).

Discussion

This large observational study of more than 280 000 patients with COPD reported an approximate 1.5-fold increased risk of a severe CVD event within 30 days of initiation of LABA or LAMA therapy, but the risk was absent, or even reduced, with

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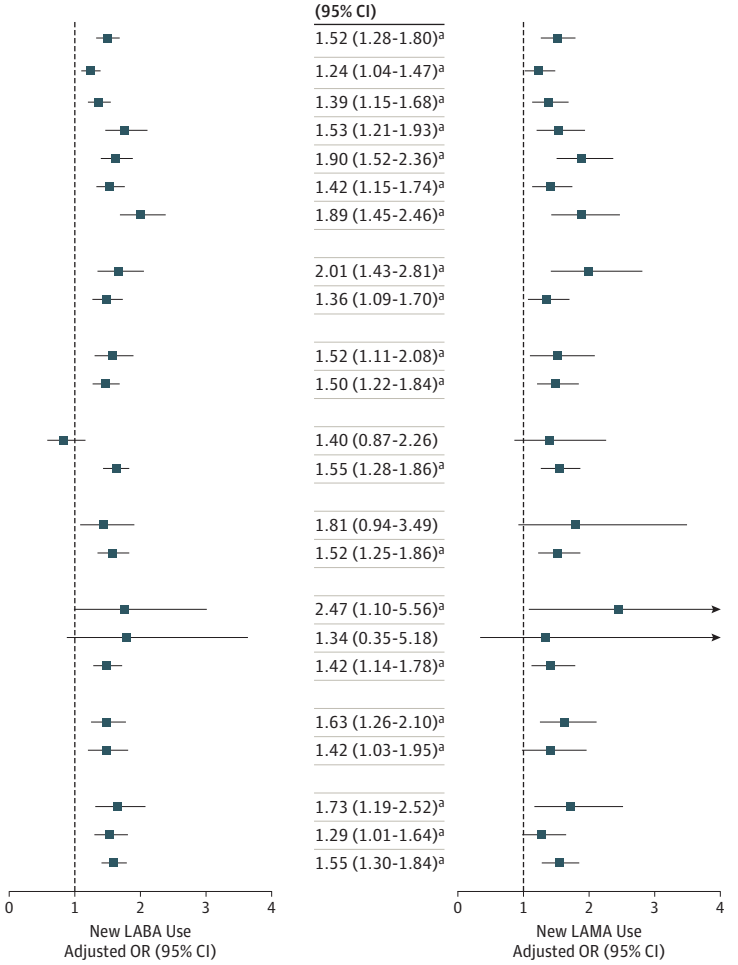
Figure 2. Sensitivity Analysis of Cardiovascular Disease (CVD) Risk With New Use of LABA and LAMA

	New LABA Use Adjusted OR (95% CI)	New LAMA Use Adjusted OR (95% CI)
Primary analysis	1.50 (1.35-1.67)[a]	1.52 (1.28-1.80)[a]
Adopt methylxanthine users as a reference group	1.24 (1.11-1.38)[a]	1.24 (1.04-1.47)[a]
Analyze with a 7-d lag time period	1.36 (1.21-1.53)[a]	1.39 (1.15-1.68)[a]
Restrict to patients with spirometry testing[b]	1.76 (1.49-2.09)[a]	1.53 (1.21-1.93)[a]
Exclude new use of CV medication[c]	1.62 (1.41-1.87)[a]	1.90 (1.52-2.36)[a]
Exclude chest pain or dyspnea difficulty[c]	1.53 (1.35-1.74)[a]	1.42 (1.15-1.74)[a]
Exclude heart failure from CVD outcome	2.01 (1.71-2.38)[a]	1.89 (1.45-2.46)[a]
Stratify by prior CVD		
Yes	1.67 (1.36-2.04)[a]	2.01 (1.43-2.81)[a]
No	1.49 (1.29-1.73)[a]	1.36 (1.09-1.70)[a]
Stratify by CVD care type		
ER	1.57 (1.31-1.88)[a]	1.52 (1.11-2.08)[a]
Inpatient	1.47 (1.29-1.67)[a]	1.50 (1.22-1.84)[a]
Stratify by CVD severity		
Fatal	0.82 (0.59-1.15)	1.40 (0.87-2.26)
Nonfatal	1.63 (1.45-1.82)[a]	1.55 (1.28-1.86)[a]
Stratify by asthma comorbidity		
Yes	1.44 (1.10-1.90)[a]	1.81 (0.94-3.49)
No	1.57 (1.36-1.82)[a]	1.52 (1.25-1.86)[a]
Stratify by COPD exacerbation		
Severe	1.76 (1.02-3.01)[a]	2.47 (1.10-5.56)[a]
Moderate	1.80 (0.89-3.64)	1.34 (0.35-5.18)
None	1.49 (1.30-1.71)[a]	1.42 (1.14-1.78)[a]
Stratify by use of methylxanthines		
Yes	1.49 (1.26-1.77)[a]	1.63 (1.26-2.10)[a]
No	1.48 (1.21-1.79)[a]	1.42 (1.03-1.95)[a]
Stratify by use of oral or injection SABA		
Yes	1.66 (1.33-2.07)[a]	1.73 (1.19-2.52)[a]
No	1.53 (1.31-1.80)[a]	1.29 (1.01-1.64)[a]
Adjust all covariates	1.59 (1.42-1.78)[a]	1.55 (1.30-1.84)[a]



COPD indicates chronic obstructive pulmonary disease; OR, odds ratio; SABAs, short-acting β_2-agonists.

[a] $P < .05$.

[b] We confined analysis to patients who had been tested with spirometry for lung function in the 30 days before or on the date of the new prescription of inhaled long-acting β_2-agonists (LABAs) and inhaled antimuscarinic antagonists (LAMAs).

[c] These analyses were measured in the 30 days before the index date.

prevalent use of these medications. The findings were replicated in a case-crossover design analysis and unaffected by patients' baseline CVD status. Collectively, we have provided the first evidence to indicate that new use and duration since initiation of inhaled long-acting bronchodilators are associated with the therapy-related risk of CVD in patients with COPD.

Previous studies[15-18,30,31] that observed an increased risk of CVD from LABAs or LAMAs evaluated elderly patients with COPD,[15] identified few CVD events,[18,30] or included patients with prior LABA or LAMA usage.[15-18,30,31] None of these studies[15-18,30,31] examined drug use within a time period as short as 30 days after the initiation of therapy. The ability to observe an acute cardiovascular effect with inhaled long-acting bronchodilators in our study primarily resulted from the adoption of a new-user design and examination of a nationwide population of patients with COPD.

Our observed duration-response associations may explain why previous relevant RCTs did not find an increased risk of CVD with LABA or LAMA use. We report herein that the greatest risk of CVD emerged at around the 30th day following initiation of LABA and LAMA therapy. Nevertheless, a substantial proportion of participants with prior LABA or LAMA usage was included in previous RCTs.[9-12,32] For instance, more than one-third of the enrolled patients received LABAs at baseline in the TORCH trial[9]; therefore, cardiovascular events arising following first use of LABAs or LAMAs, if any, could not be observed. In addition, patients with severe CVD or life-threatening cardiovascular events at baseline were excluded in prior trials.[9-12] Both factors could have led to the inclusion of patients with tolerability to cardiovascular events in the RCTs.

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The phenomenon of depletion of susceptibles effect may contribute to the observed duration-response associations. Depletion of susceptibles effect has been described as an increased rate of an event from the initial exposure to a medication, followed by a decreased incidence rate with a longer drug exposure,[33,34] such as the temporal sequence of hormone replacement therapy and its relationship with venous thromboembolism.[34] We suspect that there may exist a subgroup of patients with COPD who are particularly at risk of CVD with initial exposure to LABAs or LAMAs owing to predisposing factors that could amplify sympathetic overactivation or systemic inflammation with inhaled long-acting bronchodilators. Future studies should identify and characterize the most vulnerable subgroups of patients with COPD. We also suspect that after depletion of susceptible patients who experienced CVD events early on, the remaining patients with COPD who continued to use LABAs or LAMAs may exhibit improved systemic inflammation,[35] or may have a more stable lung function status,[36] which could lessen the CVD burden in these patients.

Our findings contribute significantly to investigation of the cardiovascular safety of inhaled long-acting bronchodilators, in which the risk window of adverse cardiovascular events from inhalation therapies is specified. Based on our findings, we suggest that the use of inhaled long-acting bronchodilators in COPD need to be carefully assessed, and a thorough cardiovascular physical examination, especially heart rate measurement and electrocardiograms, need to be performed when prescribing LABAs and LAMAs to patients. Health care professionals should be vigilant for any cardiovascular symptoms during the first 30 days of inhalation therapy. Given that CVD is highly prevalent among patients with COPD, clinicians should also pay attention to the management of CVD risk factors throughout the duration of LABA or LAMA therapy. We also suggest that physicians assess patients' cardiovascular risk before initiation of LABAs or LAMAs, and, if needed, a preventive therapy for CVD should be considered during the initial treatment of inhaled long-acting bronchodilators.

Two potential mechanisms have been proposed to underpin the cardiovascular risk arising from LABA and LAMA use. Acting as autonomous nervous system agents, LABAs and LAMAs are believed to cause sympathetic overactivation by activating sympathetic β_2-adrenergic receptors (β2R) and suppressing parasympathetic muscarinic-3 receptors (M3R), respectively.[6,37,38] However, LABA and LAMA use in COPD has been observed to increase the inflammatory cytokine levels, such as an increased level of interleukin-8,[39,40] which could lead to an increased risk of CVD.

Strengths and Limitations

Several important strengths of our study merit discussion. We investigated the whole spectrum of timing and duration effects of LABA and LAMA usage on the development of severe CVD events in a population with COPD, which is a clinically important aspect that, to our knowledge, no study has addressed previously. In addition, this study was the first to examine the effect of LABA-LAMA regimens with various concomitant COPD medications, which provided pivotal information given that COPD care usually involves multiple therapies. Furthermore, a new-user design served to minimize tolerance effects in prevalent drug users. Moreover, our findings can be generalized to the entire COPD population with multiple coexisting comorbidities.

Several study limitations of the current report need to be addressed. First, worsening of COPD could have prompted the use of LABAs or LAMAs and caused the observed CVD. To control for this confounding effect, we adjusted for multiple proxies of COPD severity and compared new LABA users and new LAMA users, respectively, with new theophylline users, which yielded consistent results. Second, selection bias may have been present, although this bias was expected to be minimal, because we balanced all covariates at cohort entry between cases and controls, treated them as time-varying effects, and obtained consistent findings with an adopted case-only design. Third, protopathic bias could have existed. Nevertheless, we reached the same conclusions when adopting multiple approaches to address this bias, such as the use of a lag-time approach. Fourth, patients' CVD status at baseline may have confounded our findings. However, we believe this confounding effect not to be substantial because all baseline CVD statuses and CVD medications were balanced between the 2 groups, and the LABA- or LAMA-associated CVD risk remained significant among patients without a CVD history. Fifth, several important determinants of CVD, for example, smoking and alcohol consumption, were unavailable, which could have confounded our findings. However, their effects were unlikely to fully explain our findings, as assessed by rule-out analysis, especially for highly prevalent confounders such as smoking. Sixth, newer LABAs or LAMAs were unable to be assessed, such as aclidinium.

Conclusions

New use of LABAs or LAMAs was associated with a 1.5-fold increased cardiovascular risk in patients with COPD within 30 days of therapy initiation. We caution physicians to closely monitor new users of LABAs or LAMAs for cardiovascular symptoms.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: M.-T. Wang, Liou, Lin.
Critical revision of the manuscript for important intellectual content: All authors.
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