Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Development of a disease risk score-matched nested case-control study

A disease risk score (DRS) of encountering the cardiovascular outcome of interest for each patients of the study cohort was estimated. Specifically, we predicted the probability of developing the cardiovascular outcome during the follow-up of the entire study cohort by fitting a multiple conditional logistic regression with all factors considered in the Table 1, which were measured in the year preceding cohort entry, as well as the exposure status to inhaled long-acting bronchodilators, including inhaled long-acting β_2 agonists (LABAs) and long-acting antimuscarinic antagonists (LAMAs) that were measured during the entire follow-up period. The DRS of the cardiovascular outcomes was then computed as the fitted values from the abovementioned logistic regression model for each cohort member when setting the exposure status to inhaled long-acting bronchodilators as no use.

After obtaining the DRS for each cohort member, we matched each case of cardiovascular disease patient with up to 4 controls by cohort entry date (± 180 days) and the DRS (± 0.01) with a greedy matching approach. We detailed the DRS matching scheme as follows. For each case, we selected up to 4 controls that had the closet DRS values as the corresponding case's value, and required the controls' DRS

values to be within 0.01 of the case' value. If there were more than 4 eligible controls per case during the matching process, 4 controls were randomly selected.

eMethods 2. Modeling a nonlinear duration-response association using a restricted cubic splines function model.

In order to assess the duration of new LABA and LAMA therapies, we restricted LABA or LAMA users to those with at least one prescription record of inhaled long-acting bronchodilators within the 30 days preceding the index/event date, among whom any users of LABAs or LAMAs in the year preceding the index date were excluded. We then calculated continuous use of LABAs and LAMAs using a grace period of 30 days between successive prescriptions.

We further analyzed duration of new LABA and LAMA therapy as a continuous exposure variable, respectively, using restricted cubic splines function models. Specifically, we fitted the duration-response curves using a restricted cubic spines function with five knots, located at 15, 30, 45, 90, and 180 days in a multiple conditional logistic regression model, which adjusted the covariates with standardized difference > 0.1 listed in Table 1.

eMethods 3. A case-crossover study for assessing the association between the CVD risk and use of LABAs and LAMAs

A case-crossover study is a mean to control measured and unmeasured confounders that stay stable over time, in which exposures are compared at individual case levels between two or more time periods preceding the outcomes. From the final 37,719 CVD cases identified in our nested case-control study of COPD patients, we excluded people who did not have at least 120 days of follow-up before their index date, and the remaining CVD patients were included in the case-crossover study (n=27,036). For each of the 27,036 CVD patients, we defined day 1-30 before the index date as the case period and day 91-120 as the control period (as shown in eFigure 2). The CVD patients were considered exposed if the date that they filled LABA or LAMA prescriptions occurred within the case or the control time period. The odds ratio (OR) of CVD events that required a hospital or an ER visit from exposure to LABA or LAMA was determined using conditional logistic regression models that adjusted for imbalanced covariates between the two time periods (as indicated in eTable 5).

eTable 1. Diagnosis codes used to define the comorbidities and individual drugs of comedications

Comorbidities	**ICD-9-CM codes**
Hypertension	401-405
Diabetes Mellitus	250
Asthma	493
Pulmonary disease	
Acute bronchitis	466.0
Pneumonia	480-486
Influenza	487.1, 487.8
Pulmonary embolism	415.1
Cardiovascular disease	
Peripheral vascular disease	440-448
Rheumatic heart disease	391, 393-398
Hemorrhagic stroke	430-432
Hyperlipidemia	272
Cancer	140-239
Renal failure	584-588
Dementia	290
Chronic liver disease	571
Parkinsonism	332
Comedications	**Individual drugs**
Antibiotics (for defining moderate COPD exacerbation)	Amikacin, amoxicillin, ampicillin, azithromycin, bacampicillin, benzylpenicillin, cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefepime, cefmenoxime, cefmetazole, cefonicid, cefoperazone, cefotaxime, cefotetan, cefotiam, cefoxitin, cefpirome, cefpodoxime, cefradine, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, ciprofloxacin, clarithromycin, clindamycin, doxycycline, doxycyline, ertapenem, erythromycin, flucloxacillin, gemifloxacin, gentamicin, imipenem, isepamicin, latamoxef, levofloxacin, linezolid, meropenem, metampicillin, minocycline, moxifloxacin, ofloxacin, oxacillin, penicillin, piperacillin, sparfloxacin, teicoplanin, telithromycin, tetracycline, ticarcillin, tigecycline, Trimethoprim/sulfamethoxazole, tobramycin, and vancomycin
Oral corticosteroid (for defining moderate COPD exacerbation)	Betamethasone, cortisone, dexamethasone, fludrocortisone, methylprednisolone, paramethasone, prednisolone, and

	triamcinolone

eTable 1. Diagnosis codes used to define the comorbidities and individual drugs of comedications (continued)

Comedications	Individual drugs
Cardiovascular medication	
Antiplatelets	Abciximab, alteplase, aspirin (≤325mg), cilostazol, clopidogrel, dipyridamole, epoprostenol, eptifibatide, iloprost, ticagrelor, ticlopidine, tirofiban, and treprostinil
Calcium channel blockers	Amlodipine, barnidipine, benidipine, diltiazem, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and verapamil
Diuretics	Amiloride, bendroflumethiazide, benzylhydrochlorothiazide, bumetanide, canrenoate, clopamide, eplerenone, ethacrynic acid, furosemide, hydralazine, hydrochlorothiazide, indapamide, metolazone, spironolactone, thiabutazide, triamterene, and trichlormethiazide
Angiotensin receptor blockers	Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan
Angiotensin-converting enzyme Inhibitor	Benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, indapamide, lisinopril, perindopril, quinapril, and ramipril
β-blockers	
CV-selective	Acebutolol, atenolol, betaxolol, bisoprolol, and metoprolol
Non-CV-selective	Alprenolol, carteolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, and timolol
Digoxin	Digoxin
Antiarrhythmic agents	Adenosine, amiodarone, disopyramide, dronedarone, flecainide, lidocaine, mexiletine, prajmaline, procainamide, propafenone and quinidine
Nitrates	Glyceryl trinitrate, isosorbide dinitrate, pentaerythritol tetranitrate, and thiamine mononitrate
Anticoagulants	Dalteparin, dibigatran, enoxaparin, fondaparinux, unfractionated heparin, nadroparine, phenindione, rivaroxaban, streptokinase, tenecteplase, tinzaparin, urokinase, and warfarin
Lipid-lowering agents	
Statins	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin
Others	Acipimox, bezafibrate, cholestyramine, clofibrate,

	colestipol, etofibrate, ezetimibe, fenofibrate, gemfibrozil, inositol, niacin, niceritrol, nicomol, probucol, simfibrate, and xanthinol
COPD medications	
Methylxanthines	Aminophylline, diprophylline and theophylline
Short-acting β_2 agonists	Fenoterol, levalbuterol, procaterol, salbutamol, and terbutaline

eTable 1. Diagnosis codes used to define the comorbidities and individual drugs of comedications (continued)

Comedications	Individual drugs
Short-acting muscarinic antagonists	Ipratropium
Inhaled corticosteroids	Beclomethasone, budesonide, and fluticasone
Oral long-acting β_2 agonists	Formoterol
Systemic anticholinergics	
Antihistamine	Brompheniramine, buclizine, chlorpheniramine, clemastine, cyclizine, cyproheptadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine, and triprolidine
Gastrointestinal antispasmodics	Alverine, anisotropine, atropine, dicyclomine, dicycloverine, glycopyrronium, glycopyrrolate, homatropine, mebeverine, mepenzolate, methscopolamine, otilonium, oxapium, oxyphencyclimine, piperidolate, prifinium, propantheline, scopolamine, timepidium, trimebutine and valethamate
Bladder antimuscarinics	Flavoxate, oxybutynin, solifenacin, tolterodine, and trospium
Others	Benztropine, biperiden, prioheptine and trihexyphenidyl
NSAIDs	Aceclofenac, acemetacin, alclofenac, alminoprofen, aspirin(>325mg), benzydamine, celecoxib, diclofenac, etodolac, etofenamate, etoricoxib, fenbufen, fenoprofen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, meclofenamic acid, mefenamic acid, meloxicam, mepirizole , nabumetone, naproxen, nefopam, niflumic acid, nimesulide, phenylbutazone, piroxicam, rofecoxib, salsalate, sulindac, tenoxicam, tiaprofenic acid, tiaramide, tolfenamic acid, and tolmetin
Systematic corticosteroids	Betamethasone, cortisone, dexamethasone, fludrocortisone, fluocortolone, hydrocortisone, methandrostenolone, methylpredisolone , nandrolone, oxymetholone, paramethasone, phenylbutazone, prednisolone,stanozolol, and triamcinolone
Antipsychotic	Amisulpride, aripiprazole, chlorpromazine,chlorprothixene, clopenthixol, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, levomepromazine, loxapine, methotrimeprazine, olanzapine,

	paliperidone, perphenazine, prochlorperazine, quetiapine, risperidone, sulpiride, thioridazine, trifluoperazine, ziprasidone, and zotepine
Antidepressant	Amitriptyline, bupropion, citalopram, clomipramine, dothiepin, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, maprotiline, melitracen, milnacipran , mirtazapine, moclobemide, paroxetine, sertraline, trazodone, and venlafaxine

Abbreviations: COPD = Chronic obstructive pulmonary disease; CV = Cardiovascular; NSAIDs = nonsteroidal anti-inflammatory drugs.

eTable 2. Comparison of CVD risk between new LAMA use and new LABA use

Bronchodilator	**Crude OR (95% CI)**	***P* value**	**Adjusted OR[a] (95% CI)**	***P* value**
New LABA use, n (%)	Reference		Reference	
New LAMA use, n (%)	0.93 (0.76-1.14)	0.491	1.01 (0.82-1.23)	0.93

Abbreviations: LABA = inhaled long-acting β_2 agonist; LAMA = long-acting antimuscarinic antagonists; CI = confidence interval; OR = odds ratio.

[a] Adjusted for all covariate with SD > 0.1 in Table 1.

eTable 3. Risk of each primary cardiovascular outcome with new LABA and LAMA use

Cardiovascular event	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
CVD subtype				
Coronary artery disease				
LABA new use vs nonuse	2.15 (1.83-2.52)	<0.001	2.01 (1.71-2.38)	<0.001
LAMA new use vs nonuse	1.92 (1.48-2.48)	<0.001	1.89 (1.45-2.46)	<0.001
Both new use vs nonuse	3.60 (2.22-5.84)	<0.001	3.25 (1.97-5.36)	<0.001
New LAMA vs New LABA	0.89 (0.66-1.21)	0.47	0.95 (0.70-1.29)	0.74
Heart failure				
LABA new use vs nonuse	1.82 (1.50-2.21)	<0.001	1.42 (1.16-1.75)	0.001
LAMA new use vs nonuse	1.55 (1.14-2.10)	0.005	1.56 (1.14-2.14)	0.006
Both new use vs nonuse	2.18 (1.04-4.57)	0.038	1.72 (0.79-3.75)	0.17
New LAMA vs New LABA	0.85 (0.59-1.22)	0.38	1.09 (0.75-1.59)	0.64
Ischemic stroke				
LABA new use vs nonuse	1.10 (0.85-1.42)	0.48	1.06 (0.81-1.37)	0.69
LAMA new use vs nonuse	1.00 (0.62-1.62)	0.99	0.93 (0.58-1.51)	0.78
Both new use vs nonuse	0.45 (0.10-1.96)	0.29	0.38 (0.09-1.67)	0.20
New LAMA vs New LABA	0.91 (0.53-1.58)	0.75	0.87 (0.50-1.50)	0.61
Cardiac arrhythmia				
LABA new use vs nonuse	1.58 (1.18-2.11)	0.002	1.27 (0.94-1.72)	0.12
LAMA new use vs nonuse	1.89 (1.16-3.08)	0.011	1.67 (1.02-2.76)	0.042

eTable 3. Risk of each primary cardiovascular outcome among new LABA and LAMA use (continued)

Cardiovascular event	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Both new use vs nonuse	2.03 (0.76-5.41)	0.16	1.87 (0.68-5.13)	0.23
New LAMA vs New LABA	1.19 (0.68-2.11)	0.54	1.31 (0.73-2.33)	0.36

Abbreviations: LABA = inhaled long-acting β_2 agonist; LAMA = long-acting antimuscarinic antagonists; OR, odds ratio; CI, confidence interval.

[a] Adjusted for all covariates with SD > 0.1 in Table 1.

eTable 4. Case-crossover analysis for the risk of CVDs with use of LABA and LAMA within 30 days

Bronchodilator	Case period (n=27,036)	Control period (n=27,036)	Crude OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Nonuse of LABAs or LAMAs, n (%)	24,669 (91.3)	25,020 (92.5)	Reference		Reference	
LABA use	1,472 (5.4)	1,243 (4.6)	1.49 (1.33-1.67)	<0.001	1.36 (1.21-1.53)	<0.001
LAMA use	656 (2.4)	586 (2.2)	1.39 (1.17-1.65)	<0.001	1.26 (1.05-1.51)	0.032
LABA & LAMA use	239 (0.9)	187 (0.7)	1.84 (1.40-2.41)	<0.001	1.63 (1.23-2.16)	<0.001

Abbreviations: LABA = inhaled long-acting β_2 agonist; LAMA = long-acting antimuscarinic antagonists; CVD = cardiovascular disease; CI = confidence interval; OR = odds ratio.

[a] Adjusted for covariates with SD > 0.1 in eTable 5.

eTable 5. Clinical characteristics of CVD patients during the case and control periods in an alternative case-crossover study

Characteristics	Case period (n=27,036)	Control period (n=27,036)	SD[a]
Age, mean (SD), y	75.33 ±10.22	75.33 ±10.22	0.001
Sex, male No. (%)	19,294 (71.4)	19,294 (71.4)	<0.001
COPD severity indicators, No. (%)			
Number of severe COPD exacerbation[b]			
0	19,045 (70.4)	18,736 (69.3)	0.014
1	5,942 (22.0)	6,320 (23.4)	
≥ 2	2,049 (7.6)	1,980 (7.3)	
Number of moderate COPD exacerbation[c]			
0	26,400 (97.7)	26,494 (98.0)	0.023
1	587 (2.2)	499 (1.9)	
≥ 2	49 (0.2)	43 (0.2)	
Number of type of COPD medications			
0	23,954 (88.6)	24,551 (90.8)	0.070
1~2	2,012 (7.4)	1,638 (6.1)	
≥ 3	1,070 (4.0)	847 (3.1)	
Healthcare use, No. (%)			
No. of outpatient visits			
≤ 5	23,184 (85.8)	24,312 (89.9)	0.129
6-10	3,155 (11.7)	2,303 (8.5)	
≥ 11	697 (2.6)	421 (1.6)	
Comorbidities, No. (%)			
Pulmonary disease			
Asthma	3,710 (13.7)	3,085 (11.4)	0.070
Acute bronchitis	3,486 (12.9)	2,814 (10.4)	0.078
Pneumonia	3,120 (11.5)	2,308 (8.5)	0.010
Influenza	383 (1.4)	282 (1.0)	0.034
Pulmonary embolism	75 (0.3)	50 (0.2)	0.019
CV disease			
Hypertention	15,511 (57.4)	14,480 (53.6)	0.077
Peripheral vascular disease	1,066 (3.9)	906 (3.4)	0.032
Rheumatic heart disease	498 (1.8)	409 (1.5)	0.026
Hemorrhagic stroke	351 (1.3)	307 (1.1)	0.015
Diabetes Mellitus	7,009 (25.9)	6,533 (24.2)	0.041

Hyperlipidemia	3,830 (14.2)	3,438 (12.7)	0.043

eTable 5. Clinical characteristics of CVD patients during the case and control periods in an alternative case-crossover study (continued)

Characteristics	**Case period (n=27,036)**	**Control period (n=27,036)**	**SD[a]**
Cancer	2,421 (9.0)	2,109 (7.8)	0.042
Renal failure	2,155 (8.0)	1,838 (6.8)	0.045
Dementia	2,103 (7.8)	1,867 (6.9)	0.033
Chronic liver disease	1,190 (4.4)	1,057 (3.9)	0.025
Parkinsonism	1,009 (3.7)	905 (3.4)	0.021
Comedication, No. (%)			
CV medication			
Antiplatelets	14,634 (54.1)	12,317 (45.6)	0.115
Calcium channel blockers	13,990 (51.8)	12,817 (47.4)	0.087
Diuretics	12,388 (45.8)	10,735 (39.7)	0.124
Angiotensin receptor blockers	9,254 (34.2)	8,424 (31.2)	0.065
Angiotensin-converting enzyme inhibitor	4,446 (16.4)	3,878 (14.3)	0.058
β-blockers			
CV-selective	4,048 (15.0)	3,399 (12.6)	0.070
Non-CV-selective	4,380 (16.0)	3,527 (13.1)	0.089
Digoxin	2,971 (11.0)	2,382 (8.8)	0.073
Antiarrhythmic agents	2,386 (8.8)	1,841 (6.8)	0.075
Nitrates	1,964 (7.3)	1,425 (5.3)	0.082
Anticoagulants	1,486 (5.5)	1,114 (4.1)	0.064
Lipid-lowering agents			
Statins	4,145 (15.3)	3,688 (13.6)	0.048
Others	60 (0.2)	49 (0.2)	0.009
COPD medications			
Methylxanthines	1,203 (4.5)	955 (3.7)	0.039
Short-acting β_2 agonists			
Oral / injection	6,971 (25.8)	6,385 (23.6)	0.050
Nebulized	709 (2.6)	544 (2.0)	0.041
Inhaled			
0 canister	24,872 (92.0)	25,285 (93.5)	0.058
≤ 6 canisters	2,045 (7.6)	1,655 (6.1)	
> 6 canisters	119 (0.4)	96 (0.4)	

Short-acting muscarinic antagonists			
Nebulized	1,599 (5.9)	1,263 (4.7)	0.056

eTable 5. Clinical characteristics of CVD patients during the case and control periods in an alternative case-crossover study (continued)

Characteristics	**Case period (n=27,036)**	**Control period (n=27,036)**	**SD[a]**
Inhaled			
0 canister	25,802 (95.4)	26,093 (96.5)	0.054
≤ 6 canisters	1,190 (4.4)	911 (3.4)	
> 6 canisters	44 (0.2)	32 (0.1)	
Inhaled corticosteroids	396 (1.5)	306 (1.1)	0.029
Oral long-acting β_2 agonists	241 (0.9)	203 (0.8)	0.016
Systemic Anticholinergic			
Antihistamine	7,876 (29.1)	6,753 (25.0)	0.094
Gastrointestinal antispasmodics	1,831 (6.8)	1,607 (5.9)	0.034
Bladder antimuscarinics	1,059 (3.9)	930 (3.4)	0.025
Others	1,392 (5.2)	1,150 (4.3)	0.042
NSAIDs	13,335 (49.3)	11,969 (44.3)	0.101
Systematic corticosteroids	7,804 (28.9)	6,617 (24.5)	0.099
Antipsychotic	3,541 (13.1)	2,897 (10.7)	0.074
Antidepressant	3,254 (12.0)	2,985 (11.0)	0.031
Vaccine[d]	1,497 (5.5)	1,295 (4.8)	0.034

Abbreviations: SD, standardized difference; CVD, cardiovascular disease; ER, emergency room; COPD, chronic obstructive pulmonary disease; NSAIDs, Nonsteroidal anti-inflammatory drugs.

[a] SD with a more than 0.1 difference represents meaningful difference between groups

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

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

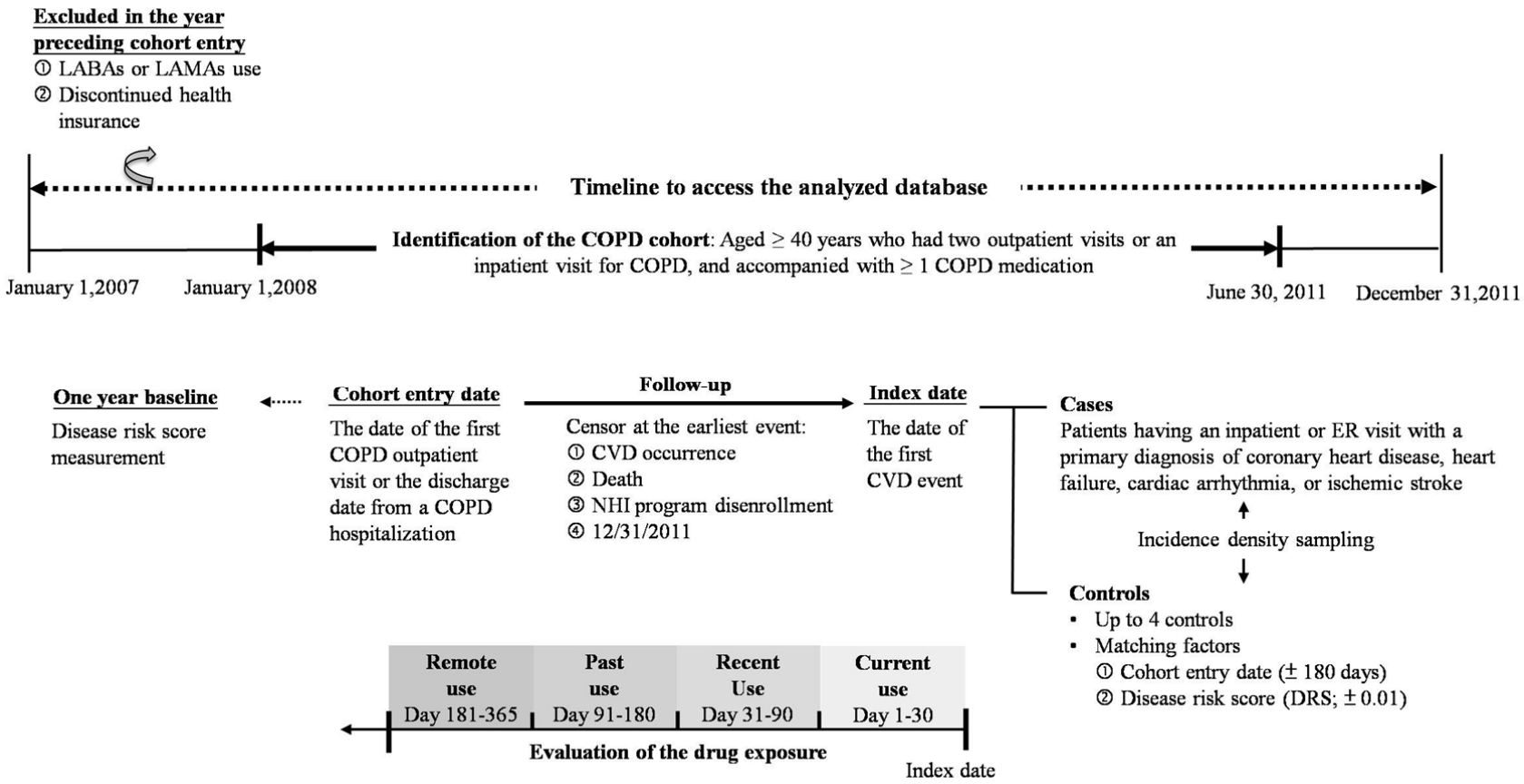
[d] Only the vaccines of influenza and pneumonia were included.

eTable 6. Numbers needed to harm for CVD risk from using LABAs and LAMAs in our primary and secondary analyses

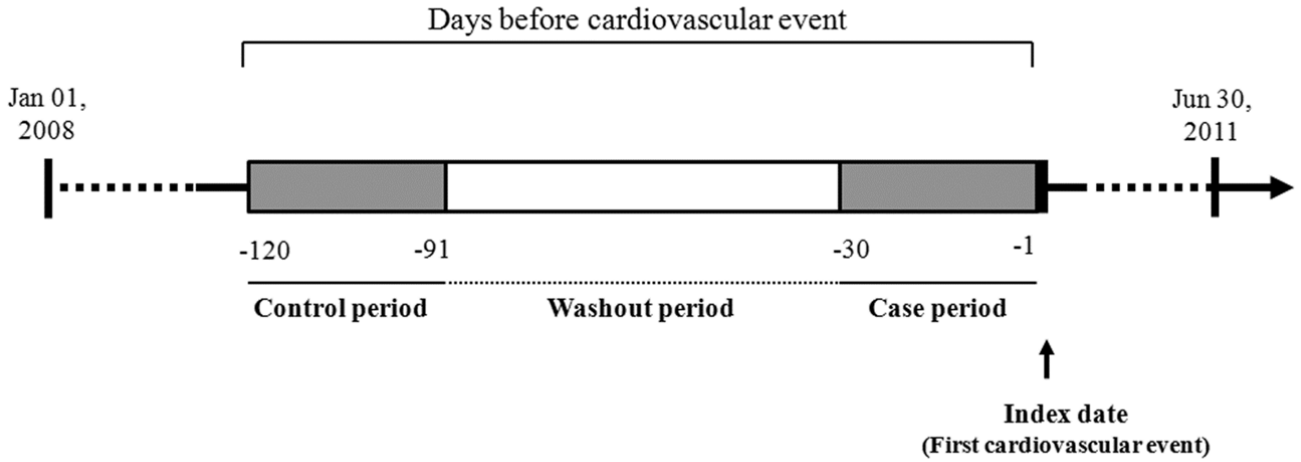
Bronchodilator	**Number needed to harm[a] (95% CI)**
LABA new use	406 (303-580)
Regimen	
+ICS	398 (299-564)
+SABA	483 (299-966)
+Ipratropium	483 (290-1,067)
+Methylxanthines	406 (268-725)
Individual drugs	
Salmeterol	415 (295-655)
Formoterol	391 (239-811)
LAMA new use	391 (254-725)
Regimen	
LAMA only	350 (184-1067)
+SABA	521 (234-5,066)
+Ipratropium	432 (189-5,066)
+Methylxanthines	432 (237-1,267)
Route	
DPI only	383 (245-725)
LABA & LAMA new use	198 (107-483)

Abbreviations: CI = confidence interval; DPI = dry powder inhaler; ICS = inhaled corticosteroid; SABA = short-acting β_2 bronchodilator.

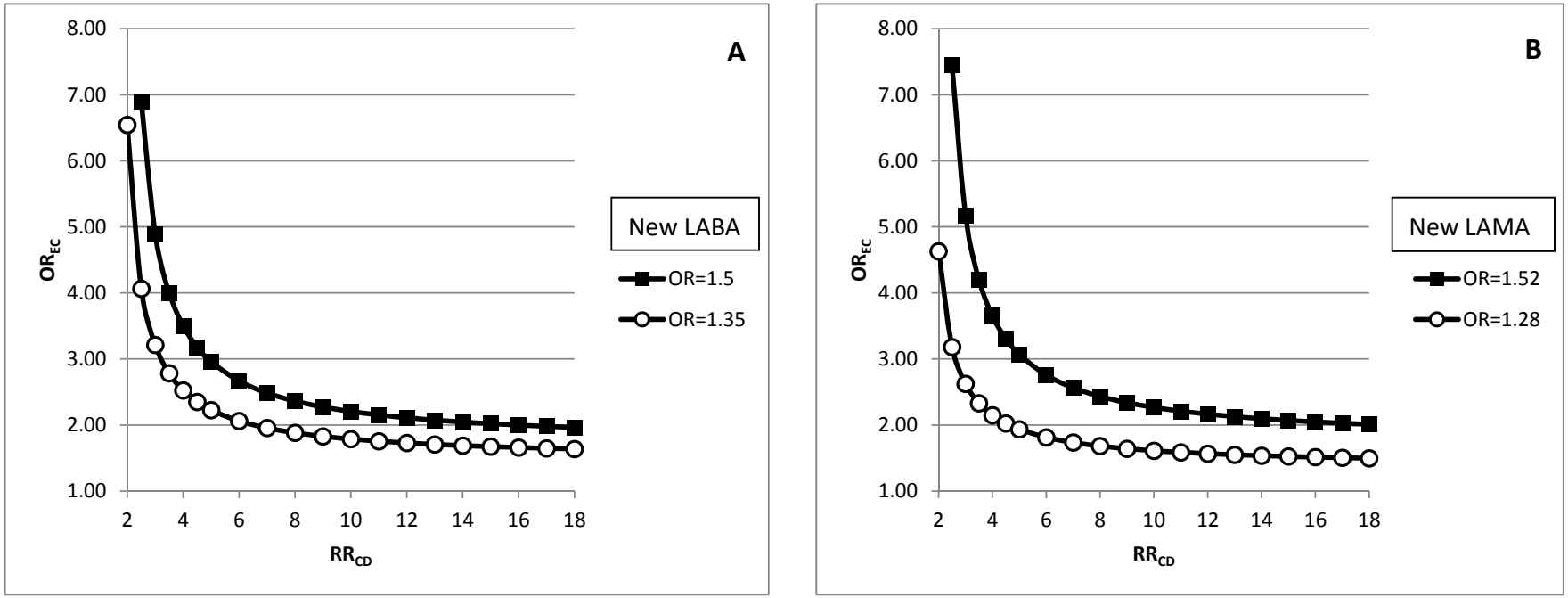
[a]The number needed to harm was calculated based on the formula: 1/[(OR-1)*UER] + OR/[(OR-1)*(1-UER)], where OR and UER represent the adjusted odds ratio and unexposed event rate, respectively. We estimated an unexposed cardiovascular event as 4.96 per 1,000 persons within 30 days of therapy.



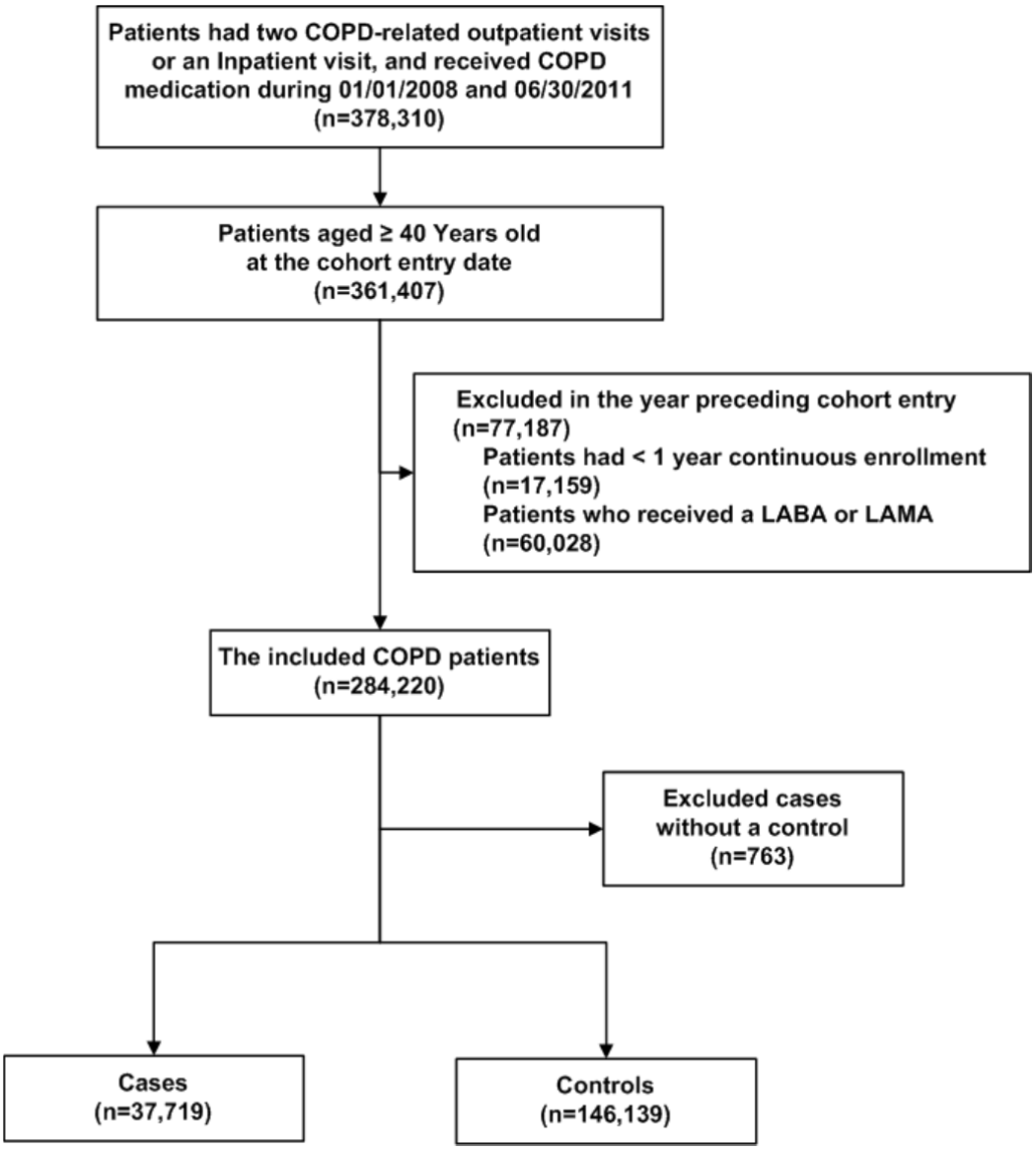
eFigure 1. Overview for the adopted nested case-control study design. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; ER, emergency room; NHI represents National Health Insurance.



eFigure 2. Specification of case and control periods in an alternative case-crossover study.



eFigure 3. The impact of unmeasured confounders assessed by the rule-out method. In the model, we assumed that the prevalence of an unmeasured confounder was 20% and new users of LABA and LAMA were 1% and 0.05%, respectively. The results of assessment are presented in panel A for new LABA use and panel B for new LAMA use. In both panels, all combinations of RR_{CD} and OR_{EC} that lie in the upper right area of each lines represents that the confounding effect could reverse our positive association between CVD risk and long-acting bronchodilators towards the null. RR_{CD} = relative risk of CVDs from unmeasured confounders; OR_{EC} = odds ratio between long-acting bronchodilators and unmeasured confounders.



eFigure 4. Study flow diagram outlining the selection of study cohort.