의학박사 학위논문

만성폐쇄성폐질환 환자의 약물 치료와 심혈관질환의 위험도

Pharmacotherapy and risk of cardiovascular event in chronic obstructive pulmonary disease patients: Korean national health insurance service data

울산대학교 대학원

의학과

이보영

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이 논문을 의학박사 학위논문으로 제출함

2018년 12월

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감사의 글

먼저 박사학위 과정 동안 연구에 매진할 수 있도록 아낌없는 격려와 지도를 해주신 오연목 교수님과 연구를 위하여 많은 도움을 주시고 항상 진지하게 토의해 주셨던 김화정 교수님께 고개 숙여 깊이 감사드립니다. 저의 논문 심사를 맡아주시고, 소중한 충고와 진심어린 조언을 해주신 심태선 교수님, 이세원 교수님, 이재승 교수님, 홍윤기 교수님께도 깊은 감사를 드립니다. 의과대학을 졸업하고 모교를 떠나 전공의 수련을 받고 울산대학교 대학원 석사 과정과 박사과정을 거치며 많은 난관을 맞이했지만 교수님들의 지도와 조언 덕분에 여기까지 올 수 있었습니다. 아직 부족한 점이 많고 서툴지만 앞으로도 더 열심히 연구를 계속 해나가도록 하겠습니다. 끝으로 박사학위 과정동안 학업에 전념할 수 있게 도와주신 부모님, 남편과 항상 엄마를 기다려준 아들 재승이에게 감사를 전합니다.

Abstracts

Background: Chronic obstructive pulmonary disease (COPD) is prevalent and is one of the major causes of death. COPD is expected to increase in the future. pharmacotherapy in COPD aims to relieve symptoms, improve quality of life and prevent acute exacerbations. Inhaled bronchodilators, such as ß-agonists and anticholinergics, are being recommended as major medications. ß-agonists cause relaxation of the smooth muscle of the bronchi, but they also stimulate the sympathetic nervous system, leading some side effects such as arrhythmias, tremor, agitation and hypokalemia. In case of inhaled anticholinergic agents, the stimulation of the parasympathetic nervous system is inhibited which can also lead to diverse side effects. Many patients with COPD have cardiovascular disease as a comorbid condition. And bronchodilators may have side effects on cardiovascular disease because of the action mechanism mentioned above.

Purpose: To evaluate the effect of inhaled bronchodilators on cardiovascular events in patients with COPD.

Methods: A 2% sample cohort database from Korean National Health Insurance claim data was used to identify drug prescription patterns. And nested case-control study was done to assess effect of inhalers on cardiovascular events. We compared the patients who had admission or emergency department visits due to cardiovascular disease with the matched control group. Cases and controls were matched by sex, age (±2years), and the number of cardiovascular events in the previous year in 1: 4 ratio. The use of inhaled bronchodilator was identified retrospectively within 1 year from index date (the first date of cardiovascular events).

Results: Prescription of inhaled bronchodilators is increasing over the decade. However, about 90% of patients diagnosed as COPD received methylxanthine or systemic ß-agonist at first prescription. Nested case-control study to examine the

effect of the inhaled bronchodilators on cardiovascular events showed conflicting results depending on the target cohort. In current new users of LABA or LAMA, OR was decreased to 0.2 (95% CI, 0.05 - 0.87) and 0.59 (59% CI, 0.38 - 0.91), respectively if target cohort included only inhaled bronchodilators. Conversely, if the target cohort is defined as those prescribed with either oral or inhaled bronchodilators, the risk of cardiovascular events was found to be increased in LABA and LAMA current new users (OR, 3.12 and 6.31 respectively)

Conclusions: Despite studies in the same population, the effect of inhaled bronchodilators on the risk of emergency room visits or hospitalizations due to cardiovascular disease was conflicting. This may be due to differences in characteristics of the patients. In severe COPD, control of COPD may protect patient from cardiovascular events because these two diseases interact each other. On the contrary, in mild COPD, physicians need to be cautious and monitor for possible adverse events, because the use of new bronchodilators may increase the risk of cardiovascular disease.

목차

Tables & Figures

약어목록

COPD: Chronic Obstructive Pulmonary Disease

cAMP: 3′,5′-cyclic monophosphate

SABA: Short-acting β-2 agonist

ICD-10: International Classification of Diseases-10th Revision

LABA: Long-acting β-2 agonist

LAMA: Long-acting muscarinic antagonist

SAMA: Short-acting muscarinic antagonist

ICS: inhaled corticosteroid

OR: odds ratio

DM: diabetes mellitus

RR: Relative risk

UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium

TORCH: Towards a Revolution in COPD Health

FEV1: forced expiratory volume in the first second

MACE: Major adverse cardiovascular events

Introduction

1. Epidemiology and burden of COPD

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by irreversible airflow limitation, which is known to be caused by chronic inflammation and destruction of lung parenchyma. COPD is a leading cause of morbidity and mortality worldwide. Although prevalence of COPD varies widely due to difference in study population and diagnostic methods, it is known to be around 11.7% worldwide[1]. In South Korea, prevalence of airway obstruction was 13.4% among adults older than 40 years according to the data from nationwide epidemiologic survey called Korean National Health and Nutrition Examination Survey IV (KNHANES IV)[2]. It is believed that the prevalence of COPD will increase in the future due to the increase in the elderly population and the increase of smokers in less developed countries. Thus, the economic burden and social burden due to COPD will increase. Global burden of disease study predicts that COPD death will be third in 2020 and fourth in 2030[3].

2. Pharmacological treatment of COPD

Pharmacologic treatment in COPD is aimed to achieve symptomatic relief, improve quality of life, and to reduce the frequency and severity of exacerbations. Among many therapeutic agents, bronchodilators such as β-2 agonist, and anticholinergic agent, inhaled corticosteroid, and phosphodiesterase 4 inhibitor are considered to be the mainstay of COPD treatment[4]. Bronchodilators can be given by oral, inhalation, intravenously, or subcutaneously. As inhalation can maximize effect and minimize side effect, currently inhalation of bronchodilators is recommended over oral or subcutaneous ones.

β-2 agonist can relax airway smooth muscle through β-2 adrenergic receptor distributed throughout entire airway. Stimulation of β-2 adrenergic receptor

activates stimulatory G protein, which in turn, activates adenylate cyclase and increase concentration of adenosine 3′,5′-cyclic monophosphate (cAMP). Short-acting β-2 agonist (SABA) is recommended as first line therapy in mild COPD with intermittent symptoms. For moderate to severe COPD, long-acting β-2 agonists are recommended. Because β-2 agonist stimulates sympathetic nervous system by β-2 adrenergic receptor, it can cause various side effects like tremor, agitation, hypokalemia and disturbances in cardiac rhythm such as sinus tachycardia[5–7].

Anticholinergic agents can also induce bronchodilation by inhibiting bronchoconstriction through interrupting the action of acetylcholine at muscarinic receptors in airway smooth muscle. Systemic absorption of inhaled anticholinergic drugs is minimal thus it is considered to be safe. Most common side effect is dryness of mouth[8].

Methylxanthines can have a modest bronchodilator effect by non-selective inhibition of phosphodiesterase and the increase of intracellular cAMP. However, this also cause several side effects (nausea, headache, vomiting, abdominal pain, seizures and arrhythmias).

3. Comorbidities of COPD and interactions of comorbidities

COPD is a complex respiratory disorder with many comorbidities such as cardiovascular diseases, osteoporosis, depression and lung cancer. [9–12]. Co-existence of comorbidities and COPD may result in worse outcomes than either condition alone. Cardiovascular diseases are one of the most important comorbidities including ischemic heart disease, congestive heart failure, arrhythmia, and hypertension.

Previous studies about cardiac safety of COPD medications are conflicting. Recently, there was a report showing increased risk of cardiovascular events in

new starters of LABA and LABA within 30 days[13]. On the contrary, other pooled safety-analysis of LAMA concluded that LAMA does not increase risk of adverse cardiovascular events[14]. Therefore, we aimed to assess the effect of COPD pharmacotherapy to cardiovascular events using National Health Insurance claims data.

Methods

1. Data source and study design

This study was conducted using the National Health Insurance claims data for medical services provided to South Koreans from January 1, 2005 to December 31, 2015. We performed this study using 2% sampling data to represent the entire population. South Korea has a compulsory universal health insurance system that includes medical reimbursement records for entire population. We repeated nested case-control analysis of COPD patients with the 2% sampling data using different criteria for study cohort identification

2. Identification of study cohort

We defined COPD patients as follows;

1) Patients aged ≧ 40 years
2) Diagnosis of COPD (ICD-10 codes J42.x–J44.x, except J430) during the study period (from January 1, 2005 to December 31, 2014)
3) Patients without diagnosis of asthma (ICD-10 codes J45.x-J46) within 6 months before and after the diagnosis of COPD
4) Record of filling at least 1 COPD medication

The cohort entry date was set as the date of the first COPD medication prescription. COPD medications included in the definitions of COPD were changed and analysis was repeated. In the part 1 analysis, medications included long-acting β-2 agonist (LABA), long-acting muscarinic antagonist (LAMA), SABA and Short-acting muscarinic antagonist (SAMA) inhalers. In the part 2 analysis, oral methylxanthine and systemic ß agonists were also included. Subjects were followed up for at least 1 year until the earliest cardiovascular outcome, national

health insurance program withdrawal, death, or the end of the study period (December 31, 2015)

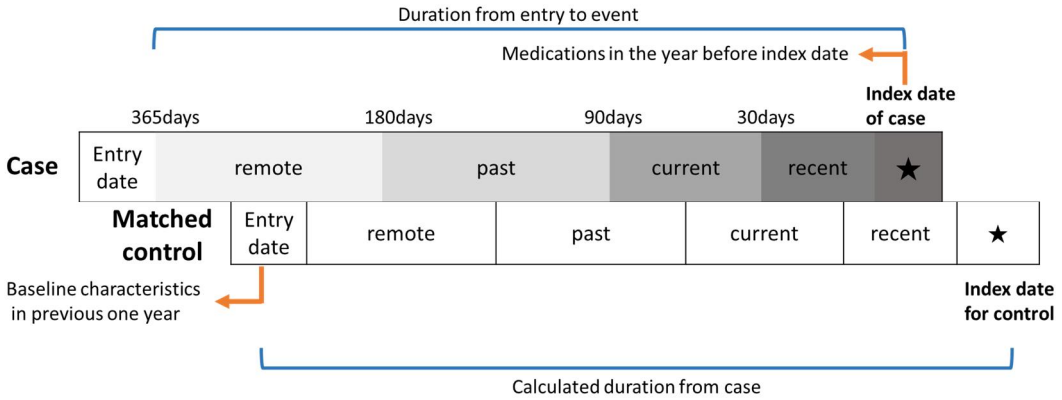
3. Study outcome

We identified admission or emergency department visits for cardiovascular disease during follow up period after cohort entry. Cardiovascular diseases included ischemic heart disease (ICD-10 codes I20-I25), congestive heart failure (I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0) and arrythmia (I46.x-I49.x, R00.0 and R00.1). Those who had cardiovascular events were cases. In cases, index date was defined as the first date of cardiovascular event. For each case, 4 random controls who did not have cardiovascular events were matched for age (± 2 years), sex and number of cardiovascular events in the previous year. In controls, index date is calculated by adding the period from the cohort entry to the occurrence of cardiovascular event of the matched case.

4. Medication exposure

We reviewed COPD medication prescriptions within 1 year from index date. In control group, as patients are still at risk for a cardiovascular event, index date from the matched case were used as index date. Patient with history of drug use within 30 days were defined as current user. Those with drug usage between 31 and 90 days defined as recent, between 91 and 180 days as past, and before 180 days from index date as remote user. Current user was divided into new and prevalent user depending on whether there was any prescription of COPD medication between 31 and 365 days before index date. Figure 1 depicts example of drug exposure measurement and setting of index date in matched controls.

Figure 1. Example of drug exposure measurement



5. Baseline characteristics

Comorbidities including hypertension, hyperlipidemia, diabetes mellitus (D and those included in Charlson Comorbidity Index were reviewed from health record in the previous year from entry date. As COPD itself is a powerful confounding factor for cardiovascular events, number of COPD acute exacerbations in 1 year from entry date was also reviewed. We only included severe exacerbations defined as inpatient or emergency department visit with diagnosis of dyspnea, ARDS, pneumonia and pulmonary thromboembolism. ICD-10 codes for comorbidities and acute exacerbation are shown in Table S1 at supplementary material.

6. Statistical analysis

Baseline characteristics of cases and controls were compared using Student's t-test or χ^2 test. Kaplan Meier survival analysis was used to compare the incidence of cardiovascular events stratified by the number of cardiovascular events in the previous year. Logistic regression was used to estimated odds ratio (OR) of cardiovascular disease with LAMA or LABA use. Data sets were constructed and analyzed by using SAS (version9.3; SAS Institute Inc) statistical software.

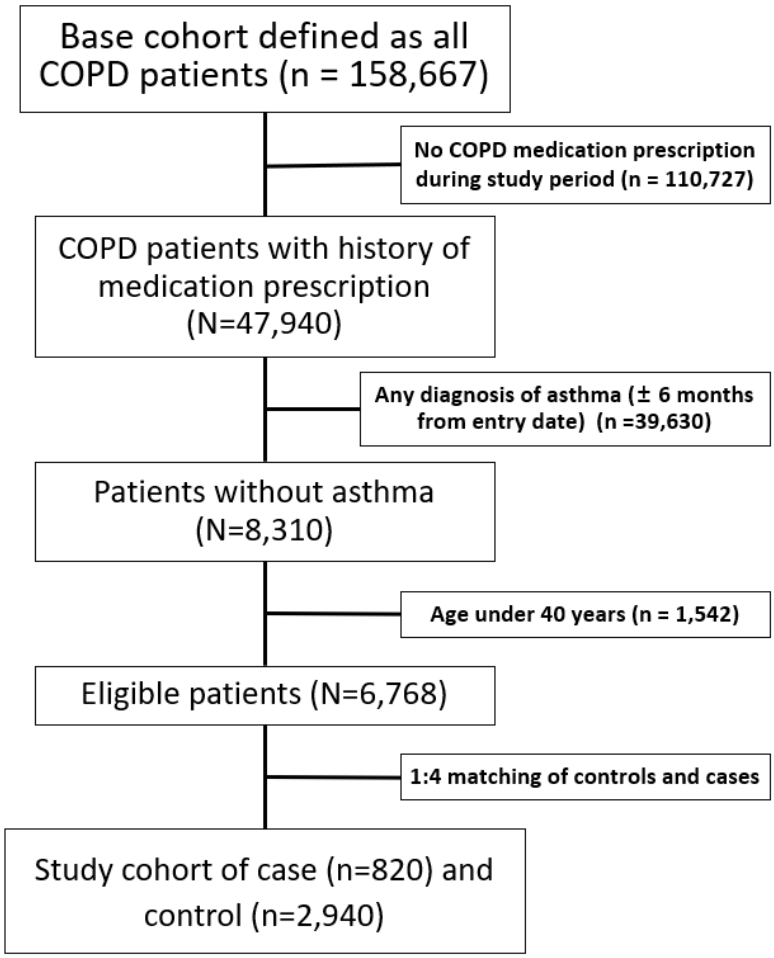
The study protocol was approved by the Institutional Review Board, which waived the requirements for informed consent because of the retrospective nature of the analysis.

Result

1. Part 1 Analysis

Cohort construction in Part 1 analysis was done as shown in Figure 2. COPD medications included LAMA, LABA, SAMA, and SABA. The total number of subjects was 6768, and 3760 subjects were studied by matching case and control (cases to controls ratio 1:4).

Figure 2. Flowchart of study cohort formation



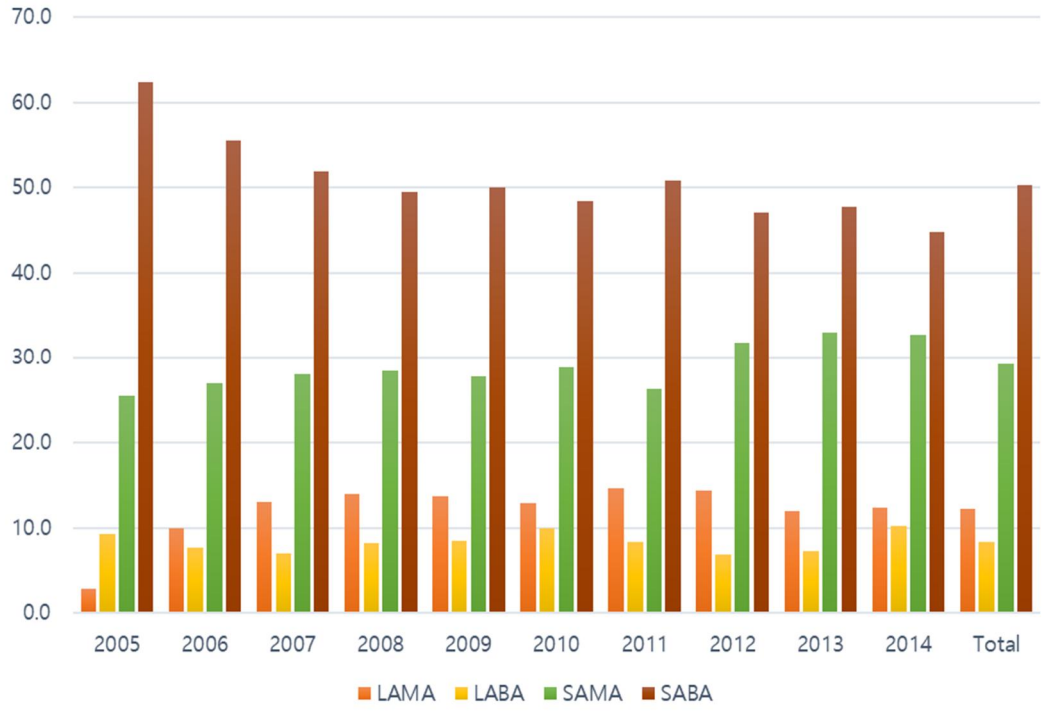
In order to determine the study method before confirming the effect on the cardiovascular event of the bronchodilator, the drug prescription pattern in the whole cohort was analyzed first.

From 2005 to 2014, the short-acting bronchodilators SAMA and SABA consistently accounted for 77% to 88% of the total regimen, while the long-acting bronchodilator accounted for about 12% to 20% (Table 1). There was no big change in 10 years (Figure 3).

Table 1. Distribution of medication prescription by year

	COPD+medication	LAMA	LABA	SAMA	SABA
2005	679	23 (2.8)	75 (9.3)	206 (25.5)	504 (62.4)
2006	605	82 (9.9)	64 (7.7)	223 (26.9)	460 (55.5)
2007	768	140 (13.0)	75 (7.0)	302 (28.1)	559 (52.0)
2008	727	149 (13.9)	87 (8.1)	304 (28.4)	530 (49.5)
2009	630	137 (13.7)	85 (8.5)	277 (27.7)	500 (50.1)
2010	636	132 (12.8)	102 (9.9)	297 (28.9)	497 (48.3)
2011	637	151 (14.7)	85 (8.3)	270 (26.2)	523 (50.8)
2012	689	168 (14.4)	80 (6.8)	371 (31.8)	549 (47.0)
2013	691	141 (12.0)	85 (7.2)	388 (33.0)	562 (47.8)
2014	706	153 (12.3)	126 (10.1)	407 (32.7)	557 (44.8)
Total	6,768	1,276 (12.2)	864 (8.3)	3,045 (29.2)	5,241 (50.3)

Figure 3. Distribution of medication prescription by year

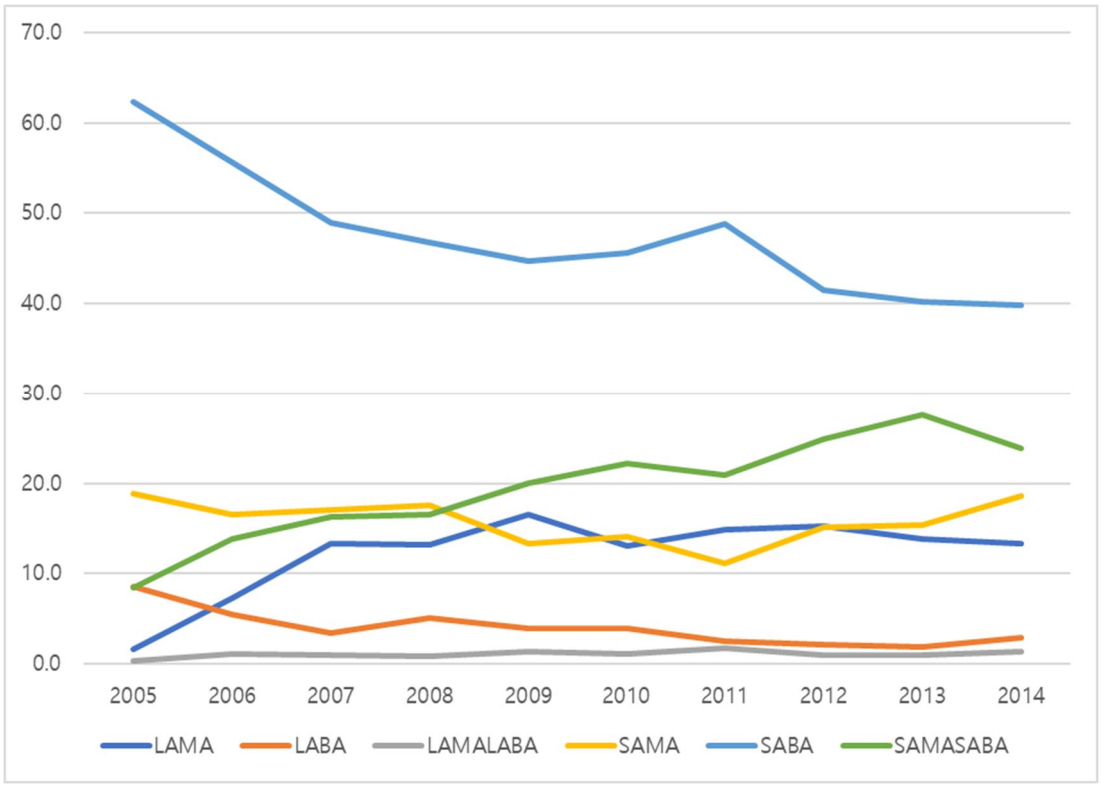


To confirm the pattern that was maintained after the first drug prescription, second prescription during study period was identified. As shown in Table 2, the most common first drug was the short acting bronchodilator, which was the same as the whole prescription pattern. However, shown in Figure 4, the SABA prescription decreased gradually as the first prescription to about 40% from 62% of the total prescription, and the LAMA prescription steadily increased.

Table 2. Classes of first medication after diagnosis over study period

	LAMA	LABA	LAMA/LABA	SAMA	SABA	SAMA/SABA
2005	11 (1.6)	58 (8.5)	2 (0.3)	128 (18.9)	423 (62.3)	57 (8.4)
2006	44 (7.3)	33 (5.5)	7 (1.2)	100 (16.5)	337 (55.7)	84 (13.9)
2007	102 (13.3)	26 (3.4)	8 (1.0)	131 (17.1)	376 (49.0)	125 (16.3)
2008	96 (13.2)	37 (5.1)	6 (0.8)	128 (17.6)	340 (46.8)	120 (16.5)
2009	104 (16.5)	25 (4.0)	9 (1.4)	84 (13.3)	282 (44.8)	126 (20.0)
2010	83 (13.1)	25 (3.9)	7 (1.1)	90 (14.2)	290 (45.6)	141 (22.2)
2011	95 (14.9)	16 (2.5)	11 (1.7)	71 (11.1)	311 (48.8)	133 (20.9)
2012	105 (15.2)	15 (2.2)	7 (1.0)	104 (15.1)	286 (41.5)	172 (25.0)
2013	96 (13.9)	13 (1.9)	7 (1.0)	106 (15.3)	278 (40.2)	191 (27.6)
2014	94 (13.3)	21 (3.0)	10 (1.4)	131 (18.6)	281 (39.8)	169 (23.9)

Figure 4. Change in classes of first medication



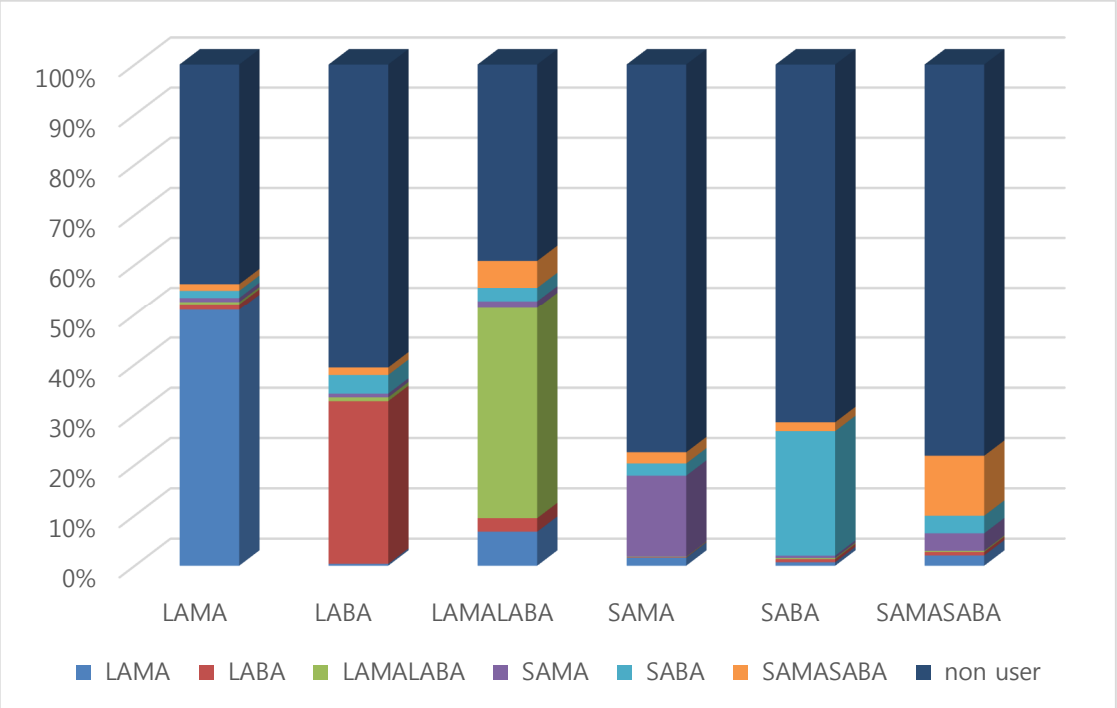
After receiving the first prescription for each medication, it was found that the second medication was not prescribed at any time during the study period in 39% to 78% (Table 3). Many patients were found to stop using the medication after the initial diagnosis. In patients with long-acting bronchodilators LAMA or LABA or both, 40-60% of patients maintained the drugs or switched to other classes, while in the case of short acting bronchodilators, only approximately 20 to 30% of the patients maintained or switched (Figure 5).

With this drug use review, we concluded that retrospective cohort analysis is not appropriate to study the effect of COPD drugs on the cardiovascular events due to too much switching and uncertainty of adverse drug effect period. Thus, we conducted a nested case-control study.

Table 3. Drug prescription pattern of 2nd medications after 1st prescription

		2nd prescription							
		LAMA	LABA	LAMA/LABA	SAMA	SABA	SAMA/SABA	none	Total
1st	LAMA	423	9	4	7	12	11	364	830
	LABA	1	87	2	2	10	4	163	269
	LAMA/LABA	5	2	31	1	2	4	29	74
	SAMA	17	1	1	173	26	24	831	1073
	SABA	22	20	7	15	793	57	2290	3204
	SAMA/SABA	27	9	3	46	46	157	1030	1318

Figure 5. Distribution of 2nd prescription



To assess the extent of baseline cardiovascular disease in the entire cohort, we examined hospitalization and emergency room visits due to cardiovascular disease one year before the start of the medication (Table 4). Ischemic heart disease was the most common comorbidity (7%) and congestive heart failure and arrhythmia were 3.8% and 3.4%, respectively.

Table 4. Number of cardiovascular events before and after one year since COPD medication

	1 year before medication	1 year after medication
Ischemic heart disease		
none	6293 (93.0)	6162 (91.0)
≧1	475 (7.0)	606 (9.0)
Congestive heart failure		
none	6512 (96.2)	6354 (93.9)
≧1	256 (3.8)	414 (6.1)
Arrhythmia		
none	6538 (96.6)	6342 (93.7)
≧1	230 (3.4)	426 (6.3)
Any cardiovascular events		
none	6016 (88.9)	5720 (84.5)
≧1	752 (11.1)	1048 (15.5)

Table 5 shows the baseline characteristics of cases and matched controls. As number of prior cardiovascular events, hypertension, hyperlipidemia, DM and COPD severity were significantly different, we included these covariates for logistic regression.

Table 5. Baseline characteristics of cases and matched controls

Characteristics	Cases (n=820)	Controls (n=2940)	p-value
Age	71.9±10.4	71.4±10.4	
Sex			0.003
Male	488 (59.5)	1795 (61.1)	
Female	332 (40.5)	1145 (38.9)	
Prior cardiovascular events			
Ischemic heart disease			<0.0001
0	760 (92.7)	2860 (97.3)	
1	48 (5.9)	68 (2.3)	
≥2	12 (1.5)	12 (0.4)	
Congestive heart failure			<0.0001
0	809 (98.7)	2927 (99.6)	
1	7 (0.9)	9 (0.3)	
≥2	4 (0.5)	4 (0.1)	
Arrhythmia			<0.0001
0	808 (98.5)	2926 (99.5)	
1	8 (1.0)	9 (0.3)	
≥2	4 (0.50	5 (0.2)	
Hypertension	539 (65.7)	1578 (53.7)	<0.0001
Hyperlipidemia	328 (40.0)	905 (30.8)	<0.0001
Diabetes mellitus	349 (42.6)	909 (30.9)	<0.0001
Ischemic stroke	804 (98.0)	2896 (98.5)	0.6078

Table 5. continued

Charlson Comorbidity Index	0.39±0.97	0.23±0.77	
COPD			<0.0001
Inpatient	617 (75.2)	1602 (54.5)	
Outpatient	203 (24.8)	1338 (45.5)	
COPD severity			
0	569 (69.4)	2734 (93.0)	<0.0001
1	169 (20.6)	141 (4.8)	
≧2	82 (10.0)	65 (2.2)	
Comedication			
SAMA			
Nebulized	461 (56.2)	1049 (35.7)	<0.0001
Inhaled	38 (4.6)	102 (3.5)	0.0323
SABA			
Nebulized	567 (69.1)	1779 (60.5)	<0.0001
Inhaled	111 (13.5)	403 (13.7)	0.5237
Systemic ß-agonist	301 (36.7)	1123 (38.2)	<0.0001
Methylxanthine	270 (32.9)	981 (33.4)	<0.0001

As shown in the Table 6, overall use of inhaled long acting bronchodilators was not associated with an increased risk of cardiovascular events except for current LABA prevalent users. Hypertension, DM, hyperlipidemia and the number of acute exacerbations in the first 1 year were risk factors for cardiovascular events increasing risk from 17% to 66%. In current LABA prevalent users, use of LABA was associated with 4.38-fold (95% CI, 1.14 – 16.81) increased cardiovascular risk whereas new use of LABA and LAMA showed 78% and 46% reduction in risk.

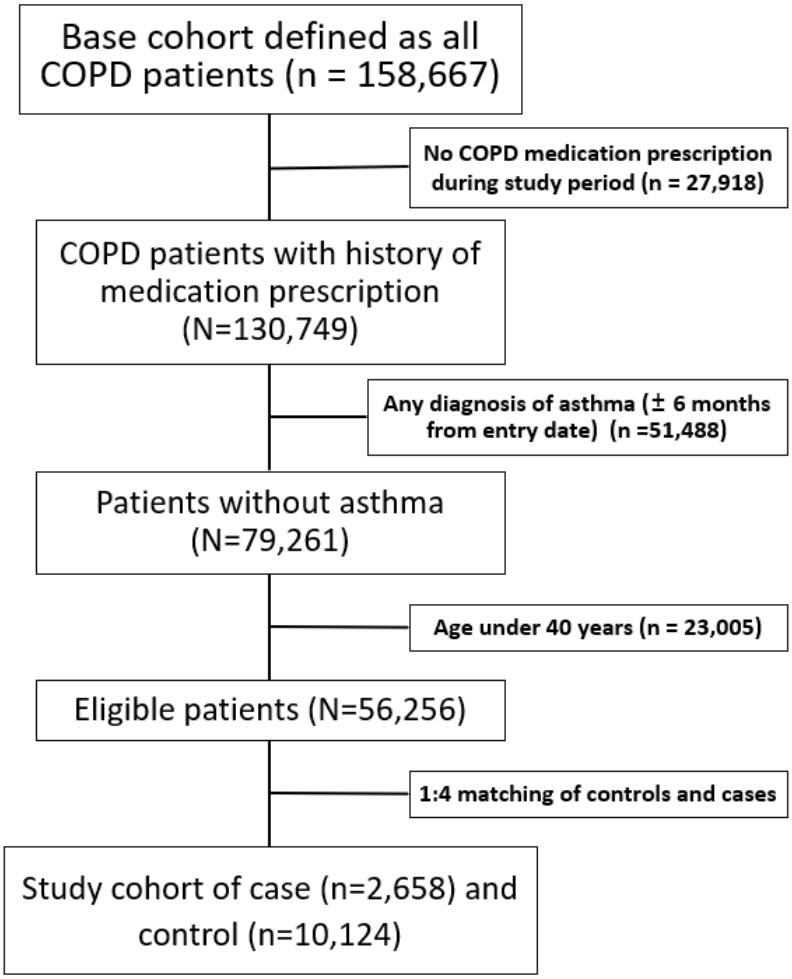
Table 6. Crude and adjusted ORs of cardiovascular events associated with LAMA and LABA

Bronchodilator	Control (n=2940)	Case (n=820)	Crude OR	95% CI	adjusted OR	95% CI
No use of LAMA or LABA	1713 (58.3)	492 (60.0)	1	reference	1	reference
Current						
LABA						
New	32 (1.1)	2 (0.2)	0.22	0.05 - 0.91	0.20	0.05 - 0.87
Prevalent	4 (0.1)	5 (0.6)	4.35	1.16 - 16.27	4.38	1.14 - 16.81
LAMA						
New	161 (5.5)	25 (3.0)	0.54	0.35 - 0.83	0.59	0.38 - 0.91
Prevalent	59 (2.0)	16 (2.0)	0.94	0.54 - 1.66	1.01	0.57 - 1.79
LAMA/LABA						
New	15 (0.5)	8 (1.0)	1.86	0.78 - 4.41	2.13	0.88 - 5.13
Prevalent	1 (0.0)	0 (0.0)	ND	ND	ND	ND
Recent						
LABA	684 (23.3)	219 (26.7)	1.12	0.93 - 1.34	1.03	0.85 -1.25
LABA/LAMA	112 (3.8)	22 (2.7)	0.68	0.43 - 1.09	0.77	0.48 - 1.23
Past						
LABA	17 (0.6)	3 (0.4)	0.61	0.18 - 2.11	0.76	0.22 - 2.64
LAMA	40 (1.4)	5 (0.6)	0.44	0.17 - 1.11	0.50	0.20 -1.29
LABA/LAMA	7 (0.2)	1 (0.1)	0.50	0.06 - 4.05	0.57	0.07 - 4.69
Remote						
LABA	39 (1.3)	9 (1.1)	0.80	0.39 - 1.67	1.02	0.49 - 2.13
LAMA	55 (1.9)	13 (1.6)	0.82	0.45 - 1.52	0.95	0.51 - 1.77
LABA/LAMA	1 (0.0)	0 (0.0)	ND	ND	ND	ND

2. Part 2 analysis

Cohort construction in Part 2 analysis was done as shown in Figure 6. COPD medications included LAMA, LABA, SAMA, SABA, systemic ß-agonist and methylxanthine. The total number of subjects was 56256, and 12782 subjects were studied by matching case and control (cases to controls ratio 1:4). Medication prescription pattern was again analyzed in this second cohort.

Figure 6. Flowchart of study cohort formation



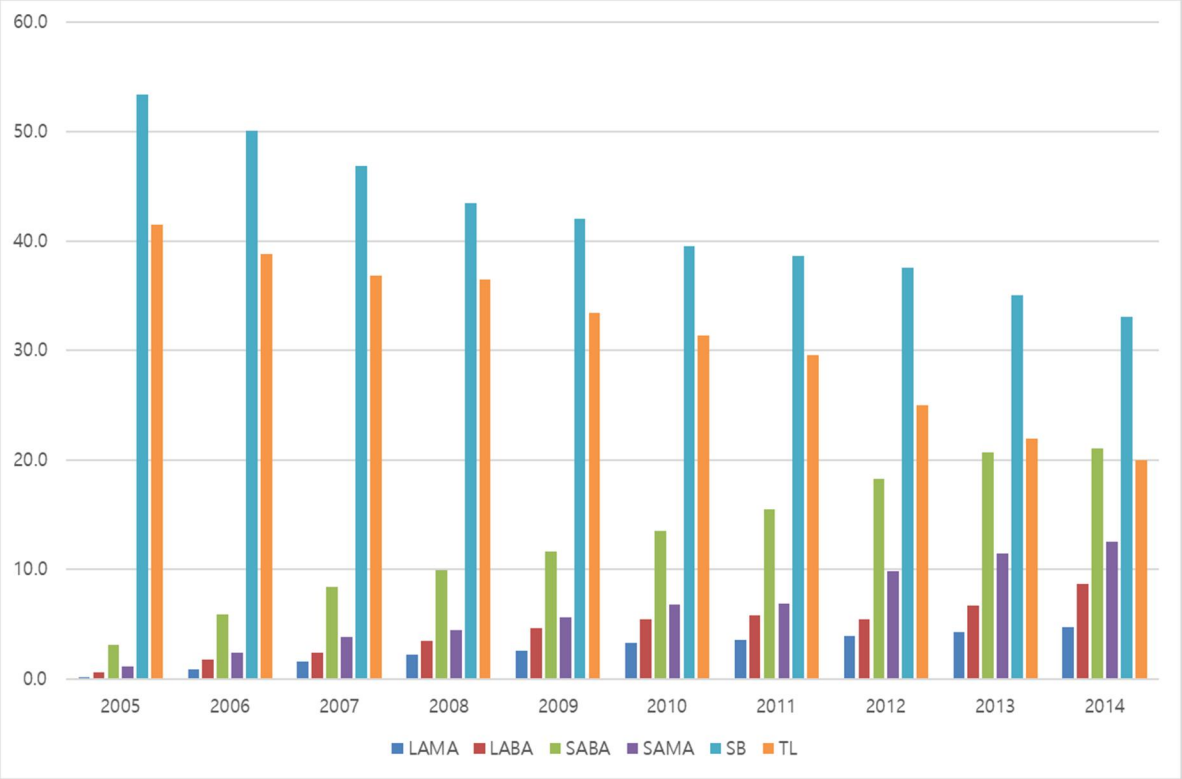
From 2005 to 2014, systemic ß-agonist and methylxanthines were the most commonly prescribed first medication for COPD followed by short-acting bronchodilators and long-acting bronchodilators. Systemic ß-agonist accounted for 33% to 53.4% of the total regimen and, as for methylxanthine, 20% to 41.6% (Table 7).

Table 7. Distribution of medication prescription and total number of patients diagnosed with COPD by year

	COPD + medication	**LAMA**	**LABA**	**SAMA**	**SABA**	**Systemic ß-agonist**	**Methyl xanthine**
2005	16,504	31 (0.2)	118 (0.6)	238 (1.2)	621 (3.1)	10675 (53.4)	8308 (41.6)
2006	9,968	136 (0.9)	270 (1.8)	359 (2.4)	868 (5.9)	7391 (50.1)	5732 (38.8)
2007	7,161	209 (1.7)	305 (2.4)	486 (3.9)	1056 (8.4)	5901 (46.9)	4638 (36.8)
2008	5,639	248 (2.2)	387 (3.5)	496 (4.5)	1102 (9.9)	4846 (43.5)	4060 (36.4)
2009	4,370	249 (2.6)	453 (4.7)	545 (5.6)	1128 (11.6)	4083 (42.1)	3244 (33.4)
2010	3,578	294 (3.3)	489 (5.5)	612 (6.8)	1211 (13.5)	3544 (39.6)	2810 (31.4)
2011	2,988	290 (3.6)	475 (5.8)	559 (6.9)	1265 (15.5)	3147 (38.7)	2406 (29.6)
2012	2,409	297 (4.0)	409 (5.4)	738 (9.8)	1376 (18.3)	2816 (37.5)	1875 (25.0)
2013	1,899	283 (4.3)	444 (6.7)	760 (11.4)	1378 (20.7)	2331 (35.0)	1459 (21.9)
2014	1,740	302 (4.7)	554 (8.7)	795 (12.5)	1340 (21.1)	2100 (33.0)	1274 (20.0)
Total	56,256	2339 (2.2)	3904 (3.7)	5588 (5.3)	11345 (10.7)	46834 (44.3)	35806 (33.8)

The ranking of the most prescribed medicines did not change for 10 years (Figure 7). However, the proportion of oral medications is gradually decreasing while the proportion of inhalers is increasing over the decade.

Figure 7. Distribution of medication prescription by year



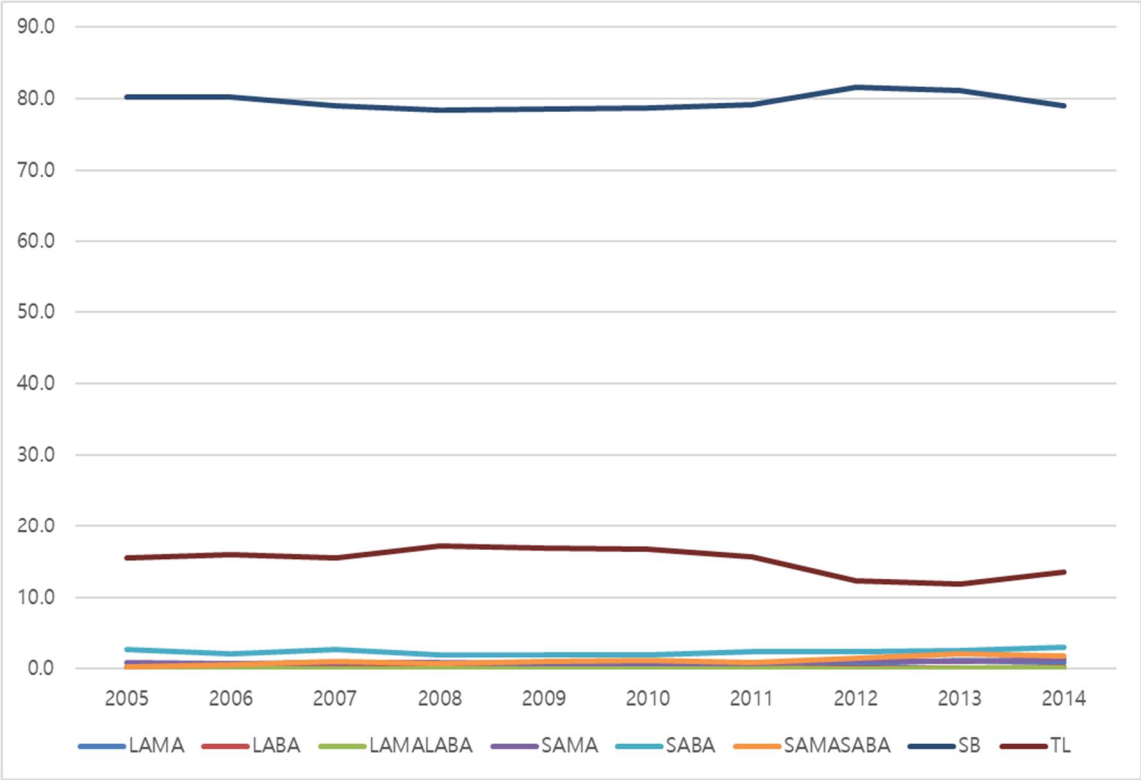
The most common first drug was oral systemic ß-agonist accounting for about 80% each year followed by methylxanthine (Table 8).

Table 8. Classes of first medication after diagnosis over the study period

	LAMA	LABA	LAMA/LABA	SAMA	SABA	SAMA/SABA	Systemic ß-agonist	Methyl -xanthine
2005	7 (0.1)	38 (0.3)	1 (0.0)	101 (0.9)	324 (2.7)	43 (0.4)	9463 (80.2)	1817 (15.4)
2006	18 (0.2)	11 (0.1)	3 (0.0)	57 (0.7)	178 (2.1)	55 (0.7)	6766 (80.2)	1348 (16.0)
2007	44 (0.6)	6 (0.1)	4 (0.1)	66 (1.0)	188 (2.8)	71 (1.0)	5354 (79.0)	1048 (15.5)
2008	35 (0.6)	10 (0.2)	1 (0.0)	52 (0.9)	113 (2.0)	46 (0.8)	4476 (78.3)	984 (17.2)
2009	34 (0.7)	4 (0.1)	4 (0.1)	36 (0.7)	93 (1.9)	51 (1.1)	3793 (78.6)	813 (16.8)
2010	25 (0.6)	5 (0.1)	0 (0.0)	32 (0.8)	85 (2.0)	51 (1.2)	3310 (78.6)	703 (16.7)
2011	34 (0.9)	4 (0.1)	6 (0.2)	28 (0.8)	87 (2.3)	34 (0.9)	2941 (79.2)	581 (15.6)
2012	25 (0.8)	5 (0.2)	0 (0.0)	41 (1.3)	76 (2.4)	50 (1.6)	2621 (81.5)	397 (12.3)
2013	32 (1.2)	4 (0.1)	3 (0.1)	27 (1.0)	67 (2.5)	55 (2.1)	2176 (81.2)	317 (11.8)
2014	21 (0.9)	7 (0.3)	2 (0.1)	35 (1.4)	76 (3.1)	45 (1.8)	1946 (78.9)	334 (13.5)

The use of inhalers is slowly increasing, but by 2014 it has still remained below 8% of total prescription (Figure 8).

Figure 8. Change in classes of first prescription

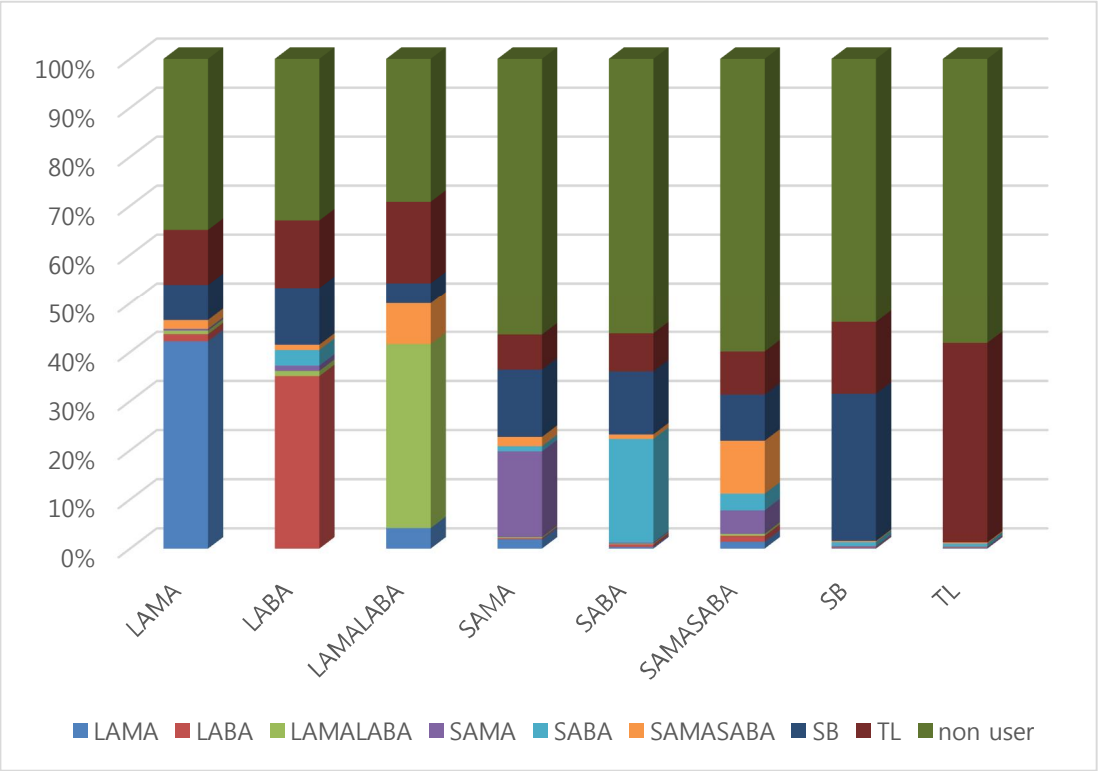


After receiving the first prescription for each medication, it was found that the second medication was not prescribed at any time during the study period in 29.1% to 59.8% (Table 9). As in the first cohort analysis in part 1, many patients were found to stop using the medications especially in those with short-acting bronchodilators and oral medications (Figure 9). In patients with long-acting bronchodilators, LAMA or LABA or both, 70% of patients maintained the drugs or switched to other classes, while the others maintained or switched only in about 40%. As with the first analysis, there were many discontinuation and changes.

Table 9. Drug prescription pattern of 2nd medications after 1st prescription

		2nd prescription									
		LAMA	LABA	LAMA/LABA	SAMA	SABA	SAMA/SABA	Systemic ß-agonist	Methyl -xanthine	none	Total
1st	LAMA	116	4	2	1	0	5	20	31	96	275
	LABA	0	33	1	1	3	1	11	13	31	94
	LAMA/LABA	1	0	9	0	0	2	1	4	7	24
	SAMA	9	1	1	83	5	9	65	34	268	475
	SABA	4	7	2	3	271	12	165	100	723	1287
	SAMA/SABA	7	6	2	24	17	54	47	44	300	501
	Systemic ß-agonist	44	73	9	87	361	94	12835	6276	23067	42846
	Methyl -xanthine	8	11	1	13	53	20	0	3389	4847	8342

Figure 9. Distribution of 2nd prescription



The extent of baseline cardiovascular disease in the entire cohort is shown in Table 10. Among all patients, 3.4% had any cardiovascular events 1 year before the use of medications, and 5.2% after medication use.

Table 10. Number of cardiovascular events before and after one year since COPD medication

	1 year before medication	1 year after medication
Ischemic heart disease		
none	54915 (97.6)	54256 (96.4)
≧1	1341 (2.4)	2000 (3.6)
Congestive heart failure		
none	55783 (99.2)	55395 (98.5)
≧1	473 (0.8)	861 (1.5)
Arrhythmia		
none	55745 (99.1)	55295 (98.3)
≧1	511 (0.9)	961 (1.7)
Any cardiovascular events		
none	54365 (96.6)	53314 (94.8)
≧1	1891 (3.4)	2942 (5.2)

Table 11 shows the baseline characteristics of cases and matched controls. Hypertension, hyperlipidemia, and diabetes mellitus were more common in cases than controls, and acute exacerbation of COPD was also more frequent.

Table 11. Baseline characteristics of matched cases and controls

Characteristics	Cases (n=2658)	Controls (n=10124)	p-value
Age	68.4±10.8	68.2±10.7	
Sex			<0.0001
Male	1424 (53.6)	5377 (53.1)	
Female	1234 (46.4)	4747 (46.9)	
Prior cardiovascular events			
Ischemic heart disease			<0.0001
0	2442 (91.9)	9647 (95.3)	
1	184 (6.9)	431 (4.3)	
≥2	32 (1.2)	46 (0.5)	
Congestive heart failure			<0.0001
0	2615 (98.4)	10068 (99.4)	
1	38 (1.4)	51 (0.5)	
≥2	5 (0.2)	5 (0.0)	
Arrhythmia			<0.0001
0	2623 (98.7)	10057 (99.3)	
1	34 (1.3)	66 (0.7)	
≥2	1 (0.0)	1 (0.0)	
Hypertension	1647 (62.0)	4646 (45.9)	<0.0001
Hyperlipidemia	895 (33.7)	2415 (23.9)	<0.0001
Diabetes mellitus	987 (37.1)	2533 (25.0)	<0.0001
Ischemic stroke	2580 (97.1)	9877 (97.6)	0.2393
Charlson Comorbidity Index score	0.32±0.89	0.14±0.54	
COPD			<0.0001
Inpatient	249 (9.4)	317 (3.1)	
Outpatient	2409 (90.6)	9807 (96.9)	
COPD severity			
0	2145 (80.7)	9905 (97.8)	<0.0001
1	360 (13.5)	157 (1.6)	
≥2	153 (5.8)	62 (0.6)	

Table 11. continued

Comedication			
SAMA			
Nebulized	341 (12.8)	296 (2.9)	<0.0001
Inhaled	43 (1.6)	52 (0.5)	<0.0001
SABA			
Nebulized	443 (16.7)	520 (5.1)	<0.0001
Inhaled	84 (3.2)	119 (1.2)	<0.0001
Systemic ß -agonist	24 (0.9)	33 (0.3)	<0.0001
Methylxanthine	2652 (99.8)	9862 (97.4)	<0.0001

Overall use of inhaled long-acting bronchodilators was not associated with an increased risk of cardiovascular events except for current users and remote use of LABA (Table 12). In current LABA or LAMA new users, inhaler use was associated with 3.12-fold (95% CI, 1.19 – 8,19) and 6.31-fold increased risk (95% CI, 2.96 – 13.47) after adjustment for covariates.

Table 12. Crude and adjusted ORs of cardiovascular events associated with LAMA and LABA

Bronchodilator	**Control (n=10124)**	**Case (n=2658)**	**Crude OR**	**95% CI**	**adjusted OR**	**95% CI**
No use of LAMA or LABA	10019 (99.0)	2586 (97.3)	1	reference	1	reference
Current						
LABA						
New	11 (0.1)	9 (0.3)	3.17	1.30-7.73	3.12	1.19-8.19
LAMA						
New	12 (0.1)	22 (0.8)	6.80	3.35-13.81	6.31	2.96-13.47
Prevalent	3 (0.0)	4 (0.2)	5.12	1.15-22.93	5.66	1.24-25.9
Recent						
LABA	3 (0.0)	3 (0.1)	4.00	0.81-19.82	2.67	0.48-15.01
LAMA	16 (0.2)	1 (0.0)	0.25	0.03-1.93	0.23	0.03-1.77
LABA/LAMA	4 (0.0)	1 (0.0)	0.94	0.11-8.44	1.39	0.14-13.45
Past						
LABA	7 (0.1)	3 (0.1)	1.46	0.37-5.83	0.92	0.18-4.67
LAMA	4 (0.0)	1 (0.0)	1.00	0.11-8.95	0.74	0.08-6.75
LABA/LAMA	2 (0.0)	0 (0.0)	ND	ND	ND	ND
Remote						
LABA	17 (0.2)	19 (0.7)	4.35	2.25-8.39	4.63	2.28-9.40
LAMA	26 (0.3)	9 (0.3)	1.30	0.61-2.80	1.61	0.73-3.54

Patients in Part 1 analysis were more likely to be diagnosed with COPD at hospital admission than in patients in the part 2 cohort and they had more acute exacerbation episodes defined as hospitalizations or emergency department visits for one year (Table 13)

Table 13. Comparison of cohort characteristics in part 1 and part 2 analysis

	Part 1 analysis		**Part 2 analysis**	
Characteristics	Case (n=820)	Control (n=2940)	Case (n=2658)	Control (n=10124)
COPD				
Inpatient	617 (75.2)	1602 (54.5)	249 (9.4)	317 (3.1)
Outpatient	203 (24.8)	1338 (45.5)	2409 (90.6)	9807 (96.9)
COPD severity				
0	569 (69.4)	2734 (93.0)	2145 (80.7)	9905 (97.8)
1	169 (20.6)	141 (4.8)	360 (13.5)	157 (1.6)
≧2	82 (10.0)	65 (2.2)	153 (5.8)	62 (0.6)
Comedication				
SAMA				
Nebulized	461 (56.2)	1049 (35.7)	341 (12.8)	296 (2.9)
Inhaled	38 (4.6)	102 (3.5)	43 (1.6)	52 (0.5)
SABA				
Nebulized	567 (69.1)	1779 (60.5)	443 (16.7)	520 (5.1)
Inhaled	111 (13.5)	403 (13.7)	84 (3.2)	119 (1.2)
Systemic ß-agonist	301 (36.7)	1123 (38.2)	24 (0.9)	33 (0.3)
Methylxanthine	270 (32.9)	981 (33.4)	2652 (99.8)	9862 (97.4)

Discussion

In this study, we used National Health Insurance claims data to analyze medication prescription pattern of COPD and to assess the effect of COPD medications on cardiovascular disease. In this study, we found that systemic ß-agonist and methylxanthine account for the largest proportion of all prescriptions and are also the most commonly prescribed as the first medication. As for long-acting bronchodilators, its prescription is increasing. Proportion of LABA increased to 8.7% from 0.6%. In case of LABA, indacaterol (onbrez®), which is a LABA single agent, was available in Korean market since February 2012. Thus, most of LABA included in this study was ICS/LABA combination preparations. Use of LAMA increased from 0.2% to 4.7%. Considering that tiotropium bromide (Spriva handihaler®) was in the market since 2005 February, its use increased from 0.9% to 4.7% since 2006. The use of short-acting bronchodilators, especially SABA, is also increasing, and the proportion of systemic ß-agonist has been reduced from 53.4% to 33% and methylxanthine has also been decreased from 41.6% to 20%. However, systemic ß-agonists or methylxanthines still constitute more than 50% of patients in the whole prescription pattern. Especially as the first medication after diagnosis, more than 90% of them are prescribed oral medications, most commonly, systemic ß-agonist. The result from previous study about trend of COPD medication utilization revealed similar results as this one[15]. Currently, inhaled bronchodilators are recommended as a treatment of COPD and methylxanthine is recommended those with persistent symptoms despite the use of inhalers. Systemic ß-agonist are not recommended by guideline. However, these two drugs appeared to be the most commonly prescribed, indicating that there is a gap between real practice and guidelines. There are several explanations about this discrepancy. Without result of spirometry, it is difficult to prescribe inhalers in Korea because the reimbursement of these medications depends upon these results. Pulmonary function test using spirometry is a prerequisite for diagnosis and treatment of COPD. But, many of primary clinics

don't have spirometer or don't perform the tests, due to several reasons such as difficulties in testing and patients not wanting the test. Although, education for appropriate use of inhalers is crucial to achieve optimal treatment, there are not enough time for education and many elderly patients have difficulties in learning it. So both the patients and the primary clinic physicians prefer oral medications to inhalers[16]. It can also be assumed that compliance is low because many cases appeared to be interrupted. Though it's well known that compliance is an important factor of COPD morbidity and mortality[17], underuse and improper use of drugs are fairly common[18]. Because this study looked into prescription data, it is likely that the use of medicines can be overestimated. This study showed that there are high rate of drug discontinuation and switching to other medications. If the cardiovascular event occurs after changing of the medication, it cannot be clearly identified whether this is due to the previous medication or the new one. Retrospective cohort analysis would be a good way to confirm the effect of medications. However, due to issues in medication prescription patterns mentioned above, we performed nested case control study to assess relationship of cardiovascular events and pharmacotherapy of COPD.

In this study, the effects of COPD medications on cardiovascular events in part 1 analysis and part 2 analysis were conflicting. The use of long-acting bronchodilators did not increase the risk after adjustment when definition of COPD drugs included short-acting bronchodilators and long-acting bronchodilators. In current new users of LABA or LAMA, OR was decreased to 0.2 (95% CI, 0.05 - 0.87) and 0.59 (59% CI, 0.38 - 0.91), respectively in part 1 analysis. In current prevalent LABA users, risk of cardiovascular events seemed to increase with adjusted OR of 4.38. But there was no significant increase of risk in LABA. This result might be related with the small number of controls and cases among the LABA prevalent users which was 4 and 5, respectively.

Part 2 analysis included systemic ß-agonist and methylxanthine as well as

inhalers as COPD drugs, taking into account prescription patterns from drug use review of this study. As a result, contrary to part 1 analysis, the risk of cardiovascular events was found to be increased in LABA and LAMA current new users (OR, 3.12 and 6.31 respectively). In LAMA current prevalent users, the OR was increased to 5.66, which is due to the small number of controls and cases (3 and 4, respectively) as in LABA current prevalent users in part 1 analysis. There were many studies on safety of bronchodilators, especially about cardiovascular safety, but the results were conflicting and inconclusive[7,13,19–21]. Several previous studies have shown that the use of bronchodilators increases adverse cardiac events. Wilchesky et al. reported that a new use of SABA or LABA to increase risk of arrhythmia[6]. Macie et al. also reported that LABA increases cardiovascular risk[19]. In a study by Gershon et al., it has shown that LABA increases the cardiovascular event significantly with an adjusted OR of 1.31, and that LAMA has a 14% increase in risk similar to LABA in elderly patients[21]. Singh et al. conducted a meta-analysis studying the effects of LAMA on cardiovascular disease and found a relative risk (RR) of 1.58.[20]. However, the study was limited to short-term, small numbered trials, and the severity of COPD was not corrected. A recent study using Taiwan National Health Insurance Research Database for health care claims data reported that LAMA and LABA both increase cardiovascular risk by about 50% in current and new users who have started the medication within 30 days and have never used it before[13].

However, there are a number of previous studies that do not increase risk. There are also studies using data from those well-known multicenter randomized double blind placebo controlled trials, like Towards a Revolution in COPD Health (TORCH), and Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT)[22,23]. Tashkin et al. found that the effect of tiotropium on cardiovascular events compared with placebo was not increased by studying patients who did not withdraw from the study, in spite of adverse cardiovascular event after enrollment in UPLIFT[22]. Post-hoc analysis using the results of the

TORCH trial showed similar results[23]. The probability of cardiovascular adverse events was 24.2% for placebo, 22.7% for salmeterol, and 20.8% for salmeterol / fluticasone propionate. The probability of cardiovascular events was doubled with the history of myocardial infarction, but not related to treatment regimen. Vestebo et al's study included moderate COPD patients with high risk of cardiovascular disease as a multicenter randomized double blind placebo-controlled event driven trial[24]. In this study, ICS / LABA (fluticasone furoate / vilanterol) did not affect cardiovascular outcome and reduced exacerbations. Lahousse et al concluded that treatment with long-acting bronchodilators does not increase the risk of cardiovascular disease when they are used in appropriate dose in adherent patients after reviewing literatures[25]. Halpin et al also reported no increase in MACE with tiotropium[14]. Moreover, like the first analysis of our study in part 1, Xia et al reported a meta-analysis showing reduction of cardiovascular risk (RR, 0.65; 95% CI, 0.50 – 0.86) in long-term trials in those with severe COPD defined as FEV1 less than 50%[26].

In this study, the first analysis showed a decrease in cardiovascular risk, and the second analysis showed an increase in cardiovascular risk. These conflicting results are considered to be due to differences in the subjects. By repeating the analysis while changing the criteria of the target cohort, we could find the reason for previous conflicting results. As is well known, COPD patients often have cardiovascular disease as a part of complex comorbidities, and these two diseases interfere with each other and affect each other's morbidity and mortality. Repeated COPD exacerbations, hypoxia, lung function decline, and respiratory failure are known as risk factors of cardiovascular events. As a result, treatment and control of COPD symptoms can reduce cardiovascular morbidity and mortality. Many previous studies have shown that LABA and LAMA reduce exacerbation and improve lung function compared to placebo. In our study, patients with COPD was limited only to those using bronchodilators in part 1. It can be assumed that those in part 1 analysis were more symptomatic than those

included in part 2 analysis. Whereas in part 2 analysis there were 99% and 97.3% of non-users in controls and cases, in part 1 analysis, there were 60% of non-users. Differences in COPD severity can also be seen in exacerbation frequency in baseline characteristics.

This study has several limitations. First, using 2% sampling data, the number was small and it was difficult to clearly identify the effect in some drug groups. It is difficult to tell that this cohort represents COPD patients because 2% sampling is chosen to represent the entire population of Korea not just COPD patients. And because it is prescription data, it does not mean actual use of medications. Other major factors that may affect cardiovascular disease, such as alcohol and smoking, cannot be identified in this study, working as confounding factors. Many previous studies have shown controversial and conflicting results, and their effects on cardiovascular events are difficult to interpret. Randomized controlled trials are advantageous because they can control several confounding factors leading to very homogeneous populations. But they exclude patients with comorbid conditions such as very severe obstruction, exacerbations, and overt cardiovascular disease. However, in a real-world, COPD is a very heterogenous disease making observational studies more appropriate, reflecting the characteristics of COPD including patients with comorbidities and various severities. And this study gives hints on the conflicting results known so far by inspecting the different result according to the selection of the research subjects in the same period and the same population. We believe that additional randomized controlled trials with a wider patient population than the previous ones would provide more robust results on the cardiac safety of the bronchodilators.

Conclusion

This study suggests that bronchodilators may reduce the risk of cardiovascular disease by controlling COPD. Patients with severe COPD may benefit best from this treatment. However, in the case of mild COPD, physicians need to be cautious and monitor for possible adverse events, because the use of new bronchodilators may increase the risk of cardiovascular disease.

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Supplementary material

Table S1.

Diagnosis	ICD-10 codes
Hypertension	I10.x, I11.9 and I13.9
Hyperlipidemia	E78
Diabetes mellitus	E10-E14
Ischemic stroke	I63,G45.0, G45.1, G45.2, G45.8, or G45.9
Dyspnea	R06.0
Acute respiratory distress syndrome	J80
Pneumonia	J12.x-J17.x
Pulmonary thromboembolism	I26, I26.0, I26.9

국문요약

연구 배경: 만성 폐쇄성 폐질환은 유병률이 높고 주요 사망원인 중 하나로 점차 증가할 것으로 예상되고 있다. 이러한 만성 폐쇄성 폐질환의 주요 치료 방법으로는 약물치료가 있는데 약물치료는 증상을 완화시키고 삶의 질을 향상시키며 급성 악화를 예방하는데 목적이 있다. 주요 약물치료제로는 베타 작용제와 항콜린제와 같은 흡입 기관지 확장제가 권유되고 있다. 베타 작용제는 기관지의 평활근의 이완을 가져오지만 자율신경계를 자극하여 떨림, 불안감, 저칼륨혈증 및 동성빈맥과 같은 부정맥을 유발하기도 한다. 항콜린제의 경우에는 부교감 신경의 자극을 막아 그 효과를 낸다. 많은 만성폐쇄성폐질환 환자들은 심혈관 질환을 동반질환으로 가지고 있는 경우가 많고 기관지 확장제는 위와 같은 작용기전이 있어 심혈관 질환에 부작용이 있을 수 있다는 문제점이 있다.

연구 목적: 본 연구에서는 만성 폐쇄성 폐질환 환자에서 흡입 기관지 확장제가 심혈관 질환에 미치는 영향에 대하여 알아보고자 한다.

연구 방법: 한국의 국민건강보험 청구 자료 중 표본 코호트 데이터 베이스를 사용하여 약제 처방 패턴을 확인하고 환자-대조군 연구를 시행하였다. 구축된 코호트에서 심혈관 질환으로 인한 입원이나 응급실 방문이 있었던 환자군과 이에 성별, 나이, 이전 1년감 심혈관 질환력으로 1:4의 비율로 짝을 맞춘 대조군을 비교하였다. 심혈관 질환으로 인한 입원이나 응급실 방문이 있었던 시점을 기준으로 1년이내의 흡입 기관지 확장제 사용여부를 확인하여 로지스틱 회귀분석을 시행하였다.

연구 결과: 약제 처방 패턴을 분석한 결과 흡입 기관지 확장제의 사용이 증가하고 있으나 여전히 약 90%의 환자가 만성 폐쇄성 폐질환으로 진단받은 후 첫 처방으로 경구약제인 메틸잔틴이나 전신 베타 작용제를 처방받았다. 흡입 기관지 확장제의 심혈관 질환에의 영향을 보기 위하여 시행한 환자-대조군 연구에서는 대상 코호트를 정의하는 것에 따라 상반된 결과를 보였다. 만성폐쇄성 폐질환의 진단과 함께 전신 베타 작용제와 메틸잔틴과 같은 경구약제를 제외한 속효성 및 지속성 기관지 확장제를 처방받은 환자들만을 대상으로 분석을 하는 경우 흡입

지속성 베타작용제나 흡입 지속성 항콜린제를 30일 이내에 처방받아 새로 시작한 경우 오즈비가 각각 0.2와 0.59로 유의하게 심혈관 질환 부작용 발생의 확률이 감소하는 것으로 확인되었다. 이와는 반대로 전신 베타 작용제와 메틸잔틴과 같은 경구약제와 흡입 기관지 확장제 중 하나라도 처방받은 환자들을 대상 코호트로 정의하는 경우 흡입 지속성 베타 작용제를 30일 이내 새로 시작한 경우 심혈관 질환으로 인한 응급실 방문 및 입원 확률이 3.12배로 증가하는 것으로 나타났다. 흡입 지속성 항콜린제의 경우에도 베타작용제와 비슷하게 위험도가 6.31배 증가하는 것으로 나타났다.

결론: 동일한 인구집단에서 연구가 시행됐음에도 불구하고 대상자의 정의에 따라 흡입 기관지 확장제가 심혈관 질환으로 인한 응급실 방문 또는 입원의 위험도에 미치는 영향은 서로 상반된 결과를 보였다. 이는 대상 환자들의 특성의 차이에서 기인하는 것으로 생각된다. 주로 만성 폐쇄성 폐질환의 중증도가 심한 경우에는 약제 사용으로 인한 부작용보다 만성 폐쇄성 폐질환의 조절로 인한 심혈관 질환에 긍정적인 효과가 더 크며 반대로 경도의 만성폐쇄성 폐질환에서는 심혈관 질환 부작용이 증가할 수 있으므로 약제 시작 시 주의 깊은 모니터링이 필요하겠다.