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Review Article

Risk of adverse cardiovascular events with use of inhaled long-acting bronchodilators in management of chronic obstructive pulmonary disease

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ABSTRACT

Inhaled long-acting bronchodilators, including long-acting β_2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are the mainstay therapy in the treatment of chronic obstructive pulmonary disease (COPD), a disease that poses a heavy burden on morbidity and mortality worldwide. Use of LABAs and LAMAs in patients with COPD, however, has been concerned about an increased risk of adverse cardiovascular events, despite inconsistent findings reported from randomized controlled trials (RCTs) and observational studies. In this review, we detailed the relevant evidence generated from RCTs and observational studies with respect to the risk of cardiovascular disease with use of LABAs and LAMAs in management of COPD, and analyzed the contradictory findings in the literature, as well as recommended future research directions to clear the air regarding the cardiovascular safety of inhaled long-acting bronchodilators.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and irreversible progressive airway obstructive disease, which usually results from a significant exposure to noxious particles or gases. This disease is characterized with persistent respiratory syndromes and exacerbations as well as progressive pulmonary function decline [1,2]. COPD imposes a significant burden to health; It has been linked with multiple comorbid conditions [3] and remains a major cause of death

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[4]. Specifically, a total of 3.2 million people died from COPD in 2015 worldwide [4].

Inhaled long-acting bronchodilators, including long-acting β_2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), are the mainstay therapy for management of COPD [5]. LABAs stimulate the β_2-adrenergic receptors located in airway smooth muscles and relax the smooth muscle of airways; LAMAs bind to muscarinic receptors—predominantly the M_3 subtype—that are expressed in the airway and lung tissue, and block acetylcholine-medicated bronchoconstriction accordingly [6]. Randomized controlled trials (RCTs) have reported that COPD patients receiving LABA or LAMA therapies have a reduced risk of COPD exacerbation, decreased number of COPD hospitalization, and improved health-related quality of life [7,8]. LABA and LAMA therapy are the most central to the symptomatic management of COPD. The newest treatment guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have suggested that LABA or LAMA therapy can be considered in Group A patients (low symptoms/low risk of exacerbation), and should be initiated in Group B patients (high symptoms/low risk) [9]. Initiation of LAMA monotherapy is recommended in Group C patients (low symptoms/high risk), and an add-on LABA to the LAMA therapy is a preferred treatment for this group of patients with further exacerbations [9]. Additionally, starting therapy with a LABA/LAMA dual therapy is suggested as the initial therapy for the most severe COPD patients, classified as group D patients (high symptoms/high risk) [9].

Despite the pivotal role of LABAs and LAMAs for management of COPD, concerns have been raised that exposure to LABAs and LAMAs may lead to adverse cardiovascular events [6]. There is biological plausibility of adverse cardiovascular events from use of LABAs and LAMAs: the pharmacological effects of LABAs and LAMAs are found to exert beyond the site of pulmonary, especially in the heart [10,11]. Although multiple observational studies have revealed an increased risk of adverse cardiovascular events from LABA and LAMA use [12–16], clinical trials have reported contradictory results [17–19]. Therefore, the objectives of this review were to discuss the biological plausibility of the adverse cardiovascular risk with LABA and LAMA therapy first, and then to examine the relevant randomized trials and observational studies for identifying possible reasons that may explain the discrepant findings between RCTs and observational studies, which can serve as a strong basis for designing future studies to clear the air regarding the cardiovascular risk with the inhalation therapy in COPD.

2. Possible pharmacological mechanisms underlying adverse cardiovascular events from LABA and LAMA use

The stimulation of β_2-adrenoreceptors (β_2-ARs) by LABAs outside the lung is a possible cause of the adverse cardiovascular events associated with the inhaled therapy [10]. β_1-adrenoreceptors and β_2-ARs coexist in an approximate ratio of 7:3 and 4:1 in atria and ventricles, respectively [20]. The presence of β_2-ARs is also found in adrenergic nerve terminals in human heart, which facilitates the release of norepinephrine [21]. Through stimulation of β_2-ARs, LABAs can accordingly cause positive inotropic and chronotropic responses, resulting in an increased heart rate and myocardial oxygen demand, and direct myocardial injury, which could consequently cause adverse cardiovascular events, such as tachycardia and myocardial infarction [10,22]. Additionally, peripheral vasodilation could also be induced with the stimulation of β_2-ARs, and therefore lead to reflex tachycardia [10]. Furthermore, inhaled β_2 agonists could also lower plasma K^+ levels by simulating the Na^+, K^+-ATPase coupled to β_2-ARs in skeletal muscles, which pumps extracellular potassium ions into the cell, thereby causing hypokalemia that has been associated with ventricular tachycardia and fibrillation [23].

The potential cardiovascular risk of LAMAs is generally considered to result from the suppression of the parasympathetic activity in the heart via antagonism at cardiac muscarinic receptors [11]. These receptors are predominated by M_2-muscarinic receptors (M_2-receptors) [24], stimulation of which elicits a negative chronotropic and inotropic response in the vagal control of the heart. Use of atropine, a muscarinic antagonist, has been found to increase tachycardia from suppressing the vagal effect of M_2-receptors of the sinoatrial nodal pacemaker in an in vivo study [25]. Given most LAMAs have the affinity on M_2-receptors, it is suggested that LAMAs could antagonize the subtype of the muscarinic receptors in the human heart, potentially inducing heart rate and tachycardia [11].

Activation of M_3 receptors in the heart is also considered to play an important role in regulating and maintaining cardiac function [26], which could be inhibited with use of LAMAs. Stimulation of M_3 receptors protects the heart from ischemic injuries by activating antiapoptotic signaling substances, enhancing endogenous antioxidant levels, and decreasing intracellular Ca^{2+} overload [27], as well as stimulates a M_3 receptor-activated delayed rectifying K^+ current, which exerts negative chronotropic responses and exhibits antidysrhythmic activity [28]. On the other hand, the beneficial effects from stimulation of M_3 receptors are counteracted by 4-diphenylacetoxy -N-methylpiperidine methiodide (4-DAMP), an M_3 selective antagonist [27]. Therefore, it is suspected that potential adverse cardiovascular events associated with LAMAs may also be attributable to antagonizing the M_3-receptor-mediated cardiac functions [11].

3. The employment of randomized trials to examine adverse cardiovascular events from inhaled long-acting bronchodilators for management of COPD

Randomized trials employ the most rigorous design to maintain a high level of causality due to the adoption of random allocation and blinding, both of which minimize confounding and bias [29]. Accordingly, RCTs are expected to generate findings with a higher internal validity compared with those from other study designs, and provide the strongest evidence of whether use of inhaled long-acting bronchodilators causes an excess risk of adverse cardiovascular events in patients with COPD. However, randomized trials are not entirely free of study limitations. For example, patients enrolled in RCTs are

typically highly selected with strict exclusion criteria, resulting in limited external validity to real-world application [29]. Specifically, it has been reported that less than 20% of COPD patients in real-life settings would meet the selection criteria commonly adopted in COPD RCTs [30], and patients participating in large clinical trials had worse lung function and poorer quality of life than those identified from primary care settings [31].

3.1. *RCTs reporting cardiovascular safety results with LABA or LAMA monotherapy versus placebo*

Table 1 describes relevant RCTs reporting cardiovascular end points among patients with COPD receiving either LABA or LAMA monotherapy versus placebo. These trials generally enrolled moderate-to-severe COPD patients, had a differential duration of follow-up, ranging from 6 weeks to 52 weeks, and investigated the individual LABA salmeterol [17], formoterol [32,33], indacaterol [33–35], olodaterol [32] and vilanterol [19] and individual LAMA tiotropium [18,34], aclidinium [36] and glycopyrronium [37]. Spirometry-based lung function measurements [18,32–40] and all-cause mortality [17,19] were the primary outcomes of interest, and cardiovascular events were all measured as a secondary outcome among these trials [17–19,32–41].

Up to till now, all pivotal large RCTs have reported no excess risk of cardiovascular disease (CVD) from use of LABAs and LAMAs as a monotherapy in treatment of COPD [17–19]. The TOwards a Revolution in COPD Health (TORCH) study employed a 3-year randomized and double-blind trial design, and revealed no increased rates of self-reported cardiac disorders for salmeterol used alone (0.114 events per year) or in combination with fluticasone propionate (0.087 events per year) as compared with placebo (0.113 events per year) among 6184 moderate to severe COPD patients [17]. Approximately 40% of patients enrolled in the TORCH trial, however, ever used LABA with or without inhaled corticosteroid at baseline, among whom the cardiovascular adverse events from an initiation therapy of LABA, if any, could not be observed during follow-up. The Study to Understand Mortality and MorbidITy (SUMMIT) [19] study was a double-blind, placebo controlled trial of 16,000 moderate COPD patients with a history or at increased risk of cardiovascular disorder, who were randomly allocated to receive either the once daily inhaled LABA vilanterol 25 μg, inhaled corticosteroid fluticasone 100 μg, vilanterol/fluticasone 25/100 μg combination, or inhaled placebo. In this trial, use of vilanterol alone (hazard ratio [HR] 0.99; 95% CI 0.80–1.22) or in combination with fluticasone (HR 0.93; 95% CI 0.75–1.14) did not increase the risk of the cardiovascular composite endpoint as compared to placebo [19]. Patients were allowed to use other COPD medications for exacerbation during follow-up, including tiotropium, in the SUMMIT trial; nevertheless, the impact of the additional use of other COPD medications on the cardiovascular safety findings was not assessed. The 4-year Understanding Potential Long-term Impact on Function with Tiotropium (UPLIFT) randomized, double-blind trial concluded a lower risk of cardiovascular events (relative risk [RR] 0.84; 95% CI 0.73–0.98) with use of 18 μg tiotropium versus placebo in approximately 6000 moderate-to-very-severe COPD patients [18]. The UPLIFT trial, however, excluded patients with recent cardiovascular disorders, and lacked monitoring whether adverse events occurred for more than 40% of the patients who discontinued the trial. Other individual LABA and LAMA agents, such as indacaterol [33–35], olodaterol [32], aclidinium [36], and glycopyrronium [37] have also been shown not to increase the risk of adverse cardiovascular disease in patients with COPD, despite the inherent study limitations such as few cardiovascular events and exclusion of patients with history of cardiovascular disease.

3.2. *RCTs reporting adverse cardiovascular events from LABA/LAMA combination therapy for management of COPD*

LABA and LAMA both exert airway bronchodilation through distinct pharmacological mechanisms, and LABA-LAMA combinations are expected to have an efficacy benefit in COPD patients, which have been examined in RCTs along with assessment of adverse cardiovascular effects, including cardiovascular outcomes. Table 1 also details relevant clinical trials assessing the impact of a LABA/LAMA combination therapy on the risk of CVD among COPD patients. A 52-week, randomized, double-blind FLAME trial of 1680 COPD patients revealed that use of the LABA indacaterol 110 μg plus the LAMA glycopyrronium 50 μg yielded similar fatal cardiac events compared to use of the LABA salmeterol 50 μg plus inhaled corticosteroid fluticasone 500 μg (9 versus 11 events), although the fatal events were quite small [41]. Martinez et al. conducted two RCTs of 2103 and 1615 moderate-to-very severe COPD patients, respectively, and reported that patients randomly allocated to glycopyrrolate/formoterol 18/9.6 μg had a similar incidence rate of CVD compared to those receiving glycopyrrolate or formoterol monotherapy or placebo, despite few reported cardiovascular events [42]. Use of olodaterol-tiotropium 5/5 μg versus tiotropium 5 μg once daily for management of moderate-to-severe COPD was not found to increase major adverse cardiovascular events (2% versus 2%) in a 52-week, randomized, double-blind, active-controlled trial, whereas more than 90% of patients were already receiving medication regimens including LABAs or LAMAs at baseline [43]. The InforMing the PAthway of COPD Treatment (IMPACT) study was a randomized, double-blind, multicenter trial of 10,355 patients with COPD, who were randomly allocated to receive 52 weeks of a once daily triple therapy of fluticasone/umeclidinium/vilanterol 100/62.5/25 μg, a dual therapy of fluticasone/vilanterol 100/62.5 μg, or a dual combination of umeclidinium/vilanterol 62.5/25 μg. No clinically relevant differences in electrocardiographic (ECG) measurements were observed among the treatment groups, nor were differences found in the proportion of patients encountering cardiovascular events among the three inhalation regimens (triple therapy: 11%; fluticasone-vilanterol: 10%; umeclidinium-vilanterol: 11%). However, approximately 70% of the patients enrolled in the IMPACT trial had received either LABA or LAMA on trial entry, and patients with severe cardiac disease or abnormal 12-lead ECG were excluded at baseline [44]. Other

Table 1 – Randomized trials reporting adverse cardiovascular events with LABA and LAMA use for COPD management.

Reference	Design	Follow-up time	Subjects	Exclusion for CVD	Intervention arms	Primary outcomes	Secondary CVD outcomes	CVD related results
Calverley et al. (2007) [17]	Randomized double-blind, placebo controlled study	3 years	Moderate-to-severe COPD patients aged between 40 and 80 years	Diseases that could interfere with the study outcome, including fatal cardiovascular events	Salmeterol 50 μg (n = 1542) *vs.* Fluticasone 500 μg (n = 1552) *vs.* Salmeterol + Fluticasone 50/500 μg (n = 1533) *vs.* Placebo (n = 1524)	All-cause mortality	Any adverse cardiovascular events	No excess of cardiac disorders among patients treated with the combination regimen or salmeterol alone.
Tashkin et al. (2008) [18]	Randomized, double-blind, placebo-controlled study	4 years	Moderate-to-severe COPD patients aged ≧40 years	Prior history of MI, any unstable or life threatening cardiac arrhythmia and HF	Tiotropium 18 μg (n = 2987) *vs.* Placebo (n = 3006)	Annual rates of decline in FEV_1 and FVC	Cardiac disorders of MI, stroke, HF, AF	16% reduced risk of CVD with tiotropium *vs.* placebo.
Donohue et al. (2010) [34]	Randomized, double-blind, placebo- controlled study	26 weeks	Moderate-to-severe COPD patients aged ≧40 years	Not mentioned	Indacaterol 150 μg (n = 416) *vs.* Indacaterol 300 μg (n = 416) *vs.* Tiotropium 18 μg (n = 415) *vs.* Placebo (n = 418)	Spirometry data, dyspnea by TDI score and COPD exacerbations	ECG and general cardiac disorders	5.7% cardiac disorders for the two indacaterol doses combined and 5.6% for tiotropium group, compared with 3.8% for placebo.
Dahl et al. (2010) [33]	Randomized, double-blind, double-dummy, placebo- controlled study.	52 weeks	Moderate-to-severe COPD patients aged ≧40 years	Not mentioned	Indacaterol 300 μg (n = 437) *vs.* Indacaterol 600 μg (n = 425) *vs.* Formoterol 12 μg (n = 425) *vs.* Placebo (n = 432)	Spirometry FEV1	ECG assessment, blood pressure and pulse rate measurements	No observed CVD events.
Jones et al. (2012) [36]	Randomized double-blind, placebo- controlled study	24 weeks	Moderate-to-severe COPD patients aged ≧40 years	Unstable cardiac conditions, including MI	Aclidinium 400 μg (n = 272) *vs.* Aclidinium 200 μg (n = 280) *vs.* Placebo (n = 276)	Spirometric measurements, health status using SGRQ, dyspnea with BDI and TDI score and COPD exacerbations	Any CVD events and 12-lead ECG	Two cardiovascular deaths in the two aclidinium treatment groups. No clinically relevant changes in the primary outcome measurements.
Decramer et al. (2013) [35]	Randomized, double-blind, placebo- controlled study	52 weeks	Severe COPD patients aged ≧40 years	Not mentioned	Indacaterol 150 μg (n = 1721) *vs.* Tiotropium 18 μg (n = 1718)	Spirometry (FEV_1 and FVC), COPD exacerbations, and dyspnea using SGRQ scores	ECG and serious cardiac adverse events, including myocardial ischaemia, MI, Angina, AF, HF	No statistically significant differences in CVD between the two groups.
Wedzicha et al. (2013) [38]	Randomized, double-blind, placebo- controlled study	64 weeks	Severe COPD patients aged ≧40 years	History of CAD, left ventricular failure, MI and most of type arrhythmia; long QT syndrome and abnormal ECGs	Indacaterol + Glycopyrronium 110/50 μg (n = 729) *vs.* Glycopyrronium 50 μg (n = 740) *vs.* Tiotropium 18 μg (n = 737)	The rate of moderate or severe COPD exacerbations	Cardio- and cerebrovascular safety, including MACE, AF or atrial flutter and ECG reports	A comparable proportion of patients with cardio- and cerebrovascular events across three groups.
Koch et al. (2014) [32]	Randomized, double-blind, double-dummy, placebo- controlled studies	48 weeks	Moderate-to-severe COPD patients aged ≧40 years	History of MI, cardiac arrhythmia, HF and clinically evident paroxysmal tachycardia	Olodaterol 5 μg (n = 227) *vs.* Olodaterol 10 μg (n = 225) *vs.* Formoterol 12 μg (n = 227) *vs.* Placebo (n = 225)	Spirometry data such as FEV1 and dyspnea by TDI focal score	12-lead ECG and 24-h Holter monitoring	No observed cardiac adverse events.

Mahler et al. (2014) [39]	Randomized, blinded, double-dummy, placebo-controlled with three-period crossover study	6 weeks	Moderate-to-severe COPD patients aged ≧40 years	Long QT syndrome or QTc > 450 ms at screening; a clinically significant ECG abnormality	Indacaterol + Glycopyrronium 110/50 μg (n = 223) *vs.* Tiotropium 18 μg (n = 220) *vs.* Placebo (n = 218)	Dyspnea with BDI and TDI score	ECGs, cardio- and cerebrovascular adverse events including sudden cardiovascular death	The overall incidence of adverse cardiovascular events was similar across two treatment groups, which was slightly lower than the placebo group.
Decramer et al. (2014) [45]	Randomized, blinded, double-dummy studies	24 weeks	Moderate-to- very severe COPD patients aged ≧40 years	Patients with an abnormal and significant 12-lead ECG finding or clinically significant CVD	Study 1 and 2: total eight comparisons (n = 203–222) Umeclidinium + Vilanterol 125/25 μg or Umeclidinium + Vilanterol 62.5/25 μg *vs.* Tiotropium 18 μg or Vilanterol 25 μg or Umeclidinium 125 μg	Spirometry FEV_1	12-lead ECG and any other serious adverse events	Two deaths in study 1 including HF in the vilanterol group and cardiac arrest in the umeclidinium + vilanterol 62.5/25 μg group. No significant differences recorded in ECG.
Celli et al. (2014) [46]	Randomized, double-blind, placebo- controlled study	24 weeks	Moderate-to-severe COPD patients aged ≧40 years	Any clinically significant uncontrolled disease or an abnormal and significant ECG or 24-h Holter finding	Umeclidinium + Vilanterol 125/25 μg (n = 403) *vs.* Umeclidinium 125 μg (n = 407) *vs.* Vilanterol 25 μg (n = 404) *vs.* Placebo (n = 275)	Spirometry FEV_1	12-lead ECG, 24-h Holter monitoring and any other adverse events	Similar incidence rate of adverse events across treatment groups and no clinically meaningful changes in 12-lead and Holter ECG parameters.
Buhl et al. (2015) [47]	Randomized, double-blind, active- controlled, five-arm studies	52 weeks	Moderate-to- very severe COPD patients aged ≧40 years	History of MI, life-threatening cardiac arrhythmia, HF and paroxysmal tachycardia	Tiotropium + Olodaterol 2.5/5 μg (n = 1030) *vs.* Tiotropium + Olodaterol 5/5 μg (n = 1029) *vs.* Tiotropium 5 μg (n = 1033) *vs.* Tiotropium 2.5 μg (n = 1032) *vs.* Olodaterol 5 μg (n = 1038)	Three primary end points, including FEV_1 area under the curve (AUC), trough FEV_1 and SGRQ total score	12-lead ECG and 24-h Holter monitoring and any cardiac adverse events	No significant abnormalities in ECG and Holter monitoring and no significant risk of MACE and any cardiac adverse events respectively in rate ratios across all comparisons.
Vestbo et al. (2016) [19]	Randomized double-blind placebo controlled, with event-driven study	3 years	Moderate COPD patients aged between 40 and 80 years	Severe heart failure (New York Heart Association Class IV or ejection fraction <30%)	Fluticasone 100 μg (n = 4135) *vs.* Vilanterol 25 μg (n = 4118) *vs.* Fluticasone + Vilanterol 100/25 μg (n = 4121) *vs.* Placebo (n = 4111)	All-cause mortality	Composite cardiovascular endpoint of cardiovascular death, MI, stroke, unstable angina, and TIA	No excess of cardiac disorders across all treatment groups compared with placebo.
LaForce et al. (2016) [37]	Randomized double-blind, placebo- controlled study	12 weeks	Moderate-to-severe COPD patients aged ≧40 years	History of long QT syndrome, other abnormal ECG; clinically significant CAD, HF and arrhythmia	Glycopyrrolate 15.6 μg (n = 222) *vs.* Placebo (n = 219)	Standardized area under the curve (AUC) for FEV_1	ECG and all serious cardio- and cerebrovascular events	CVD outcomes are similar between two treatment group, except for MACE (Glycopyrrolate: 0.9% vs Placebo: 2.3%).
Wedzicha et al. (2016) [41]	Randomized, double-blind, double-dummy, non-inferiority trial	52 weeks	Severe COPD patients aged ≧40 years	History of abnormal QTc and ECG, CAD, HF and paroxysmal atrial fibrillation	Indacaterol + Glycopyrronium 110/50 μg (n = 1680) *vs.* Salmeterol + Fluticasone 50/500 μg (n = 1682)	Annual rate of mild, moderate, or severe COPD exacerbations	Serious cardio- and cerebrovascular events, and AF or atrial flutter events	A similar incidence of the adverse cardiovascular events between the two treatment groups.

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Table 1 – (*continued*)

Reference	Design	Follow-up time	Subjects	Exclusion for CVD	Intervention arms	Primary outcomes	Secondary CVD outcomes	CVD related results
Vogelmeier et al. (2016) [40]	Randomized, double-blind, double-dummy, active- controlled trial	24 weeks	Moderate-to-severe COPD patients aged ≧40 years	Not mentioned	Aclidinium + Formoterol 400/12 μg (n = 467) *vs.* Salmeterol + Fluticasone 50/500 μg (n = 466)	Spirometry peak FEV_1	Cardiac and cerebrovascular events and 12-lead ECG	A similar incidence of cardiac events in both treatment groups.
Singh et al. (2016) [48]	A randomized, parallel group, double-blind, active-controlled trial	52 weeks	Severe-to-very-severe COPD patients aged ≧40 years	Excluded significant cardiovascular conditions or laboratory abnormalities	Extrafine Beclometasone + Formoterol + Glycopyrronium (n = 687; fixed triple) *vs.* Beclometasone + Formoterol (n = 681)	FEV_1 and the TDI score	Major adverse cardiovascular events, including MI, arrhythmias, cardiovascular death, HF, and stroke	A similar incidence of major adverse cardiovascular events (triple therapy: 2%; dual therapy: 2%).
Martinez et al. (2017) [42]	Two randomized, double-blind, placebo controlled trials	24 weeks	Moderate-to- very severe COPD patients aged between 40 and 80 years	Excluded significant diseases other than COPD	Glycopyrrolate + Formoterol 18/9.6 μg (n = 526 in trial 1, 510 in trial 2) vs Glycopyrrolate 18 μg (n = 451, 439) *vs.* Formoterol 9.6 μg (n = 449, 437) *vs.* Placebo (n = 219, 223) *vs.* Tiotropium 18 μg (n = 541; only in trial 1)	Spirometry trough FEV_1 and health-related quality of life using SGRQ total score	ECG and any cardiovascular events	Low and similar incidence of cardiovascular events across treatment groups in both studies and no important trends in ECG.
Vestbo et al. (2017) [49]	A double-blind, parallel-group, randomized, controlled trial	52 weeks	Moderate-to-severe COPD patients aged ≧40 years	Excluded clinically significant cardiovascular conditions	Extrafine Beclometasone + Formoterol + Glycopyrronium (n = 2691; fixed triple) *vs.* Tiotropium (n = 1075) *vs.* Beclometasone + Formoterol + Tiotropium (n = 538; open triple)	The rate of moderate to severe COPD exacerbation	Ischemic heart disease, cardiac failure and arteriosclerosis coronary artery	A comparable incidence of ischemic heart disease among the three regimens (fixed triple: 31%; tiotropium: 33%; open triple: 29%).
Lipson et al. (2018) [44]	A phase 3, randomized, double-blind, multicenter trial	52 weeks	Moderate-to-severe COPD patients aged ≧40 years	Excluded abnormal QTc and ECG as well as unstable or life threatening cardiac disease	Fluticasone + Umeclidinium + Vilanterol 100/62.5/25 μg (n = 4151) *vs.* Fluticasone + Vilanterol 100/62.5 μg (n = 4134) *vs.* Umeclidinium + Vilanterol 62.5/25 μg (n = 2070)	Annual rate of moderate or severe exacerbations	Cardiovascular events; ECG measurements	The incidence of cardiac events was comparable among treatment groups (triple therapy: 11%; futicasone-vilanterol: 10%; umeclidium-vilanterol: 11%).
Calverley et al. (2018) [43]	A double-blind, randomized, parallel group, active controlled trial	52 weeks	Moderate-to-severe COPD patients aged ≧40 years	Excluded history of life-threatening cardiac arrhythmia and MI	Tiotropium + Olodaterol 5/5 μg (n = 3939) *vs.* Tiotropium 5 μg (n = 3941)	The rate of moderate and severe COPD exacerbations	Major cardiac adverse events	A similar incidence of adverse cardiovascular events between the two groups (2% *vs.* 2%).

Abbreviations: LABA, long-acting β_2 agonists; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonists; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; disease; MI, myocardial infarction; HF, heart failure; FEV_1, forced expiratory volume in 1 second; FVC, forced volume vital capacity; TDI, transition dyspnea index; ECG, electrocardiography; SGRQ, St. George's Respiratory Questionnaire score; BDI, baseline dyspnea index; CAD, coronary artery disease; MACE, major adverse cardiovascular events; AF, atrial fibrillation; TIA, transient ischemic attack.

Table 2 – Observational studies evaluating risk of cardiovascular events with LABA and LAMA use in COPD patients.

Reference	Study design	Population	Exclusion for CVD	New-user design (yes/no)	Exposures	Cases or outcome definitions	Results
AU et al. (2000) [12]	Case-control design	Cases: postmenopausal women and hypertensive male aged 30–79 years Controls: patients aged 30–79 years	Excluded prior MI	Yes, but no exclusion of exposure prior to cohort entry.	Any MDI β-agonist prescriptions in the two years before the index/ event date, and new use, defined as β-agonists prescription only filled for one time in the 90 days before the index date.	Incident nonfatal or fatal MI	MDIβ-agonists vs non-use: aOR (95%CI) New use: 1.67 (1.07–2.60)[a]
Grosso et al. (2009) [58]	Self-controlled case-series design	Patients receiving any tiotropium prescription and diagnosed with ≧ 1 stroke event	Excluded carotid endarterectomy > 6 weeks prior to events	No.	Exposure periods in which patients using tiotropium or fluticasone plus salmeterol *vs.* other unexposed observation periods.	First-ever diagnosis of ischaemic, haemorrhagic or unspecified stroke within the study time window	IRR (95%CI) • Tiotropium: 1.5 (0.7–3.1) • ≦ 1 year exposed period of tiotropium: 1.0 (1.0–2.0) • Fluticasone + salmeterol: 1.3 (0.5–3.1)
Wilchesky et al. (2012) - Part 1 [13]	Nested case-control design	Saskatchewan cohort, COPD patients aged ≧55 years with at least one bronchodilator use	No exclusion of CVD	Yes, but no exclusion of exposure of interest preceding cohort entry.	One of the exposures was LABA use. Current use: a LABA prescription in 60 days preceding the index/ event date. Current new use: current use but no prescription in 61–365 days before the index/ event date.	Arrhythmic death or hospital admission with a primary discharge diagnosis of arrhythmia	LABA *vs.* non-use: aOR (95%CI) • Current use: 1.13 (0.53–2.43) • Current new use: 4.55 (1.43–14.45)[a] • No current new use: 0.72 (0.27–1.90)
Wilchesky et al. (2012) - Part2 [14]	Nested case-control design	Quebec Cohort, COPD patients aged ≧67 years with at least one bronchodilator use	No exclusion of CVD	Yes, but no exclusion of LABA use preceding cohort entry	One of the exposures was LABA use. Current use: a LABA prescription in 60 days preceding the index/ event date. Current new use: current use but no prescription in 61–365 days before the index/ event date.	Arrhythmic death or hospital admission with a primary discharge diagnosis of arrhythmia	LABA *vs.* non-use: aOR (95%CI) • Current new use: 1.47 (1.01–2.15)[a] • No current new use: 1.06 (0.88–1.27)

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Table 2 – (*continued*)

Reference	Study design	Population	Exclusion for CVD	New-user design (yes/no)	Exposures	Cases or outcome definitions	Results
Gershon et al. (2013) [15]	Nested case–control design	COPD patients aged ≧66 years and receiving ≧1 COPD medication	No exclusion of CVD	Yes, but no exclusion of LABA or LAMA prior to cohort entry	New LABA and LAMA use defined as any LABA and LAMA prescription within 90 days of the index/event date and not receiving any same medication in the previous year.	A hospital or an ED visit for cardiovascular events, including acute coronary syndrome (including MI), HF, ischemic stroke, or cardiac arrhythmia	aOR (95%CI) New use *vs.* non-use: • LABA: 1.31 (1.12–1.52)[a] • LAMA: 1.14 (1.01–1.28)[a] New LABA vs. new LAMA: 1.15 (0.95–1.38)
Lee et al. (2015) [54]	Nested case-control design	Patients dispensing inhaled respiratory drugs for 30 days or longer	Excluded acute major CVD events including MI, stroke and tachyarrhythmia during the year prior to the cohort entry	Yes, excluded inhaled respiratory drugs during the year before cohort entry	LABA, LAMA and ICS + LABA, defined based on the inhaler prescriptions for 30 days or longer during the 90-day before the index/event date.	First-time diagnosis of tachyarrhythmia	aOR (95%CI) • LABA: 1.16 (1.02–1.32)[a] • LAMA: 1.24 (1.005–1.54)[a] • LABA + LAMA: 1.51 (1.15–1.98)[a] • LABA *vs.* LAMA: 0.93 (0.74–1.18)
Tsai et al. (2015) [56]	Cohort design	COPD patients aged ≧18 years	Excluded stroke, HF, VA, MI, or angina before the index date	No.	LAMA + LABA and LABA + ICS combinations *vs.* LABA only.	Incident cardio-cerebrovascular events including hospital for stroke, HF, VA, MI, or angina.	Combinations *vs.* LABA: aHR (95%CI) • Cardio- cerebrovascular events: 1.18 (1.04–2.93)[a] • MI: 0.20 (0.03–14.20) • Angina: 0.15 (0.04–4.95) • HF: 1.22 (0.43–3.86) • VA: 0.75 (0.24–4.27) • Stroke: 1.04 (1.06–2.99)[a]
Dong et al. (2016) [51]	Cohort design	COPD patients aged ≧ 40 years initiating inhaled long-acting bronchodilators	No exclusion of CVD	Yes. Excluded LABA or LAMA within 1 year before cohort entry date	LAMA or LABA only, and LABA + LAMA.	First hospitalization for a composite cardiovascular event, comprising MI, HF, or cerebrovascular diseases (including ICH or ischemic stroke)	aHR (95%CI) Intention to treat: • LABA *vs.* LAMA: 1.09 (0.87–1.37) • LABA + LAMA *vs.* LAMA: 1.13 (0.60–2.13) As treated analysis: • LABA *vs.* LAMA: 0.97 (0.67–1.39) • LABA + LAMA *vs.* LAMA: 1.26 (0.74–2.15)
Suissa et al. (2017) [53]	HDPS-matched cohort design	COPD patients aged ≧55 years with LABA or tiotropium use	No exclusion of CVD	Yes. Excluded any prescription of LABA or tiotropium during the previous 2 years before cohort entry	LABA added to tiotropium or vice versa *vs.* monotherapy.	MI, HF, stroke based on general practitioner's diagnostic code and arrhythmia from hospitalization diagnoses	LABA + LAMA *vs.* LABA or LAMA: aHR (95%CI) •MI: 1.06 (0.89–1.25) •HF: 1.14 (1.03–1.26)[a] • Stroke: 0.94 (0.77–1.15) • Arrhythmia: 1.01 (0.81–1.26)

Samp et al. (2017) [59]	PS-matched cohort design	COPD patients aged ≧ 40 years initiating a LABA + LAMA or LABA + ICS	No exclusion of CVD	Yes. Excluded patients with a claim for a LABA + LAMA or LABA + ICS during 30 days prior to the index date	LABA + LAMA *vs.* LABA + ICS.	One hospitalization for a cardiovascular event including CAD, HF or cardiac dysrhythmia or a cerebrovascular event comprised of stroke or TIA	LABA + LAMA *vs.* LABA + ICS: HR (95%CI) • Cardiovascular events: 0.79 (0.62–0.99)[a] • Cerebrovascular events: 1.17 (0.65–1.96)
Suissa et al. (2017) [52]	HDPS-matched cohort design	COPD patients aged ≧ 55 years using LABA or tiotropium	No exclusion of CVD	Yes. Excluded prevalent users of LABA or tiotropium at cohort entry	New users of LABA or tiotropium.	MI, HF, stroke based on general practitioner's diagnostic code and arrhythmia from hospitalization diagnoses	Tiotropium *vs.* LABA: aHR (95%CI) • MI: 1.10 (0.88–1.38) • HF: 0.90 (0.79–1.02) • Stroke: 1.02 (0.78–1.34) • Arrhythmia: 0.81 (0.60–1.09)
Liou et al. (2018) [55]	DRS-matched nested case–control design	COPD patients aged ≧40 years and receiving LABA and ICS combination	Excluded congenital heart disease and CVD at cohort entry	Yes. Excluded any tiotropium prescription filled in the year before cohort entry	Added tiotropium use in the year before the index/event date, further classified by different recency of therapy, new and prevalent use.	First inpatient or ED visit with a primary diagnosis of CAD, HF, ischemic stroke, or cardiac arrhythmia	Tiotropium *vs.* non-use: aOR (95%CI) • Any use: 1.09 (0.96–1.23) • Current use: 1.16 (0.99–1.35) • Current new use: 1.88 (1.44–2.46)[a]
Wang et al. (2018) [16]	DRS-matched nested case–control design	COPD patients aged ≧40 years and receiving ≧1 COPD medication	No exclusion of CVD	Yes. Excluded any LABA or LAMA therapy in 1 year preceding cohort entry	LABA and LAMA use in the year before the index/event date, further classified as different recency of therapy, new use and prevalent use.	Inpatient or ED visit with a primary diagnosis of CAD, HF, ischemic stroke, or cardiac arrhythmia	Current use: aOR (95%CI) • LABA: 1.06 (0.99–1.12) • LAMA: 1.00 (0.92–1.10) • LABA + LAMA: 1.16 (1.05–1.28)[a] Current new use: aOR (95%CI) • LABA: 1.50 (1.35–1.67)[a] • LAMA: 1.52 (1.28–1.80)[a] • LABA + LAMA: 2.03 (1.42–2.91)[a] • LAMA vs LABA: 1.01 (0.82–1.23)

Abbreviations: LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonists; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MDI, metered dose inhaler; aOR, adjusted odds ratio; 95%CI, 95% confidence interval; IRR, incidence rate ratio; CVD, cardiovascular disease; ED, emergency department; HF, heart failure; ICS, inhaled corticosteroid; VA, ventricular arrhythmia; HR, hazard ratio; aHR, adjusted hazard ratio; ICH, intracerebral hemorrhage; PS, propensity score; HDPS, high dimensional propensity score; DRS, disease risk score; TIA, transient ischemic attack; CAD, coronary artery disease.

[a] Statistically significant.

randomized trials examining LABA-LAMA combinations, including umeclidinium/vilanterol 125/25 μg [45,46], tiotropium plus olodaterol 5/5 μg [47], aclidinium plus formoterol 400/12 μg [40], and extrafine beclometasone/formoterol/glycopyrronium 100/6/12.5 μg [48,49] were not found to increase the cardiovascular risk relative to the comparative arm.

3.3. *Possible reasons for the null findings on cardiovascular endpoints with use of LABAs and LAMAs for management of COPD in RCTs*

There exist several possible reasons for observing no increased risk of cardiovascular disease from inhaled long-acting bronchodilators for management of COPD in randomized trials. First, all of the trials measured cardiovascular end points as a secondary outcome, and they were not statistically powered for examining adverse cardiovascular events. Second, "depletion of the susceptible" might have confounded the cardiovascular safety findings reported from RCTs. Rates of drug-induced adverse events usually peak during the initial time period of drug use and decrease thereafter with a longer treatment [50]. If that is the case for LABA- and LAMA-associated cardiovascular events, most COPD patients enrolled in randomized trials could have developed tolerability to the adverse cardiac events because the majority of the patients included in trials were not LABA-naïve or LAMA-naïve patients. Third, most RCTs excluded patients with a history of cardiovascular disease, a comorbidity highly coexisting with COPD, which may exclude a subgroup of patients at high risk for adverse cardiovascular events. For instance, patients with a history of cardiac arrhythmias, myocardial infarction, or heart failure were excluded from the UPLIFT. Fourth, the impact of additional use of other COPD medications during follow-up on adverse cardiovascular events was not addressed. For example, all of the trials allowed patients to receive rescue medications for COPD exacerbation, such as salbutamol, an individual short-acting β_2 agonist (SABA), whereas placebo groups were expected to receive more rescue medications than did treatment groups. Given inhaled SABAs have also been tied with an increased risk of CVD [12], the imbalanced use of SABAs between treatment and control groups, if any, may have masked the increased risk of cardiovascular events from the use of LABAs or LAMAs in patients with COPD.

3.4. *Overall findings from randomized trials assessing cardiovascular safety of inhaled long-acting bronchodilators in patients with COPD*

Taken together with the findings from the aforementioned RCTs, use of LABAs and LAMAs does not lead to an excess risk of adverse cardiovascular events in patients with COPD, and several clinical randomized trials have even reported a protective cardiovascular effect with use of either type of inhaled long-acting bronchodilators. These findings provide reassuring evidence of cardiovascular safety from inhaled long-acting bronchodilators in patients with COPD, whilst the aforementioned study limitations need to be acknowledged when interpreting the cardiovascular data from randomized trials.

4. Evidence of COPD observational studies examining risk of adverse cardiovascular events with LABAs and LAMAs

Observational studies examining cardiovascular safety of inhaled long-acting bronchodilators for management of COPD often generate findings more closely to reflect real-world medical practice, and consequently could provide the safety evidence with high generalizability. Observational studies have examined adverse cardiovascular events as a primary outcome, and usually evaluated cardiovascular safety of LABA and LAMA in a broad population of COPD patients, such as those with various comorbid conditions [13–16,51–53]. Additionally, LABA- or LAMA-naïve patients diagnosed with COPD had also been examined in observational studies [12–16,51–55], among whom the cardiovascular effect with new initiation of LABA or LAMA, if any, could be revealed. By contrast, observational studies are prone to confounding and bias, which poses a threat to the accuracy of the findings generated from this type of study design. Due to lack of random allocation to treatments in observational studies, measured and unmeasured confounders could be imbalanced between comparison groups, and could cause a spurious observed association. Bias could also occur and distort an observed association with adoption of observational study designs. For instance, decisions for prescribing LABA or LAMA in COPD patients are typically based on uncontrolled COPD disease or exacerbations, which may relate to the development of CVD, and the comparison of LABA or LAMA use versus nonuse of the bronchodilators regarding the differences in the cardiovascular risk could accordingly introduce confounding by indication bias.

4.1. *Observational studies reporting an increased risk of adverse cardiovascular events from LABA or LAMA use in COPD patients*

Table 2 presents characteristics of observational studies reporting that use of LABAs or LAMAs alone or in combination relative to nonuse or LABA or LAMA monotherapy was associated with an elevated risk of adverse cardiovascular events among patients with COPD, ranging from 1.04-fold to 4.55-fold [12–16,53–56]. These studies adopted either a nested case–control design [13–16,54,55] or a cohort design [53,56], and most of which analyzed COPD patients with comorbid conditions, including those with history of CVD [13–16,53].

Starting a LABA or LAMA therapy for management of COPD has been tied to an increased cardiovascular risk in several observational studies [12–16]. An earlier study revealed a 1.67-fold (95% 1.07–2.60) increased risk of myocardial infarction among patients who first filled one inhaled β_2 agonist prescription [12], but the study did not single out use of LABA nor confined to COPD patients. In addition, Wilchesky et al. conducted two studies and concluded that current new use of

LABA versus nonuse was associated with a 1.47-fold–4.55-fold increased risk of arrhythmic death, while the findings might be subjected to random error and selection bias [13,14]. Gershon et al. conducted a nested case–control study of 190,000 COPD patients aged ≥66 years, and reported that new use of LABA and LAMA was associated with a 1.31-fold (95% CI, 1.12–1.52) and 1.14-fold (95% CI, 1.01–1.28) increased risk of hospital or emergency room admission for CVD, respectively, compared to nonuse [15]. New initiation of therapy was defined as a prescription of LABA or LABA in the 90 days preceding the index/event date and without any prescription-refill records of the same medication in the year preceding the index/event date. This nested case–control study [15], however, observed unbalanced baseline characteristics between cases and controls, such as prior cardiovascular disease, and dropped more than 50% of eligible cases. A disease risk score (DRS)-matched nested case–control study of 278,000 COPD patients found that new initiation of LABA and LAMA carried an approximately 1.5-fold increased cardiovascular risk, respectively, irrespective of COPD severity and CVD history [16]. This study first revealed that new use and duration of LABA and LAMA both acted as an important effect modifier of the therapy-related adverse cardiovascular effect in COPD patients [16]. Specifically, the authors discovered that the cardiovascular risk peaked during the 30th day after new initiation of LABA or LAMA therapy, attenuated for 31 days to 60 days of therapies, and reversed to a reduced risk with 71–240 days of use [16]. Confounding was addressed in the study with use of a DRS-matched approach, which balanced all measured factors between cases and controls at cohort entry; nevertheless, residual confounding could not be completely ruled out because several confounders measured preceding the index/event date remained imbalanced between the two comparison groups, although for which statistical adjustment was performed [16]. In addition, the similar findings were reached with adoption of an active comparison with new use of theophylline, an oral bronchodilator in COPD [16], whereas the concern of confounding by indication bias for the reported data had still been raised [57].

Although timing of LABA and LAMA use was not addressed, additional two observational studies also revealed a 1.04-fold–1.24-fold increased risk of cardiovascular events associated with LABA and LAMA therapy for management of COPD [54,56]. The findings of these reports, however, should be interpreted with the context of potential selection bias and few adverse cardiovascular events.

4.2. *Observational studies reporting no association between LABA or LAMA use and risk of CVD in patients with COPD*

Two observational studies reported no increased risk of cardiovascular events from LABA and LAMA therapy for management of COPD as compared with nonuse [51,58]. While discrepancies of the cardiovascular safety findings among observational studies with positive and negative findings may reflect differences in study designs, clinical settings, and patient characteristics, the two reports with null findings observed a small number of cardiovascular events, and therefore the possibility that random error caused the non-significant observations could not be dismissed.

4.3. *A head-to-head comparison of LABA versus LAMA or vice versa regarding adverse cardiovascular events in observational studies*

Observational studies have consistently revealed a comparable risk of CVD between LABAs and LAMAs for management of COPD [15,16,51,52,54], although a reduced cardiovascular risk with LABA/LAMA versus LABA plus inhaled corticosteroid combination has been reported [59]. A head-to-head comparison of risk of adverse cardiovascular outcomes between LABA and LAMA, however, serves as a double-edged sword. Comparison of LABA with LAMA or vice versa for adverse cardiovascular outcomes can minimize confounding by indication bias, but even though a comparable cardiovascular effect is observed, it does not ensure that either type of inhaled long-acting bronchodilators is free of the cardiovascular risk.

4.4. *Study limitations of observational studies evaluating adverse cardiovascular events with LABA and LAMA in COPD*

Although a body of evidence of observational studies has linked use of inhaled long-acting bronchodilator drugs with the risk of CVD, the interpretation of these results needs to be cautious due to the possibility of the presence of bias and confounding. Specifically, several biases such as selection bias and confounding by indication bias may present, and confounders, especially unmeasured confounding, including pulmonary function and smoking status were not well addressed in observational studies. It is uncertain the degree to which the bias and confounding affect the reported positive findings on the cardiovascular safety of LABA and LAMA in these studies.

4.5. *Overall findings of observational studies assessing cardiovascular safety with use of inhaled long-acting bronchodilators in COPD*

Collectively, observational studies revealed inconsistent findings regarding cardiovascular safety of inhaled bronchodilator used for treatment of COPD, but provided new insights on the cardiovascular safety issue. Two studies reported null associations, but they could have suffered insufficient statistical power for observing few cardiovascular events. On the other hand, others reported a 1.04-fold–4.55-fold increased risk of CVD from LABA or LAMA use, but inherent study limitations of confounding and bias from these studies need to be acknowledged. If a true association between use of inhaled long-acting bronchodilators and risk of cardiovascular disease does exist, the observational studies have pinpointed out that the risk is particularly most likely to be tied with new use of LABA and LAMA in patients with COPD, especially during the first 30 days of therapy initiation. This finding allows healthcare professionals to set a specific time period for closely monitoring any symptoms of adverse cardiovascular events in COPD patients receiving inhaled long-acting bronchodilators. It should also be emphasized that the positive findings cannot

be interpreted as replacement of LABAs and LAMAs with SABAs or short-acting muscarinic antagonists (SAMAs) for management of COPD because: 1) LABA and LAMA are more effective than SABA and SAMA in management of COPD disease; and 2) SABA and SAMA are also concerned for an increased risk of adverse cardiovascular events.

5. Future research directions for studies examining risk of CVD from LABA and LAMA for management of COPD

Future RCTs that exhibit the following attributes are needed to be performed to clear the air. First, large controlled trials should be designed with a sufficient statistical power to examine cardiovascular end points with LABA and LAMA therapies in patients with COPD. Second, it is recommended to enroll patients with diverse characteristics that can reflect COPD patients seen in present clinical settings, such as those with histories of cardiovascular disease and those with mild COPD severity, both of whom were generally severely undersampled in RCTs. Third, it may not be feasible to adopt a randomized trial design for enrolling LABA-naïve and LAMA-naïve patients, but strategies are urgently required to be explored and developed. Fourth, the use of other COPD medications during follow-up indeed needs to be considered when designing RCTs for evaluating the incidence of cardiovascular events as a primary outcome because placebo patients enrolled in clinical trials generally could receive usual COPD medications as they had received before enrollment, and all patients in treatment and placebo arms were typically allowed to use rescue medications for COPD exacerbation, such as salbutamol. This issue on the concomitant use of other COPD medications during follow-up is urgently required to be addressed in RCTs, given that several COPD medications have also been concerned for their potential to exert cardiovascular effects, such as SABAs and SAMAs.

Future observational studies need also to be conducted with improvements to provide robust findings of adverse cardiovascular risk from LABAs and LAMAs in COPD patients. New techniques and approaches to address confounding and bias are strongly needed for future observational studies, such as a high-dimensional propensity score approach and an instrumental variable analysis. Observational studies are recommended to further consider pulmonary function data, comprehensive histories and symptoms of exacerbation, and even health-related quality of life data for a better classification COPD severity and COPD phenotypes. Population-based electronic medical records are also suggested to be utilized for observational studies to be able to directly measure risk factors of cardiovascular disease and its occurrence. Also, given newer individual LABA and LAMA agents begin to emerge into the market, the new agents need to be examined for the cardiovascular safety in the real world.

6. Conclusion

We reviewed the current evidence of RCTs and observational studies on use of LABA and LAMA in relation to the risk of adverse cardiovascular disease among patients with COPD. The two types of study designs generated inconsistent findings. On one hand, a body of evidence from observational studies supports the possible link between the use of LABA or LAMA for management of COPD and the cardiovascular risk, whereas confounding and bias may not be entirely ruled out for the positive findings. On the other hand, RCTs have not documented an elevated cardiovascular risk with LABA or LAMA therapy in COPD patients, but the null findings may result from insufficient statistical power, exclusion of patients at high risk for cardiovascular disease, and lack of taking additional use of other respiratory medications during follow-up into account. Future RCTs and observational studies with overcoming the mentioned limitations are urgently required to clear the air regarding the cardiovascular safety of the inhalation therapy.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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