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Dual versus single long-acting bronchodilator use could raise acute coronary syndrome risk by over 50%: A population-based nested case–control study

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Background. Coronary heart disease occurs more frequently among patients with chronic obstructive pulmonary disease (COPD) compared to those without COPD. While some research suggests that long-acting bronchodilators might confer an additional risk of acute coronary syndrome (ACS), information from real-world clinical practice about the cardiovascular impact of using two versus one long-acting bronchodilator for COPD is limited. We undertook a population-based nested case–control study to estimate the risk of ACS in users of both a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-agonist (LABA) relative to users of a LAMA.

Methods. The study was based on the primary care PREDICT Cardiovascular Disease Cohort and linked data from regional laboratories and the New Zealand Ministry of Health's national data collections. The underlying cohort (n = 29,993) comprised patients aged 45–84 years, who initiated treatment with a LAMA and/or LABA for COPD between 1 February 2006 and 11 October 2016. 1490 ACS cases were matched to 13,550 controls by date of birth, sex, date of cohort entry (first long-acting bronchodilator dispensing), and COPD severity.

Results. Relative to current use of LAMA therapy, current use of LAMA and LABA dual therapy was associated with a significantly higher risk of ACS (adjusted OR = 1.72; [95% CI: 1.28–2.31]).

Conclusion. Dual long-acting bronchodilator therapy, rather than LAMA mono-therapy, could increase the risk of ACS by more than 50%. This has important implications for decisions about the potential benefit/harm ratio of COPD treatment intensification, given the modest benefits of dual therapy.

Keywords: acute coronary syndrome, bronchodilator agents, chronic obstructive pulmonary disease

Introduction

Coronary heart disease and chronic obstructive pulmonary disease (COPD) are important causes of morbidity and mortality globally [1] and in New Zealand [2–4].

Coronary heart disease occurs more commonly among patients with COPD compared to those without COPD [5, 6]. While this is partly because of common risk factors such as age and smoking, it has been suggested that increased systemic inflammation in COPD and impaired right and left heart function secondary to emphysema and lung hyperinflation also play a role [5, 6]. There is also concern that long-acting bronchodilators (long-acting muscarinic antagonists [LAMAs] and

long-acting beta2-agonists [LABAs]) might increase the risk of acute coronary events still further [7]. This is important because coronary events are responsible for more deaths than respiratory failure in patients with COPD [8] and meta-analyses of randomised controlled trials (RCTs) have found that the use of long-acting bronchodilators (as mono-therapy [9–12] or dual therapy [13–15]) is associated with relatively small patient-relevant benefits. Moreover, successive updates of the Global Initiative for Chronic Obstructive Lung Disease guidelines [16] and a recent American Thoracic Society clinical practice guideline [17] have recommended the combined use of a LAMA and LABA in patients whose symptoms are not well controlled. Information about the cardiovascular safety of using two versus one bronchodilator is limited and there have been calls for adequately powered pragmatic RCTs, as well as observational studies, to examine cardiovascular risk in real-world clinical settings [18].

In a recent case–control study nested within a national cohort of patients who initiated long-acting bronchodilator therapy for COPD, we found that current users of LAMA and LABA dual therapy had a higher risk of acute coronary syndrome (ACS) compared with current users of LAMA alone [19]. In that study, which was based on routinely collected national health and pharmaceutical dispensing data, we did not have access to information about several important predictors of cardiovascular disease (e.g. cholesterol/high-density lipoprotein [HDL] ratio values, blood pressure measurements, smoking status, body mass index, and family history of premature cardiovascular disease), so we were unable to completely rule out residual confounding by underlying cardiovascular risk. To address this issue, we initiated a new population-based case–control study based on a unique dataset that includes the data of all people who have undergone cardiovascular risk assessment in primary care in two regions of New Zealand. As with our national study, the primary aim of the present study was to estimate the risk of ACS in users of both a LAMA and LABA relative to users of a LAMA. Secondary aims were to estimate the risk of a composite acute ischaemic cardiovascular (AICV) event (ACS, ischaemic stroke, or transient ischaemic attack [TIA]) in relation to the same long-acting bronchodilator regimens, and to explore the risk of ACS and AICV according to history of cardiovascular disease, ethnicity, and concomitant inhaled corticosteroid (ICS) use.

Methods

Data sources and derivation of the study cohort

The source population for the study was the PREDICT Cardiovascular Disease Cohort [3, 20]. New Zealand cardiovascular disease prevention guidelines recommend that all people above a certain age have a cardiovascular risk assessment; the recommended age depends on sex, ethnicity, and the presence/absence of other risk factors [21]. The PREDICT cohort includes all patients whose cardiovascular risk has been assessed, using PREDICT decision support software, in primary care practices in two geographical regions since 2002 [3, 20]. Anonymised data available for PREDICT cohort members include a 'cardiovascular risk score' (the predicted 2- and 5-year risk of a new cardiovascular event for those with [20] and without [3] known cardiovascular disease, respectively, at the time of assessment) and linked data from regional laboratories and the Ministry of Health's National Collections (including the Pharmaceutical Collection [claims by community-based pharmacists for the dispensing of prescription drugs that are government-funded – most prescribed medicines], the National Minimum Dataset [NMDS, hospital discharges since 1988] and the Mortality Collection [inpatient and community-based deaths]) [22]. The study was approved by the Northern A Health and Disability Ethics Committee (reference: MEC/07/19/EXP/AM).

The steps we took to derive the study cohort from the PREDICT cohort are outlined in Fig. 1. First, we identified all patients who were dispensed a long-acting bronchodilator with or without an ICS between 1 February 2005 (when tiotropium was first listed on the pharmaceutical schedule) and 12 October 2016 (end of follow-up). We then excluded patients who were dispensed a long-acting bronchodilator before 1 February 2006 to avoid the bias that can arise from the inclusion of prevalent users [23]. Patients aged >84 years at cohort entry (date when the first long-acting bronchodilator was dispensed) were excluded as cardiovascular risk prediction is less reliable in this age group [24]. To minimise the possible inclusion of patients who used a LABA or LABA/ICS inhaler exclusively for asthma, we also excluded those aged <45 years as well as those who were dispensed a LABA or LABA/ICS inhaler at cohort entry without a concomitant LAMA product if they also had at least one hospital discharge diagnosis of asthma and no COPD diagnoses between 1988 and cohort

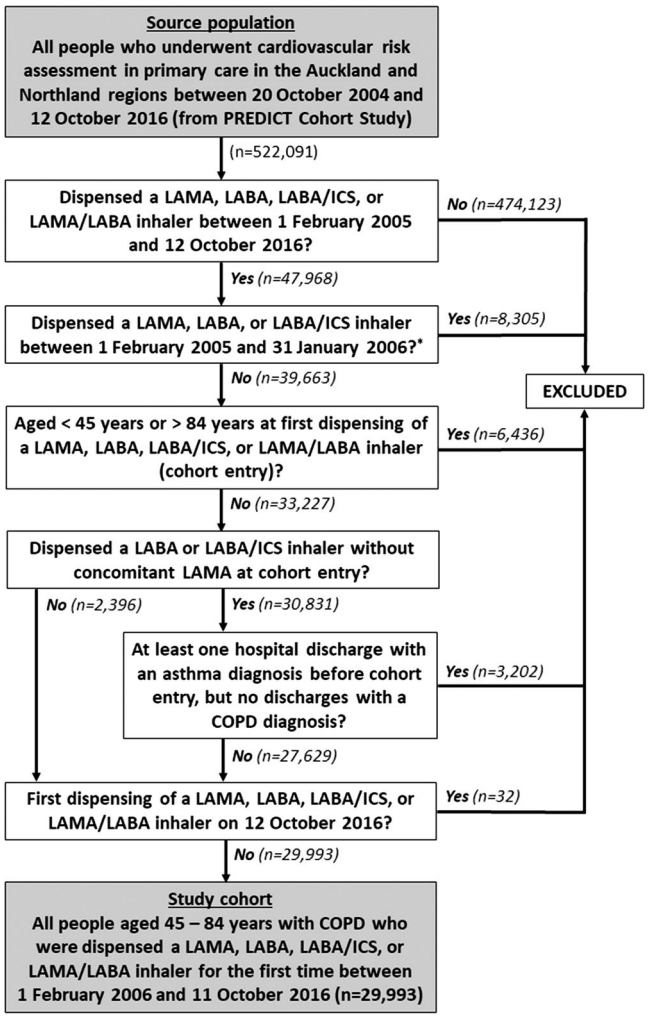

Fig. 1 Derivation of the study cohort.

entry. Finally, we excluded patients who entered the cohort on 12 October 2016 (the final day of follow-up) to ensure that long-acting bronchodilator exposure preceded any ACS and AICV events.

Summarising LAMA and LABA exposure in the study cohort

To summarise exposure to long-acting bronchodilators during follow-up, we used the same approach we have employed previously (Figs S1 and S2) [19, 25]. The data were combined into continuous episodes of use of nine mutually exclusive therapeutic regimens and then grouped into four exposure categories: LAMA and LABA dual therapy, LAMA therapy, LABA therapy, and ICS mono-therapy (Table 1). To allow secondary analyses stratified by ICS use, we grouped the nine regimens into seven exposure categories (Table S1).

Nested case–control analyses

Identification of cases. Cohort participants were classified as ACS cases if there was a record between cohort entry and 12 October 2016 of (i) a principal or additional hospital discharge diagnosis (coded using the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-AM-10)) of I200 (Unstable angina), I21 (Acute myocardial

Table 1. *Classification of exposure categories and regimens*

Exposure categories and regimens	Products included in the regimen
LAMA and LABA dual therapy	
LAMA/LABA + ICS	Concurrent use of LAMA/LABA combination product and ICS single-agent product
LAMA + LABA/ICS	Concurrent use of LAMA single-agent product and LABA/ICS combination product
LAMA + LABA + ICS	Concurrent use of three single-agent products (LAMA, LABA and ICS)
LAMA/LABA	Use of LAMA/LABA combination product only
LAMA + LABA	Concurrent use of LAMA and LABA single-agent products
LAMA therapy	
LAMA	Use of LAMA single-agent product only
LAMA + ICS	Concurrent use of LAMA and ICS single-agent products
LABA therapy	
LABA	Use of LABA single-agent product only
LABA + ICS	Concurrent use of LABA and ICS single-agent products
LABA/ICS	Use of LABA/ICS combination product only
ICS mono-therapy*	
ICS	Use of ICS single-agent product only

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist.
*By design, all cohort members had used a long-acting bronchodilator before the episode of ICS mono-therapy.

infarction), or I22 (Subsequent myocardial infarction, <28 days after a previous myocardial infarction), or (ii) death and any of the above ICD-10-AM rubrics were coded as the underlying cause of death. The AICV cases were cohort members for whom there was a principal or additional hospital discharge diagnosis coded to I200, I21, I22, I63 (Cerebral infarction), or G45 (TIA and related conditions; excluding G454), or the underlying cause of death was coded to any of these rubrics. The index date for each case and their matched controls was the date of the first event during follow-up.

Selection of controls

We used risk set sampling [26] to randomly select up to 10 controls for each case, matching by date of birth (±548 days), sex, date of cohort entry (±183 days), and COPD severity (Table S2).

Ascertainment of user status on the index date

We classified cases and controls as current users of LAMA and LABA dual therapy, LAMA therapy, or LABA therapy if there was use in the 30-day period before the index date (Fig. S3). The remaining individuals (those whose most recent therapy terminated more than 30 days before the index date and those whose only therapy in the 30 days before the index date was an ICS) were classified as unexposed. Likewise, for the analyses stratified by ICS use, we classified individuals as current users if the relevant exposure occurred in the 30-day period before the index date. If more than one therapy was used during that period, individuals were classified as being exposed to the most recent therapy.

Other covariates

Cardiovascular risk factor data, as well as other data from regional laboratories and the National Collections, were used to derive variables (including a multimorbidity index [27]) for descriptive purposes and multivariable analyses. We calculated primary and secondary cardiovascular risk prediction scores at cohort entry for descriptive purposes, and for risk equation variables that were recorded in primary care records as part of a cardiovascular risk assessment (e.g. smoking status) and/or involved laboratory tests (e.g. total cholesterol/HDL ratio), we used the values that were recorded (in primary care or laboratory records) closest to the cohort entry date (before or after). For other variables (e.g. history of atrial fibrillation), we only considered records up to, but not beyond, cohort entry.

The following covariates, which predominantly reflect the variables used in the risk prediction

equations, were chosen a priori for inclusion in the adjusted models: ethnicity (self-identified and prioritised according to the Ministry of Health Ethnicity Data Protocols [28]); deprivation (an area-based measure, NZDep [29]); family history of premature ischaemic cardiovascular disease; smoking status; systolic blood pressure; total cholesterol/HDL ratio; body mass index (BMI); a history before cohort entry of cardiovascular disease (defined as a history of any of the following: myocardial infarction, angina, ischaemic or haemorrhagic stroke, TIA, peripheral vascular disease [PVD], use of angina medications, or a cardiac, stroke, TIA, or PVD procedure); a hospital discharge diagnosis before cohort entry and (separately) between cohort entry and the index date of heart failure, atrial fibrillation, life-threatening arrhythmia, diabetes; a hospital discharge diagnosis between cohort entry and the index date of other ischaemic cardiovascular conditions (defined as stable angina, ischaemic stroke, TIA, or PVD for the ACS analyses; stable angina or PVD for the AICV analyses); use in the 6 months before cohort entry and (separately) in the 6 months before the index date of lipid lowering, antiplatelet, anticoagulant, blood pressure lowering, and non-steroidal anti-inflammatory medications.

Statistical methods

In the primary analysis, we estimated the risk of ACS in users of LAMA and LABA dual therapy, and LABA therapy, relative to LAMA therapy. A secondary analysis examined the risk of AICV in relation to the same therapeutic groups. In addition, we undertook secondary analyses for ACS and AICV that were stratified by history of cardiovascular disease at cohort entry, ethnicity (Māori, Pacific, Indian group [high-risk populations in New Zealand [3]]/non-Māori, non-Pacific, non-Indian group), and ICS exposure in the 30 days before the index date.

We used conditional logistic regression to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). As it was necessary to break the matching to undertake the secondary stratified analyses, we used logistic regression and included the matching factors in the model along with the other covariates. We used chained equations [30], based on all the data included in the analysis, to impute the small amount of missing data for BMI and the total cholesterol/HDL ratio; the data were assumed to be missing at random. Fifty datasets were imputed using a run-in of 150. STATA version 14.0 was used for all analyses.

Estimation of incidence rates

To estimate crude incidence rates of ACS and AICV in users of LAMA and LABA dual therapy, LAMA therapy, and LABA therapy, we divided the number of cases occurring during an episode of use of the therapy of interest by the total person-years of exposure to that therapy (censored at the index date for cases). The mid-P exact method was used to calculate 95% CIs [31]. We also calculated age- and sex-adjusted rates with 95% CIs [32], and crude and age- and sex-adjusted rates by ethnicity; the age and sex distribution of the total New Zealand population was the standard.

Role of funding source

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Results

The study cohort included 29,993 patients who commenced treatment with a long-acting bronchodilator between 1 February 2006 and 11 October 2016 (Fig. 1). In total, 1503 had an ACS event and 2152 had an AICV event during 121,728 and 120,122 person-years of follow-up, respectively. We excluded 13 ACS and 19 AICV cases from the case–control analyses as no controls could be found for them. The characteristics of the ACS cases and their controls at cohort entry are shown in Table 2 and Table S3. The characteristics at any time before the index date are shown in Table S4. The corresponding data for the AICV cases and controls are shown in Tables S5 and S6.

In the primary analysis, current users of LAMA and LABA dual therapy were 1.72 times as likely as current users of LAMA therapy to have an ACS event (adjusted OR = 1.72; [95% CI: 1.28–2.31] [Table 3]). Current users of LABA therapy and current users of LAMA therapy had comparable risks (adjusted OR = 1.06; [95% CI: 0.82–1.37]). The OR for patients who were not currently using a long-acting bronchodilator versus current users of LAMA therapy was consistent with a lower risk of ACS in

Table 2. *Key characteristics[*] of acute coronary syndrome cases and their controls at cohort entry. Values are numbers (percentages) unless stated otherwise*

Characteristic	Cases (n = 1490)	Controls (n = 13,550)
Median age (years, IQR)	67 (59–74)	67 (59–73)
Median follow-up from cohort entry to index date (years, IQR)	2.8 (1.4–4.8)	2.9 (1.3–4.9)
Male sex	853 (57.3)	7695 (56.8)
COPD severity[†]		
Mild/moderate	1108 (74.4)	10,956 (80.9)
Severe	264 (17.7)	2107 (15.6)
Very severe	118 (7.9)	487 (3.6)
Five-year risk of a first cardiovascular event[‡]		
<5%	143 (28.0)	3767 (40.7)
5–14%	264 (51.8)	4356 (47.1)
≥15%	103 (20.2)	1124 (12.2)
Current smoker	340 (22.8)	1957 (14.4)
Median systolic blood pressure (mm Hg, IQR)	132 (121–143)	131 (123–140)
Median total cholesterol/HDL cholesterol ratio (IQR)[§]	3.6 (2.8–4.4)	3.5 (2.9–4.3)
Median HbA1c (mmol/mol, IQR)[§]	45 (40–55)	42 (39–49)
Median glomerular filtration rate (ml/min/1.73 m^2, IQR)[§]	71.8 (54.8–86.5)	77.7 (64.6–88.8)
Medical history		
Acute coronary syndrome	440 (29.5)	1293 (9.5)
Heart failure	439 (29.5)	1708 (12.6))
Atrial fibrillation	288 (19.3)	1480 (10.9)
Life-threatening arrhythmia	111 (7.5)	499 (3.7)
Ischaemic stroke	92 (6.2)	363 (2.7)
Haemorrhagic stroke	14 (0.9)	95 (0.7)
Transient ischaemic attack	56 (3.8)	236 (1.7)
Diabetes	485 (32.6)	2593 (19.1)
Medication use in last 6 months		
Lipid lowering	841 (56.4)	5241 (38.7)
Antiplatelet	719 (48.3)	4165 (30.7)
Anticoagulant	132 (8.9)	681 (5.0)
Blood pressure lowering	1067 (71.6)	6960 (51.4)
Non-steroidal anti-inflammatory	259 (17.4)	2276 (16.8)
Oral theophylline	10 (0.7)	80 (0.6)

Abbreviations: COPD, chronic obstructive pulmonary disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range.

*Full characteristics in Supporting Information Table S3.

[†]Within each matched case/control set, all patients had the same degree of COPD severity. The apparent imbalance of COPD severity in this overall comparison of cases and controls is because the number of matched controls per case varied.

[‡]Primary prevention risk scores are not calculated for cohort members with known cardiovascular disease (defined as angina, history of hospitalisation for ischaemic heart disease, transient ischaemic attacks, cerebrovascular disease, or peripheral vascular disease), congestive heart failure, or significant renal disease [3].

[§]Values not recorded for all cases and controls. Total cholesterol/HDL ratio not recorded for four cases and 15 controls; HbA1c not recorded for 760 cases and 7656 controls; glomerular filtration rate not recorded for 352 cases and 3855 controls.

Table 3. *Risk of acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before the index date*

Exposure status	Cases (No. [%])	Controls (No. [%])	Matched unadjusted odds ratio (95% CI)	Matched adjusted odds ratio* (95% CI)	Unmatched adjusted odds ratio (95% CI)
LAMA and LABA dual therapy	192 (12.9)	968 (7.1)	1.51 (1.14–1.98)	1.72 (1.28–2.31)	1.57 (1.18–2.08)
LAMA therapy	91 (6.1)	673 (5.0)	1.0	1.0	1.0
LABA therapy	562 (37.7)	4746 (35.0)	0.90 (0.70–1.14)	1.06 (0.82–1.37)	0.99 (0.77–1.27)
Unexposed‡	645 (43.3)	7163 (52.9)	0.69 (0.54–0.88)	0.81 (0.63–1.05)	0.78 (0.61–1.01)

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; NZDep, New Zealand Deprivation Index; PVD, peripheral vascular disease; TIA, transient ischaemic attack.
*Adjusted for ethnicity; NZDep; family history of premature ischaemic cardiovascular disease; smoking status; systolic blood pressure; total cholesterol/HDL ratio; BMI; history before cohort entry of cardiovascular disease (defined as a history of any of the following: myocardial infarction, angina, ischaemic or haemorrhagic stroke, TIA, PVD, use of angina medications, or a cardiac, stroke, TIA, or PVD procedure); hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of heart failure, atrial fibrillation, life-threatening arrhythmia, diabetes; hospital discharge diagnosis between cohort entry and index date of other ischaemic cardiovascular conditions (defined as stable angina, ischaemic stroke, TIA, PVD); use in 6 months before cohort entry and (separately) in 6 months before the index date of lipid-lowering, antiplatelet, anticoagulant, blood pressure-lowering, and nonsteroidal anti-inflammatory medications.
†Adjusted for all of the above variables and the matching factors (date of birth, sex, date of cohort entry, COPD severity).
‡No long-acting bronchodilator use in 30 days before the index date.

the unexposed group, although this could have been a chance finding (adjusted OR = 0.81 [95% CI: 0.63–1.05]). An unmatched analysis, adjusted for the matching factors and other covariates, produced a slightly lower estimate for the LAMA and LABA dual therapy versus LAMA therapy comparison (OR = 1.57; [95% CI: 1.18–2.08]). Only 2.0% of cases and 1.7% of controls were exposed to more than one LAMA- or LABA-containing therapy (i.e. LAMA and LABA dual therapy, LAMA therapy, or LABA therapy) in the 30 days before the index date.

Analyses stratified by history of cardiovascular disease (Table S7) and ethnicity (Table S8) yielded very similar results to the primary analysis, and there was no evidence of effect modification. In the analysis stratified by ICS use, the ORs for the combined use of a LAMA and a LABA versus a LAMA were consistent with the results of the primary analysis, however, the estimates for the other comparisons were less so (Table S9).

The overall pattern of results for AICV mirrored those of the ACS analyses, although the estimates were attenuated somewhat (Tables S10–13).

Overall, the age- and sex-adjusted absolute excess risk of ACS associated with the use of LAMA and LABA dual therapy versus LAMA therapy was 7.7 per 1000 person-years. The age- and sex-adjusted incidence rates were 23.4 (95% CI: 18.7–28.1) and 15.7 (95% CI: 11.4–20.0) per 1000 person-years, respectively (Table S14). The AICV incidence rates are shown in Table S15. In relative terms, the excess risk of ACS and AICV in users of LAMA and LABA dual therapy versus LAMA therapy was similar in the two ethnicity strata, however, the absolute risk difference was much higher in the Māori, Pacific, Indian group (Tables S14 and S15).

Discussion

In this study of patients with COPD who initiated treatment with long-acting bronchodilator inhalers, we found that current users of LAMA and LABA dual therapy were about 1.7 times as likely to be admitted to hospital with, and/or die from, ACS as current users of LAMA therapy.

Cardiovascular safety data from RCTs that compared the use of two versus one long-acting bronchodilator, and from meta-analyses of those RCTs, are very limited [18]. However, a safety analysis

from a recent RCT found that more ischaemic coronary events occurred in the LAMA/LABA/ICS and LAMA/LABA arms than in the LABA/ICS arm [33]. Our findings are also consistent with the results of our earlier national study, which was based solely on hospital discharge, mortality, and pharmaceutical dispensing data [19]. They are also generally congruent with the results of other [34–36], but not all [37, 38], observational studies from elsewhere that explored the risk of adverse cardiovascular events in users of two versus one long-acting bronchodilator – however, in contrast to the current investigation, the primary analysis in most of these studies examined the risk of broad composite cardiovascular outcomes (which collectively included coronary heart disease, arrhythmia, heart failure, ischaemic and haemorrhagic stroke, and TIA) [34–36]. The numbers of acute ischaemic coronary and cerebrovascular events (when reported [35–38]) in these studies were smaller, only one study examined the risk associated with the use of two bronchodilators versus LAMA [34], and no investigations had access to detailed cardiovascular risk assessment data.

There are some plausible mechanisms by which long-acting bronchodilators might increase the risk of ACS. Short- and long-acting beta2-agonist therapy has been reported to increase heart rate and reduce serum potassium concentration [39], while muscarinic antagonist therapy is associated with tachyarrhythmias and myocardial ischaemia [40]. It has been suggested that these effects could cause an increase in cardiovascular events, such as arrhythmias and myocardial ischaemia, in susceptible patients.

Particular strengths of this study are that it was undertaken in a country with a universal healthcare system and we were able to individually link detailed information from cardiovascular risk assessments undertaken in primary care with data from regional laboratories and the Ministry of Health's comprehensive National Collections of pharmaceutical dispensing claims, hospital discharges, and mortality records. In addition, we took several measures to minimise the possibility of including patients who initiated the use of a LABA or LABA/ICS product solely for the treatment of asthma. We cannot entirely rule out the possibility that, among patients aged 45–84 years who were dispensed a LABA or LABA/ICS inhaler at cohort entry without a concomitant LAMA, the study algorithm excluded some patients with both asthma (for which they were hospitalised) and COPD (for which they were not hospitalised) and included some patients with asthma only (for which they were not hospitalised). However, we can be certain that the primary comparison (LAMA and LABA dual therapy versus LAMA therapy) was based on patients with COPD because LAMA products were only funded during the study period for patients with spirometry-confirmed COPD. Case ascertainment is likely to be complete because ACS and AICV events result in hospital admission and/or death, and discharge diagnoses and causes of death (including deaths in the community) are coded to ICD-10-AM rubrics by professional nosologists. Finally, because some [6], though not all [5], studies have found that patients with more severe COPD have a greater risk of coronary heart disease than those with a less severe disease we took several steps to minimise potential confounding by indication (whereby patients who were prescribed both a LAMA and a LABA had more severe COPD and, independently of that therapy, a higher risk of an ACS event); the cases and controls were matched on COPD severity and we undertook a matched analysis to address the primary aim, and we adjusted for COPD severity in the secondary unmatched analyses.

There are also some limitations to be considered. First, the Pharmaceutical Collection does not include records of inpatient dispensing, although this is unlikely to have had a meaningful impact on our findings as hospital stays for COPD are usually short (for example, mean stay = 4.3 days in 2012/2013 [41]) and medicines prescribed at discharge are obtained from community pharmacies. Second, we did not have access to detailed clinical information and the results of hospital-based investigations to validate the diagnoses of ACS and AICV; however, a comparative study has found excellent agreement between ACS diagnoses recorded in the NMDS and those recorded by clinicians in the All New Zealand Acute Coronary Syndrome Quality Improvement registry [42]. Third, we were unable to find controls for some cases; however, the numbers were very small. Fourth, it is possible that we may have underestimated the numbers of COPD exacerbations by requiring the use of both an antibiotic and prednisone; however, these criteria were applied to all members of the underlying study cohort and were therefore applied equally to cases and their potential controls and should not have resulted in a selection bias. Fifth, we cannot rule out the possibility

of residual confounding by indication, although in our earlier national study we found that the first increase in severity following initiation of a single long-acting bronchodilator was most often followed by the addition of an ICS rather than a second long-acting bronchodilator [19]. Sixth, the available ethnicity data allowed us to identify Indian cohort members, but not other members of the high risk South Asian group for the analyses stratified by ethnicity. Finally, the small numbers of cohort members who used both a LAMA and a LABA without an ICS meant there was insufficient power to ascertain whether ICS modified the associations of interest.

We considered matching on baseline cardiovascular risk score at the design stage of this project but opted to adjust for the individual components of the cardiovascular risk prediction equations (including smoking status) instead. The rationale for this decision related to minimising the number of cases for whom we could not find controls (thereby maximising study power as well as minimising selection bias) and optimising control of confounding. We had already planned to match controls to cases on date of birth, sex, date of cohort entry, and COPD severity, and if we had also attempted to match on 5-year primary prevention scores (if cases *did not* have a history of cardiovascular disease at cohort entry) or 2-year secondary prevention scores (if cases *did* have a history of cardiovascular disease at cohort entry), it is likely that we would have been unable to find controls for a substantial proportion of cases–particularly since there are some individuals for whom it is not possible to calculate a cardiovascular risk score (see footnotes to Table 2 and Table S3). For cases for whom it was possible to derive risk scores, difficulties in matching controls might have been mitigated somewhat by using very broad categories of cardiovascular risk score, however, this would have had negative consequences for the control of confounding.

Conclusion

In the context of the relatively small patient-relevant benefits of using two versus one long-acting bronchodilator, our findings have important implications for decisions about the potential benefit/harm ratio of treatment escalation, especially for those patients who have a high absolute risk of future cardiovascular events.

Conflict of Interest

The authors declare they have no conflicts of interest.

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Author Contributions

Lianne Parkin: Conceptualization, formal analysis, funding acquisition, methodology, project administration, and writing the original draft. Sheila Williams: Formal analysis, methodology, and writing-review & editing. Katrina J. Sharples: Conceptualization, formal analysis, funding acquisition, methodology, and writing-review & editing. David J. Barson: Data curation, formal analysis, funding acquisition, methodology, and writing-review & editing. Simon Horsburgh: Conceptualization, formal analysis, funding acquisition, methodology, and writing-review & editing. Rod Jackson: Conceptualization, formal analysis, funding acquisition, methodology, resources, and writing-review & editing. Billy Wu: Data curation, resources, and writing-review & editing. Jack Dummer: Conceptualization, formal analysis, funding acquisition, methodology, and writing-review & editing

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Example to illustrate how an individual's dispensing data were summarised as continuous episodes of use of specific drugs and drug classes.

Figure S2. Example to illustrate how an individual's dispensing data were summarised as continuous episodes of therapeutic regimens and exposure categories.

Figure S3. Example to illustrate classification of user status on the index date.

Appendix. Supplemental material.

