

# Is the use of two versus one long-acting bronchodilator by patients with COPD associated with a higher risk of acute coronary syndrome in real-world clinical practice?

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## ABSTRACT

**Background** Cardiovascular comorbidity is common among patients with chronic obstructive pulmonary disease (COPD) and there is concern that long-acting bronchodilators (long-acting muscarinic antagonists (LAMAs) and long-acting beta<sub>2</sub> agonists (LABAs)) may further increase the risk of acute coronary events. Information about the impact of treatment intensification on acute coronary syndrome (ACS) risk in real-world settings is limited. We undertook a nationwide nested case-control study to estimate the risk of ACS in users of both a LAMA and a LABA relative to users of a LAMA. **Methods** We used routinely collected national health and pharmaceutical dispensing data to establish a cohort of patients aged ≥45 years who initiated long-acting bronchodilator therapy for COPD between 1 February 2006 and 30 December 2013. Fatal and non-fatal ACS events during follow-up were identified using hospital discharge and mortality records. For each case we used risk set sampling to randomly select up to 10 controls, matched by date of birth, sex, date of cohort entry (first LAMA and/or LABA dispensing), and COPD severity. **Results** From the cohort (n=83 417), we identified 5399 ACS cases during 281 292 person-years of follow-up. Compared with current use of LAMA therapy, current use of LAMA and LABA dual therapy was associated with a higher risk of ACS (OR 1.28 (95% CI 1.13 to 1.44)). The OR in an analysis restricted to fatal cases was 1.46 (95% CI 1.12 to 1.91). **Conclusion** In real-world clinical practice, use of two versus one long-acting bronchodilator by people with COPD is associated with a higher risk of ACS.

## INTRODUCTION

Coronary heart disease and chronic obstructive pulmonary disease (COPD) are leading causes of health loss and death worldwide<sup>1</sup> and in New Zealand.<sup>2-4</sup> Cardiovascular comorbidity is common among patients with COPD.<sup>5</sup> This can partially be explained by shared risk factors such as smoking and age, however COPD also appears to be an

## Key messages

- In patients with chronic obstructive pulmonary disease (COPD), is concomitant use of a long-acting muscarinic antagonist (LAMA) and a long-acting beta<sub>2</sub> agonist (LABA) associated with a higher risk of acute coronary syndrome in the real-world setting of clinical practice than use of a LAMA alone?
- The combined use of a LAMA and a LABA, rather than a LAMA alone, could increase the risk of acute coronary syndrome by about 30% in patients with COPD, a population already at high risk of acute coronary events.
- The research has important implications for health-care providers and patients who are considering the potential benefits and harms of using two versus one long-acting bronchodilator.

independent risk factor for coronary heart disease.<sup>5</sup>

Successive editions of the Global Initiative for Chronic Obstructive Lung Disease Guidelines have recommended concomitant use of a long-acting muscarinic antagonist (LAMA) and long-acting beta<sub>2</sub> agonist (LABA) if COPD symptoms are not well controlled on one long-acting bronchodilator<sup>6</sup>; and a recent American Thoracic Society clinical practice guideline strongly recommended the combined use of a LAMA and LABA, rather than monotherapy, in patients with dyspnoea or exercise intolerance.<sup>7</sup> However, there is concern that long-acting bronchodilators might further increase the risk of acute coronary events in patients with COPD.<sup>8</sup> This is important, given that the impact of these drugs (singly or in combination) on clinically important outcomes is relatively modest<sup>7 9-15</sup> and patients with COPD are

more likely to die from coronary events than from respiratory failure.<sup>16</sup>

Although the findings from randomised controlled trials (RCTs) appear to be reassuring about the cardiovascular safety of long-acting bronchodilators, the trials were usually underpowered for safety endpoints, and patients with pre-existing cardiovascular disease and other comorbidities were frequently excluded.<sup>17</sup> Meta-analyses of those RCTs have also had limited power to examine cardiovascular risk<sup>9–15</sup> and the authors of one review<sup>9</sup> reported they were unable to undertake a meta-analysis of serious cardiovascular events because of a lack of consistency in reporting those outcomes. These limitations have prompted calls for more inclusive RCTs, as well as large observational studies, in real-world settings of clinical care.<sup>17</sup>

We undertook a national study to estimate the risk of acute coronary syndrome (ACS) in users of both a LAMA and a LABA relative to users of a LAMA. We also sought to explore the risk of ACS according to history of ischaemic cardiovascular disease, ethnicity, and concomitant use of an inhaled corticosteroid (ICS).

## METHODS

### Study design

Case-control study, nested within a national cohort of patients who initiated long-acting bronchodilator therapy for COPD.

### Data sources and derivation of study cohort

The study was based on linked data from the Ministry of Health's National Collections,<sup>18</sup> including the Pharmaceutical Collection (records of all claims by community-based pharmacists for the dispensing of prescription drugs which are publicly funded—most medicines prescribed in New Zealand), the National Health Index Collection (demographic data), the National Minimum Dataset (public hospital and publicly funded private hospital discharges), the Mortality Collection (inpatient and community-based deaths), and the New Zealand Cancer Registry (all cancers, except non-melanoma skin cancers).

We took several steps to derive the study cohort (figure 1). First, the Ministry identified all patients who were dispensed a LAMA, LABA, or LABA/ICS product in New Zealand at least once between 1 February 2005 and 31 December 2013 (end of follow-up) and provided us with linked demographic, health and pharmaceutical dispensing data for these patients. The date of the first dispensing of a long-acting bronchodilator was taken as the cohort entry date. We then excluded patients with incorrectly linked records (0.4%), those aged <45 years at cohort entry and those with a history of at least one hospital discharge diagnosis of asthma and no COPD diagnoses (to minimise the inadvertent inclusion of patients prescribed a LABA or LABA/ICS inhaler solely for asthma), those who entered the cohort between 1

February 2005 and 31 January 2006 (to avoid the bias that can arise from the inclusion of patients already using the drugs of interest at the start of follow-up), and those who entered the cohort on 31 December 2013 (to ensure that we identified ACS events that occurred after the first dispensing of a long-acting bronchodilator).

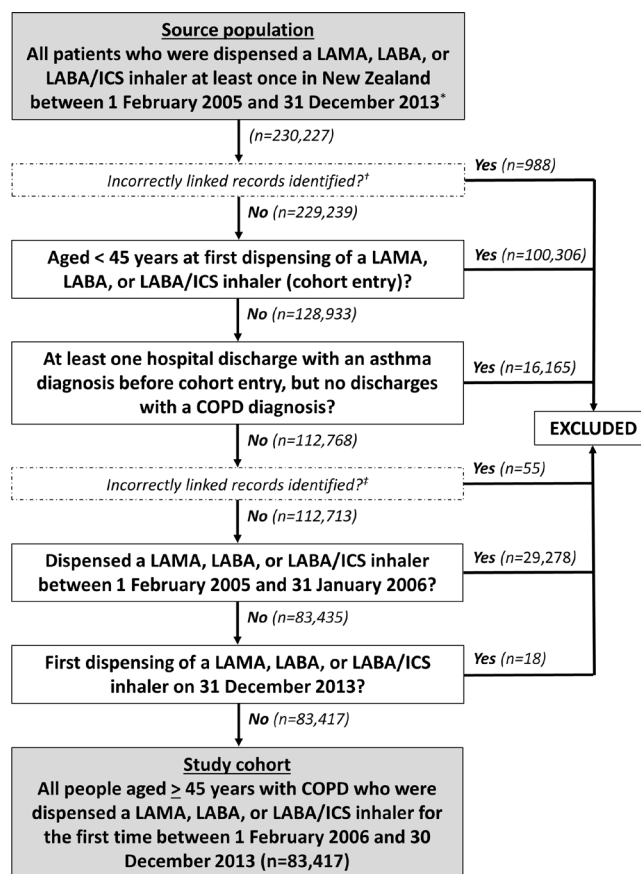
### Summarising LAMA and LABA exposure in the study cohort

We summarised exposure to long-acting bronchodilators during follow-up for each member of the study cohort, as outlined in online supplemental figures 1–3, table 1, and online supplemental table 1.

### Nested case-control analyses

#### Identification of cases

Cohort members were classified as a case if there was a record between cohort entry and 31 December 2013, of (1) a hospital admission in which there was a principal or additional discharge diagnosis coded to any of



\* LAMA/LABA combination products were not available during this period

† Identified on basis of incompatible cohort entry date and date of birth and/or date of death

‡ Identified by examining records with mismatch between patient category on dispensing record and age at dispensing

**Figure 1** Derivation of the study cohort. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist.

**Table 1** Classification of exposure categories and regimens

Exposure categories and regimens	Products included in regimen
<b>LAMA and LABA dual therapy</b>	
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	Concurrent use of LAMA and LABA single-agent products
<b>LAMA therapy</b>	
LAMA	Use of LAMA single-agent product only
LAMA+ICS	Concurrent use of LAMA and ICS single-agent products
<b>LABA therapy</b>	
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
<b>ICS monotherapy*</b>	
ICS	Use of ICS single-agent product only

\*By design, all cohort members had used a long-acting bronchodilator before the episode of ICS monotherapy. ICS, Inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist.

the following International Statistical Classification of Diseases and Related Health Problems, Australian Modification, (ICD-10-AM) rubrics: I200 (unstable angina), I21 (acute myocardial infarction), or I22 (subsequent myocardial infarction, <28 days after a previous myocardial infarction); or (2) death and any of the above ICD-10-AM rubrics were coded as the underlying cause of death. We took the date of the first ACS event during follow-up as the index date for each case and their matched controls.

### Selection of controls

For each case, we used risk set sampling to randomly select up to 10 controls, matched by date of birth ( $\pm 365$  days), sex, date of cohort entry ( $\pm 183$  days), and COPD severity (online supplemental table 2).

### Ascertainment of user status on the index date

We classified individuals as current users of LAMA and LABA dual therapy, LAMA therapy, or LABA therapy if use occurred in the 30-day period before the index date (online supplemental figure 3). Conversely, those whose most recent therapy ended >30 days before the index date were classified as unexposed, as were patients whose only therapy in the 30 days before the index date was an ICS. Similarly, for the analyses exploring the impact of concomitant ICS use, we classified individuals as current users if the relevant exposure occurred in the 30 days before the index date. Individuals exposed to more than one LAMA-containing or LABA-containing therapy in the 30 days before the index date were classified according to the therapy they used closest to that date.

We ascertained user status without knowledge of whether an individual was a case or a control.

### Other covariates

We used data from the National Collections to derive covariates for descriptive purposes and multivariate analyses. Covariates chosen a priori for inclusion in the adjusted models were demographic characteristics (self-identified ethnicity categorised according to the Ministry of Health Ethnicity Data Protocols<sup>19</sup> and an area-based measure of deprivation, NZDep06<sup>20</sup>), Charlson comorbidity score (based on hospital admissions in the preceding 5 years), a history of conditions associated with an increased risk of subsequent cardiovascular events (ACS, other ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, ischaemic stroke, transient ischaemic attack, diabetes), a history of conditions that might have influenced prescribing decisions about LAMA, LABA, and ICS products (life-threatening arrhythmia, benign prostatic hypertrophy/bladder outflow obstruction, hyperthyroidism, closed-angle glaucoma, osteoporotic fracture), and the use of medications which increase or decrease the risk of ACS (non-steroidal anti-inflammatories, oral theophylline, lipid-lowering agents, antiplatelets, anticoagulants, blood pressure-lowering medications).

### Statistical methods

The primary analysis explored the risk of ACS in users of LAMA and LABA dual therapy (LAMA and LABA *with* or *without* ICS), and of LABA therapy (LABA *with* or *without* ICS), relative to LAMA therapy (LAMA *with* or *without* ICS). Secondary analyses were undertaken based on cases for whom ACS was the principal diagnosis and for those whose ACS event was fatal. We also undertook secondary analyses stratified by history of ischaemic cardiovascular disease (history/no history of ACS, other ischaemic heart disease, ischaemic stroke, and/or transient ischaemic



attack at any time before the index date), ethnicity (Māori, the indigenous people/non-Māori), and ICS exposure in the 30 days before the index date (exposed/not exposed).

Conditional logistic regression was used in the primary analysis to estimate unadjusted and adjusted ORs and 95% CIs. For the secondary analyses stratified by history of ischaemic cardiovascular disease, ethnicity, and ICS exposure, we used logistic regression and adjusted for the matching factors in addition to the other covariates. Chained equations,<sup>21</sup> using all the data included in the analysis, were used to estimate the missing ethnicity and deprivation data (which were assumed to be missing at random). Fifty sets of data were imputed using a run-in of 150.

Analyses were carried out in Stata V.15.0.

### Estimation of incidence rates

Crude incidence rates of ACS in users of LAMA and LABA dual therapy, LAMA therapy, and LABA therapy were estimated by dividing the number of cases which occurred during an episode of use of the relevant therapy by the total person-years of exposure for that therapy (censored at the index date for cases); 95% CIs were calculated using the mid-P exact method.<sup>22</sup> We also calculated age-adjusted and sex-adjusted rates with 95% CIs,<sup>23</sup> as well as crude and age-adjusted and sex-adjusted rates for Māori and non-Māori, with the age distribution of the total New Zealand population as the standard.

### Patient and public involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## RESULTS

Overall, we identified 83 417 patients who initiated use of a LAMA, LABA, or LAMA/ICS inhaler between 1 February 2006 and 30 December 2013. A total of 5422 patients had an ACS event during 281 292 person-years of follow-up, however controls could not be found for 23 of these cases and they were excluded from the case-control analyses.

Table 2 and online supplemental table 3 show the characteristics of the 5399 cases and 51 563 controls included in the case-control analyses. Similar patterns of hospital discharge diagnoses and medication use were seen relative to the index date (online supplemental table 4).

The results of the primary analysis are shown in table 3. In the adjusted matched analysis, current users of LAMA and LABA dual therapy were 1.3 times as likely as current users of LAMA therapy to have an ACS event (OR 1.28 (95% CI 1.13 to 1.44)). Relative to current users of LAMA therapy, patients who were not currently using a long-acting bronchodilator were less likely to have an ACS event (OR 0.84 (95% CI 0.76 to 0.92)), while there was no difference in risk between current users of LABA

therapy and current users of LAMA therapy (OR 1.0 (95% CI 0.91 to 1.10)). An unmatched analysis, adjusted for the matching factors, as well as the other covariates, yielded very similar estimates. Analyses confined to cases with a principal diagnosis of ACS (online supplemental table 5) and fatal ACS events (online supplemental table 6) also produced similar findings; the matched adjusted ORs for LAMA and LABA dual therapy versus LAMA therapy were 1.22 (95% CI 1.05 to 1.41) and 1.46 (95% CI 1.12 to 1.91), respectively. There was no evidence of a different pattern of results for the comparisons between LAMA and LABA dual therapy, LABA therapy, and LAMA therapy over time ( $p=0.06$ , online supplemental table 7).

The results of the analyses stratified by a history of ischaemic cardiovascular disease (online supplemental table 8) and by ethnicity (online supplemental table 9) were consistent with those of the primary analysis and there was no evidence of effect modification ( $p=0.3$  and  $p=0.4$ , respectively). The findings for the analysis stratified by current use of an ICS differed somewhat (online supplemental table 10); while the unmatched adjusted OR for LAMA and LABA dual therapy versus LAMA therapy in the ICS-exposed stratum was similar to that found in the primary analysis, the corresponding OR in the stratum with no ICS exposure was consistent with no effect although the numbers were small and the 95% CI was correspondingly wide. The interaction effect was not significant ( $p=0.7$ ).

Overall, the age-adjusted and sex-adjusted incidence rates for LAMA and LABA dual therapy and LAMA therapy were 25.1 (95% CI 20.5 to 29.6) and 22.4 (95% CI 18.3 to 26.4) per 1000 person-years, respectively, giving an absolute excess risk of 2.7 per 1000 person-years (online supplemental table 11). Among Māori, users of LAMA therapy had a higher rate than users of LAMA and LABA dual therapy, although the numbers of cases were small and the estimates less precise.

## DISCUSSION

### Principal findings

In this large national study of patients with COPD who commenced treatment with long-acting bronchodilators, current users of LAMA and LABA dual therapy were about 1.3 times as likely to be admitted to hospital with, and/or die from, ACS as current users of LAMA therapy. Very similar estimates were found in secondary analyses based on cases for whom ACS was the principal diagnosis, those with fatal ACS, and in analyses stratified by history of ischaemic cardiovascular disease and ethnicity.

### Findings in relation to previous studies

Most RCTs that compared the use of two versus one long-acting bronchodilator and had at least 12 months' follow-up were too small to provide meaningful estimates of ACS risk.<sup>24–26</sup> Meta-analyses that included such RCTs, as well as those with shorter follow-up time, also had limited power.<sup>13–15</sup> Two of those meta-analyses examined the risk



**Table 2** Key characteristics\* of cases and controls; values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=5399)	Controls (n=51 563)
Median age at cohort entry (years, IQR)	74.3 (65.8–80.8)	73.8 (65.6–80.2)
Median follow-up from cohort entry to index date (years, IQR)	1.6 (0.6–3.1)	1.6 (0.6–3.1)
Sex		
Female	2388 (44.2)	22 709 (44.0)
Male	3011 (55.8)	28 854 (56.0)
Charlson comorbidity score at cohort entry†		
0	2224 (41.2)	29 214 (56.7)
1	1133 (21.0)	11 090 (21.5)
2	823 (15.2)	5614 (10.9)
≥3	1219 (22.6)	5645 (11.0)
COPD severity at cohort entry		
Mild/moderate	3401 (63.0)	33 460 (64.9)
Severe	1164 (21.6)	10 990 (21.3)
Very severe	834 (15.5)	7113 (13.8)
Hospital discharge diagnoses at any time before cohort entry		
Acute coronary syndrome	1883 (34.9)	7539 (14.6)
Other ischaemic heart disease	2081 (38.5)	9297 (18.0)
Raised blood pressure	2523 (46.7)	15 076 (29.2)
Dyslipidaemia	1305 (24.2)	6091 (11.8)
Heart failure	1267 (23.5)	6402 (12.4)
Life-threatening arrhythmia	630 (11.7)	3302 (6.4)
Ischaemic stroke	223 (4.1)	1430 (2.8)
Transient ischaemic attack	265 (4.9)	1526 (3.0)
Diabetes	956 (17.7)	5174 (10.0)
Benign prostatic hypertrophy/bladder outflow obstruction	374 (6.9)	3031 (5.9)
Medication use in 6 months before cohort entry		
Statin	2552 (47.3)	17 438 (33.8)
Antiplatelet	2669 (49.4)	18 077 (35.1)
Blood pressure lowering	3970 (73.5)	31 189 (60.5)
Non-steroidal anti-inflammatory	813 (15.1)	7757 (15.0)
Oral theophylline	54 (1.0)	445 (0.9)

\*Full characteristics in online supplemental table 3.

†Based on hospital discharge diagnoses in the 5 years before cohort entry. COPD, chronic obstructive pulmonary disease; IQR, Interquartile range.

of a composite outcome of all-cause non-fatal serious adverse events and did not report on the risk of cardiac events,<sup>13 14</sup> while a network meta-analysis based on just 322 severe cardiac adverse events among 20 736 patients in 22 RCTs reported an OR of 0.98 (95% CI 0.78 to 1.25) for the LAMA and LABA versus LAMA comparison.<sup>15</sup>

Our findings are consistent with a safety analysis in an RCT that was unpublished at the time the data were extracted for the network meta-analysis. In the IMPACT trial, a multicentre RCT that compared the rate of moderate or severe COPD exacerbations during a 12-month follow-up period in 10 355 patients allocated to one of three combination inhalers, ischaemic coronary

events occurred more frequently in the LAMA/LABA and LAMA/LABA/ICS arms than in the LABA/ICS arm; the rates per 1000 person-years were 30.6, 26.1 and 18.5, respectively.<sup>27</sup>

A few observational studies have compared the risk of cardiovascular events in patients concurrently using a LAMA and a LABA relative to users of one long-acting bronchodilator,<sup>28–32</sup> however the primary analyses in four investigations<sup>28–30 32</sup> focused on various composite outcomes (which collectively included coronary heart disease, arrhythmia, heart failure, ischaemic and haemorrhagic stroke, and transient ischaemic attack) rather than acute coronary events. In the fifth study, which explored

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

Exposure status	Cases (No (%))	Controls (No (%))	Matched unadjusted OR (95% CI)	Matched adjusted OR* (95% CI)	Unmatched adjusted OR† (95% CI)
LAMA and LABA dual therapy	641 (11.9)	4592 (8.9)	1.25 (1.11 to 1.41)	1.28 (1.13 to 1.44)	1.25 (1.11 to 1.41)
LAMA therapy	678 (12.6)	6044 (11.7)	1.0	1.0	1.0
LABA therapy	2017 (37.4)	18590 (36.1)	0.97 (0.89 to 1.07)	1.00 (0.91 to 1.10)	1.01 (0.92 to 1.11)
Unexposed‡	2063 (38.2)	22337 (43.3)	0.83 (0.75 to 0.91)	0.84 (0.76 to 0.92)	0.85 (0.77 to 0.93)

\*Adjusted for ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

†Adjusted for the above variables and the matching factors (date of birth, sex, date of cohort entry, and COPD severity).

‡No long-acting bronchodilator use in 30 days before index date.

COPD, chronic obstructive pulmonary disease; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic antagonist.

the risk of four cardiovascular outcomes in the primary analysis, the acute myocardial infarction estimate was based on a relatively small number of cases (n=415) and a 37% increase in risk could not be ruled out (HR 1.12 (95% CI 0.92 to 1.37)).<sup>31</sup> The sole observational study to have reported estimates for concomitant LAMA and LABA use relative to LAMA found a weak association for a composite cardiovascular outcome in the primary analysis, although this could have been a chance finding (HR 1.13 (95% CI 0.60 to 2.13)).<sup>28</sup> Importantly, the first exposure was carried forward in the analysis and that could have led to an underestimation of the association because of misclassification of exposure status. In a secondary analysis that considered changes in treatment over time, the association was stronger although the CI was still wide (HR 1.26 (95% CI 0.74 to 2.15)).

In line with other observational studies that examined the risk of composite cardiovascular outcomes or ACS, we also observed a lower risk of ACS in patients who were not currently using a long-acting bronchodilator<sup>33 34</sup> and comparable ACS risk between users of LAMA therapy and users of LABA therapy.<sup>33–38</sup>

### Strengths and limitations

This study has several strengths. First, New Zealand has a universal healthcare system, and information about the dispensing of publicly funded medicines (which included all LABA, LABA/ICS, and LAMA products that were available in New Zealand during the study period) from community pharmacies, hospital discharge diagnoses, and causes of death are all recorded in the Ministry of Health's National Collections and can be linked across the collections using a unique patient identifier (the National Health Index). This allowed us to identify a national cohort of new users of long-acting bronchodilators and to obtain information about individuals' medication use and medical history both

before cohort entry and during follow-up. Second, we are confident that the primary comparison (LAMA and LABA dual therapy versus LAMA therapy) was based on patients with COPD, because funded access to LAMA products during the study period was restricted to those with a spirometry-confirmed diagnosis of COPD. Third, our study included substantially more ACS cases than previous investigations and this allowed more precise estimates of risk. Fourth, to minimise potential confounding by indication, cases and controls were matched on severity of COPD and we addressed the primary aim in a matched analysis and adjusted for severity of COPD in the secondary unmatched analyses. In addition, we explored the degree to which worsening of COPD during follow-up (which, independently of medication, might have been associated with a higher risk of ACS) was associated with escalation to LAMA and LABA dual therapy. Among patients with mild/moderate COPD at cohort entry who were initially treated with LAMA therapy, only 19% escalated to LAMA and LABA dual therapy within 90 days following the first indication of increasing COPD severity; the majority remained on LAMA therapy for at least 9 months. The corresponding proportion for those initially on LABA therapy was only 6%. Given this prescribing behaviour, confounding by indication is unlikely to explain much of the observed increased risk of ACS.

The study also has several limitations. First, medicines dispensed in hospitals are not recorded in the Pharmaceutical Collection; however, the absence of this information is unlikely to have had a substantive impact on our study because inpatient stays for COPD are generally of short duration<sup>3</sup> and patients collect medicines prescribed at discharge from community pharmacies. Second, we did not have access to the results of investigations to validate the diagnosis of ACS; however, there

is good agreement between ACS diagnoses recorded in the national hospital discharge database and those documented by clinicians in the All New Zealand Acute Coronary Syndrome Quality Improvement registry.<sup>39</sup> Third, we could not find controls for 23 older cases; however, the exclusion of this small number of cases should not have distorted our findings. Fourth, our definition of exposure to long-acting bronchodilators was based on dispensed inhalers and, as with all studies that do not involve direct observation of medicine consumption, it is impossible to know whether patients actually used these as directed. It is possible that cohort members who were dispensed LAMA and LABA dual therapy were less likely to have adhered to their prescribed regimen than users of LAMA therapy as this would have involved the use of two inhalers (combined LAMA/LABA products were not available during the study period); the impact of this would be to have been to underestimate risk. Fifth, while we adjusted for hospital discharge diagnoses of diabetes, hyperlipidaemia, and raised blood pressure, as well as the use of lipid and blood pressure-lowering medication, we did not have access to the results of glycated haemoglobin or total cholesterol/high-density lipoprotein ratio tests, or to blood pressure measurements, so we cannot rule out residual confounding by these factors. Nor did we have information on some well-established risk factors such as smoking, obesity, and family history of premature cardiovascular disease. However, our inability to adjust for smoking status is unlikely to be an important source of confounding in this study of patients with COPD, as a very high proportion of cohort members are likely to have been current or former smokers. Finally, the analysis stratified by current ICS use had limited power.

## CONCLUSION

Given that the use of two versus one long-acting bronchodilator is associated with relatively modest improvements in patient-relevant health outcomes, our finding that LAMA and LABA dual therapy was associated with a higher risk of ACS than use of LAMA therapy has important implications for clinical decisions about the potential benefits and harms of treatment intensification.

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