ORIGINAL RESEARCH

# Long-Acting Bronchodilator Use in Chronic Obstructive Pulmonary Disease in Primary Care in New Zealand: A Retrospective Study of Treatment Patterns and Evolution Using the HealthStat Database

Dominique Milea[1]
See-Hwee Yeo[1]
Yein Nam[2]
Aldo Amador Navarro Rojas[1]
Sumitra Shantakumar[1]
Janine Beale[3]
Brett Marett[3]
Robert P Young[4]
Raewyn J Scott[4]
Barry Gribben[5]

[1]Value Evidence and Outcomes, GlaxoSmithKline plc., Greater China and Intercontinental, 139234, Singapore; [2]Real World Evidence & Epidemiology, Adelphi Real World, Macclesfield, Cheshire, UK; [3]Medical Affairs, GlaxoSmithKline plc., Auckland, New Zealand; [4]Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; [5]Public Sector Surveying, CBG Health Research Limited, Auckland, New Zealand

Correspondence: Dominique Milea
Value Evidence and Outcomes,
GlaxoSmithKline plc., Greater China and Intercontinental, 23 Rochester Park, 139234, Singapore
Tel +65 9830 7891
Email dominique.x.milea@gsk.com

**Purpose:** Long-acting bronchodilator (LABD) use is the mainstay of pharmacologic treatment for chronic obstructive pulmonary disease (COPD). Few studies describe evolving patterns of LABD use in the setting of changing inhaler availability and updated clinical guidelines.

**Methods:** A retrospective cohort study in New Zealand using the HealthStat general practice database (01/2014 to 04/2018). Eligible patients (aged ≥40 years) had COPD and ≥1 LABD prescription (long-acting muscarinic antagonist [LAMA] and/or long-acting $\beta_2$-agonist [LABA]) during the index period (05/2015 to 04/2016). Demographics and clinical characteristics of all LABD users (overall/by treatment) were described at baseline. Patients starting LABD treatment during the index period, termed "new" users, were also described, as was their treatment evolution over 24 months of follow-up. Yearly LABD initiation rates were assessed from 2015 to 2017, covering changes to Pharmaceutical Management Agency criteria and clinical guidelines.

**Results:** Across 2140 eligible patients, the most common index treatments were inhaled corticosteroid (ICS)/LABA (59.0%) and open triple therapy (LAMA+LABA+ICS; 26.7%). ICS/LABA therapy was highest in younger patients, with open triple therapy highest in older patients. Prior yearly exacerbation rates were lowest in those receiving monotherapy (LABA: 0.9/year; LAMA: 1.1/year) versus dual therapy (all 1.4/year) and open triple therapy (2.2/year). Of 312 new LABD users, ICS/LABA was the most common index treatment (69.6%), followed by LAMA monotherapy (16.0%). Continuous use with index treatment was 31.1% at 12 months and 13.5% at 24 months; mean time to treatment change was 175.5 and 244.1 days, respectively. Among patients modifying treatment at 24 months, 23.0% augmented, 7.0% switched, 45.6% re-started, and 24.4% discontinued/stepped down. Among patients initiating LABD each year from 2015 to 2017, LAMA prescription increased (17% to 46%) while ICS prescription remained stable (approximately 20%).

**Conclusion:** Predominant use of ICS/LABA (05/2015 to 04/2016) reflects available LABDs and previous restrictions on LAMA use in New Zealand.

**Keywords:** bronchodilator therapy, chronic obstructive pulmonary disease, long-acting muscarinic antagonist, long-acting $\beta_2$-agonist, inhaled corticosteroid, New Zealand

# Plain Language Summary

Long-acting bronchodilator (LABD) use, primarily comprising long-acting muscarinic antagonist (LAMA) and long-acting β2-agonist (LABA) inhalers, is key in the pharmacologic management of COPD. Depending on symptoms, disease severity, and clinical guidelines, LABDs may be used alone, together, or with an inhaled corticosteroid (ICS); however, despite widespread LABD use among patients with COPD in New Zealand, few studies have described how changes to inhaler availability and clinical guidelines may affect treatment pattern evolution.

Using data from the HealthStat general practice database collected between 2014 and 2018, we evaluated the characteristics of 2140 adult patients with COPD according to LABD treatment class, and assessed LABD treatment evolution over a 24-month follow-up period in 312 of these patients who started LABD between 1 May 2015 and 30 April 2016 ("new" LABD users). Yearly LABD initiation rates between 2015 and 2017 were also evaluated.

ICS/LABA was overall the most common treatment. This was not necessarily consistent with clinical treatment guidelines for COPD and was possibly influenced by exacerbation history, widespread comorbid asthma, and limited dual bronchodilator availability. LAMA use increased among new LABD users from 2015 to 2017, which was expected due to the availability of dual LAMA/LABA bronchodilators and eased restrictions on LAMA availability in 2016. Most new LABD users changed their initial treatment, and around a quarter discontinued/stepped down from their initial treatment after 24 months.

Our findings could help healthcare providers optimize LABD use and may provide a useful reference for future studies of treatment pattern evolution among patients with COPD.

# Introduction

Pharmacologic therapy for chronic obstructive pulmonary disease (COPD), one of the leading causes of morbidity and mortality worldwide, centers on inhaled bronchodilator therapy. This includes short-acting agents used on an as-needed basis for symptom alleviation, and long-acting bronchodilator (LABD) use for maintenance therapy.[1,2] The latter primarily comprises long-acting muscarinic antagonist (LAMA) and long-acting β2-agonist (LABA) treatments, used either as monotherapies or in combination (dual therapy). Escalation to triple therapy through the addition of an inhaled corticosteroid (ICS) is recommended for patients with a history of exacerbations who remain symptomatic despite LABD therapy.[1]

The true prevalence of COPD in New Zealand is unknown. Conservative estimates suggest a prevalence of 1 in every 15 adults over the age of 45 years,[1] while prevalence for those aged over 40 years reported in a random population survey ranged from 9.0% to 15.2% depending on the definition of COPD used.[3] COPD carries a substantial burden to the national healthcare system, with costs mainly attributed to medications, hospital care, and primary care visits.[1] Significant ethnicity-based healthcare disparities also exist in New Zealand, with COPD-related hospitalizations over 3-times and mortality rates over 2-times higher in Māori than non-Māori, Pacific, or Asian patients.[4]

Effective treatment and management of COPD in New Zealand is guided by international recommendations, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report,[1] and by the Australia and New Zealand COPD-X guidelines.[5] Further to GOLD and COPD-X, prescribing of COPD pharmacologic therapy in the New Zealand healthcare system is subject to Pharmaceutical Management Agency (PHARMAC) reimbursement approval and Special Authority criteria. These criteria typically define the clinical circumstances required for patients to receive funding for a specific medication[6] and shape medication prescribing patterns. In the context of COPD, this has included restrictions on the use of LAMA prior to 2016, followed by greater availability of newer LAMA and LAMA/LABA combination therapies since 2016. The latter were introduced to the New Zealand market in March 2016[7] and since then have required Special Authority approval and prior stabilization of patients on LAMA alone.[8] Changes in March 2016 to PHARMAC prescribing criteria for LABD, coinciding with newly introduced LABD therapies,[7] saw an increase in the number of subsidized medications and the removal (for one LAMA and one ICS/LABA) or requirement (for three LAMA/LABA combinations) for Special Authority approval. In conjunction with refinement of the GOLD recommendations[9] later the same year, such changes may have modified pharmacologic treatment patterns for COPD in New Zealand.

The treatment and management of COPD in New Zealand occurs predominantly in primary care. Access to primary care is often obtained through registration with a general practice, and 95% of the population are registered.[10] As a large, population-based, general practice database also linked to national hospital data, HealthStat[11] contains comprehensive, near real-time primary care data for over one million patients from 102 randomly selected general practices in New Zealand. Such data may thus

provide useful insights into COPD treatment patterns and evolution in a real-world setting.

We used data from HealthStat collected between January 2014 and April 2018 to conduct a retrospective analysis of LABD treatment patterns in patients with COPD in New Zealand. Specifically, we evaluated patient demographics and clinical characteristics according to LABD treatment class and evaluated the evolution (over 24 months) of LABD treatment in the sub-cohort of patients who started these treatments. Finally, we assessed yearly LABD initiation rates to evaluate the impact of changes in 2016 to the PHARMAC Special Authority criteria and GOLD recommendations on treatment patterns.

## Materials and Methods
### Study Design and Patient Population

This was a retrospective cohort study of LABD use in patients with COPD utilizing primary care data, and linked hospital data, from the HealthStat general practice database in New Zealand. Use of LABD included treatment with a LAMA, LABA, LAMA+LABA (as a fixed or open combination), ICS/LABA, LAMA+ICS, and LAMA+LABA+ICS (as open triple therapy).

The study design is shown in Figure 1. The total observation period was January 2014 to April 2018, which was split into three phases: an index period (1 May 2015 to 30 April 2016); a 12-month baseline period; and a 24-month follow-up period. All eligible LABD users were identified in the index period, and the index date was defined as the date of first prescription of a LABD in this index period. The study included a main cohort of patients with COPD who had a LABD prescription in the index period and ≥1 LABD prescription prior to the index period (Figure 1A), and a sub-cohort of patients who started LABD in the index period but had no prior LABD prescription (ie, "new" LABD users) (Figure 1B). All patients had to have ≥12 months data in the baseline period prior to their index date, which allowed demographic and clinical characteristics to be identified, and the sub-cohort of new LABD users also had to have ≥24 months of follow-up data after the index date to allow treatment patterns and evolution after starting LABD treatment to be described.

An additional analysis was carried out to investigate yearly rates of LABD initiation for patients initiating LABD between 2015 and 2017. As a measure of the impact of changes in 2016 to the PHARMAC and GOLD recommendations, the index period was the respective calendar year (January to December) for each year: patients were required to have 12 months of baseline data (there was no follow-up period) (Figure 1C).

All eligible patients were ≥40 years of age at their first COPD diagnosis and had ≥1 diagnostic read code for COPD (Supplementary Table 1) at any point in their medical history. Patients with a record of an event code for a medical condition incompatible with a diagnosis of COPD were excluded; a list of codes and associated conditions is provided in Supplementary Table 2.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and ethical review requirements of participating institutions, and received formal ethical approval from the New Zealand Health and Disability Ethics Committee (ref: 13/CEN/139/AM06). No direct patient contact or primary collection of individual human patient data occurred.

### Data Source

HealthStat is a general practice database in New Zealand. It is a random sample comprising data from approximately 10% of all New Zealand practices. The database includes 15 years of data for over one million patients from 102 randomly selected general practices, each of which captures and uploads healthcare data (related to consultations, prescriptions, laboratory results, clinical measurements, and diagnostic coding for each patient) on a weekly basis. Some practices receive additional state funding for treating patients with greater need, eg, Māori, and are more responsive to research enquiries, such that the database has a slight overrepresentation of Māori patients. Data from the National Minimum Dataset, including emergency department and hospital outpatient visits, and hospital admissions, may be linked to the primary care data in HealthStat using unique patient identifiers (National Health Index codes). While data from the National Minimum Dataset shows if a patient was admitted to hospital, the actual patient diagnosis (and reason for hospital admission) is often not available in the HealthStat database unless the patient was admitted for an extended stay (ie, ≥24 hours).

The period of usable data for each patient began from the later of the patient's current registration date or the practice's up-to-standard date, and ended at the earlier of the patient's transfer-out date or the practice's last collection date. All prescriptions were issued by a general practitioner. As our study focused solely on prescription data from the HealthStat database, it was not specified whether any prescriptions changes were issued as a result of a general practitioner's
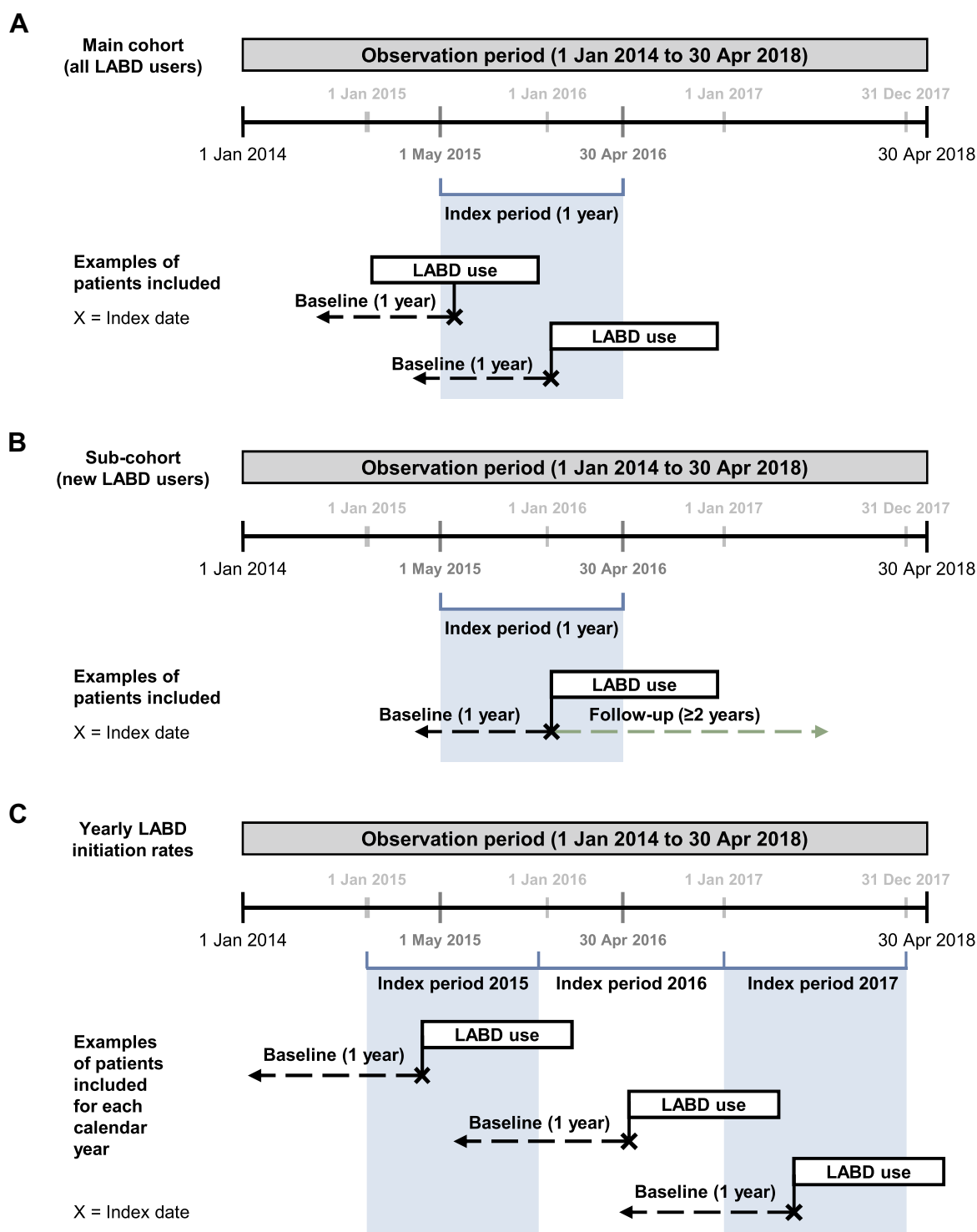
**A**

**Main cohort (all LABD users)**

Observation period (1 Jan 2014 to 30 Apr 2018)

1 Jan 2015   1 Jan 2016   1 Jan 2017   31 Dec 2017

1 Jan 2014   1 May 2015   30 Apr 2016   30 Apr 2018

Index period (1 year)

**Examples of patients included**

X = Index date

LABD use

Baseline (1 year)

LABD use

Baseline (1 year)

**B**

**Sub-cohort (new LABD users)**

Observation period (1 Jan 2014 to 30 Apr 2018)

1 Jan 2015   1 Jan 2016   1 Jan 2017   31 Dec 2017

1 Jan 2014   1 May 2015   30 Apr 2016   30 Apr 2018

Index period (1 year)

**Examples of patients included**

X = Index date

LABD use

Baseline (1 year)   Follow-up (≥2 years)

**C**

**Yearly LABD initiation rates**

Observation period (1 Jan 2014 to 30 Apr 2018)

1 Jan 2015   1 Jan 2016   1 Jan 2017   31 Dec 2017

1 Jan 2014   1 May 2015   30 Apr 2016   30 Apr 2018

Index period 2015   Index period 2016   Index period 2017

**Examples of patients included for each calendar year**

X = Index date

LABD use

Baseline (1 year)

LABD use

Baseline (1 year)

LABD use

Baseline (1 year)

**Figure 1** Study design, showing the observation and index periods for the main cohort of all LABD users (**A**); the sub-cohort of new LABD users (**B**); and the additional analysis of yearly rates of LABD initiation (**C**).
**Notes:** The timeline depicted is not to scale. The schematic shows an example index date, ie, the first prescription for an LABD during the index period, with the associated baseline period (≥12 months) shown preceding this (for all LABD users) and the relevant follow-up period (24 months), for new LABD users only, subsequently.
**Abbreviation:** LABD, long-acting bronchodilator.

own assessment of a patient, or as a result of specialist assessment that was then relayed back to general practice. The data extract from HealthStat used in this study was collected on 30 April 2018.

## Outcome Definitions

Patients receiving LABD treatment and the sub-cohort of new LABD users were characterized according to demographic information and clinical characteristics collected during the baseline period. Demographics included: 1) age (40–49, 50–59, 60–69, ≥70 years); 2) sex (female, male); 3) ethnicity (Māori, Pacific, Asian, other); 4) body mass index (BMI; underweight [<18.5], normal [18.5–24.9], overweight [25.0–29.9], obese [≥30], unknown); and 5) smoking (never smoked, ex-smoker, current smoker). Clinical characteristics were: 1) comorbidities (including asthma, ischemic heart disease, diabetes mellitus, and heart failure) ever recorded, defined according to a diagnostic coding system used within HealthStat; and 2) the number of moderate and/or severe exacerbations during baseline (categorized as 0, 1, ≥2). Moderate exacerbations were defined as either a prescription for an oral corticosteroid and/or an antibiotic on the same day; a COPD exacerbation medical diagnosis code (Supplementary Table 3); or a diagnosis of acute bronchitis (based on medical diagnosis code). Severe exacerbations were defined as an emergency department attendance or hospitalization for COPD; or a COPD exacerbation medical diagnosis code (Supplementary Table 3). To be counted as unique episodes, exacerbation episodes must have been ≥14 days apart.

Treatment patterns of new LABD users during follow-up were examined by categorizing patients as those with no change to/continuous use of index treatment (Supplementary Figure 1) and those with a modification of index treatment (Supplementary Figure 2). Based on routine prescribing practice in New Zealand, the days' supply of each product containing a LABD was assumed to be for 90 days, and the days' supply of individual ICS prescriptions was assumed based on the number of daily doses recorded in the database. An index treatment was considered to be continued if a new prescription of the index treatment was recorded within the 60 days following the theoretical end of the previous prescription. A 60-day time window (later called the "break period") has been used for defining treatment patterns in other database analyses (for example, in Bogart et al[12] and Palli et al[13]), and here accounted for variations in the management of patients in routine practice. Patients were considered as not changing their treatment if they continued their index treatment throughout the follow-up period and did not receive another LABD during this period.

For patients who modified their treatment, four mutually exclusive types of modification were defined, as follows: 1) augmentation: patients who received a prescription for another LABD while still receiving their index LABD treatment; 2) direct switch: patients who received another LABD of the same class during the 60-day break period; 3) retreatment: patients who restarted their index treatment or a different LABD treatment after a break period of more than 60 days; and 4) discontinuation/step down: patients who either stepped down from their index treatment to a dual or monotherapy, or who stopped treatment altogether. For all patients with a modification of treatment during the 12 and 24 months of follow-up, the duration of index LABD up to the point of the treatment change was determined. The first date of the break period was the theoretical end date of the last prescription of index LABD treatment.

## Data Analysis

This was a descriptive study and no formal statistical comparisons between treatment groups were planned. No minimum sample size was therefore specified a priori and all patients within the HealthStat database satisfying the inclusion/exclusion criteria were included. Descriptive statistics – mean, standard deviation (SD), median, and interquartile range for continuous data, and frequency and percentage for categorical data – were used to describe patient demographic and clinical characteristics at baseline, overall and stratified by index LABD class. Similarly, descriptive statistics (frequency and percentage) were used to examine patterns of LABD use (treatment modifications) in new LABD users over 12 and 24 months of follow-up, and yearly rates of LABD initiation between 2015 and 2017. Patients who had previously received LABD treatment were included in the analysis of all LABD users, and were excluded from the new user analysis. All analyses were conducted by a statistician from HealthStat using SAS software, Version 9.4 (SAS Institute, Cary, NC). Aggregated results were shared with the study sponsor.

## Results

### Patient Disposition and Baseline Characteristics

Of 7829 patients with COPD in the HealthStat database at the time of data extraction, a total of 2140 (27.3%) fulfilled the selection criteria and were prescribed LABD therapy during the index period (May 2015 to

April 2016) (Figure 2). Baseline demographics and clinical characteristics are presented in Table 1. Of the 2140 patients, over half (55.6%) were female and the mean (SD) age was 66.6 (10.7) years. The mean (SD) BMI was 30.1 (8.7) kg/m$^2$, with over 70% of patients classed as either overweight (27.2%) or obese (43.5%). Most patients were European (63.1%), with one-third being Māori (30.3%), and most were current (57.7%) or ex-smokers (32.3%). A prior diagnosis of asthma was reported for half (49.0%) of patients, while over one-third (37.2%) had a comorbid mental condition. The mean (SD) number of exacerbations in the year prior to index was 1.6 (1.8), with over one-third (39.5%) of patients experiencing ≥2 prior exacerbations.

## LABD Treatment Patterns and Patient Characteristics

The most common treatment at study index among the 2140 patients was ICS/LABA (59.0%), followed by open triple therapy (26.7%). The remaining patients received either LAMA monotherapy (7.6%), LABA monotherapy (2.8%), LAMA and ICS (2.5%), or LAMA/LABA (1.4%)

(Table 1). Patients that were 40–49 years of age had the highest percentage of ICS/LABA use (80.9%; n = 114/ 141) relative to other age groups, while the percentage of patients using open triple therapy generally showed an increasing trend with age (Figure 3A). Use of the different LABD treatments was largely comparable across ethnic groups (Figure 3B).

When patients were stratified by index LABD treatment, some differences in clinical characteristics between groups were observed (Table 1). Patients receiving monotherapy had the lowest mean number of prior exacerbations (0.9 for LABA, 1.1 for LAMA), with a higher frequency in patients receiving dual therapy (1.4 for ICS/LABA, LAMA/LABA, and LAMA and ICS), and the highest for those patients on open triple therapy (2.2). This pattern reflects prior moderate exacerbations since only 4.0% (n = 134) of reported exacerbations were severe. Over half (n = 297/572, 51.9%) of patients receiving open triple therapy had ≥2 prior exacerbations, compared with 15.0% receiving LABA monotherapy and 29.6–36.8% for the other treatment groups (Figure 4). Patients receiving ICS/LABA had the highest BMI (mean [SD]: 31.0 [8.7]), with 72.6% (n = 916/1262) classed as
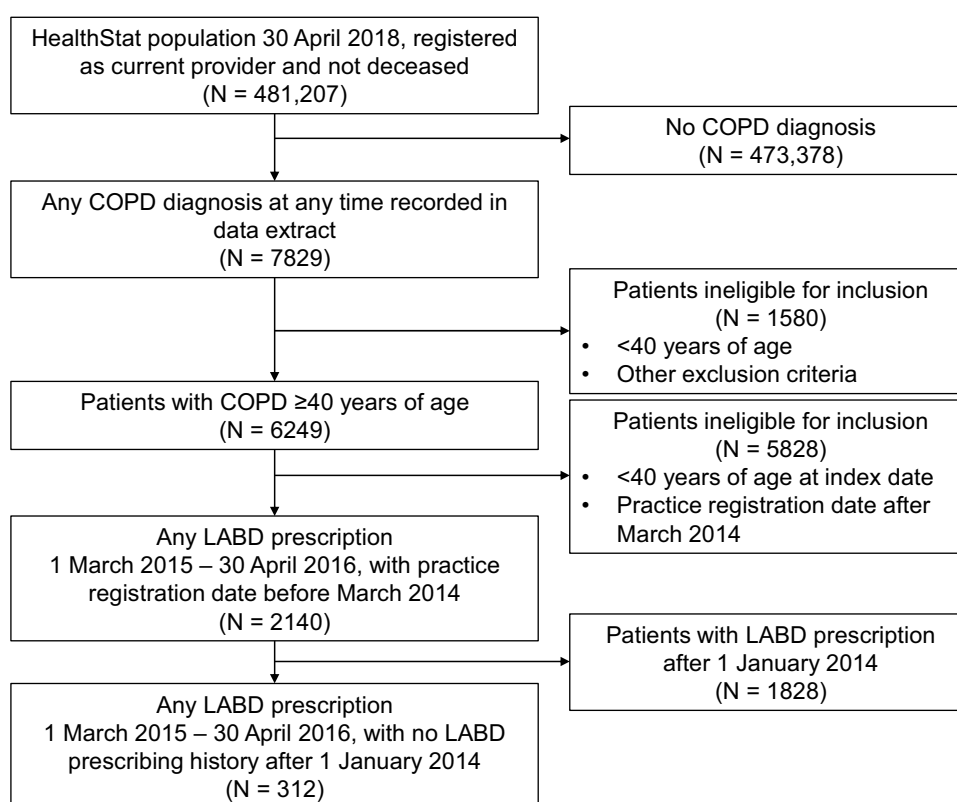


**Figure 2** Patient disposition for all LABD users.
**Abbreviations:** COPD, chronic obstructive pulmonary disease; LABD, long-acting bronchodilator.

**Table 1** Baseline Characteristics of All LABD Users, Stratified by Type of LABD Treatment

| | **Total** **(N = 2140)** | **Index LABD Treatment** | | | | | |
|---|---|---|---|---|---|---|---|
| | | **ICS/LABA** **(n = 1262)** | **Open Triple Therapy** **(n = 572)** | **LAMA Monotherapy** **(n = 162)** | **LABA Monotherapy** **(n = 60)** | **LAMA and ICS** **(n = 53)** | **LAMA/ LABA** **(n = 31)** |
| **Age, years** | | | | | | | |
| Mean (SD) | 66.6 (10.7) | 65.3 (11.1) | 68.2 (9.8) | 68.3 (9.6) | 68.1 (11.2) | 69.5 (9.7) | 68.3 (10.0) |
| Median (IQR) | 67.0 (15.8) | 65.4 (16.2) | 68.5 (14.0) | 68.3 (14.0) | 69.7 (18.9) | 70.8 (11.5) | 67.9 (14.5) |
| **Age groups, n (%)** | | | | | | | |
| 40–49 | 141 (6.6) | 114 (9.0) | 18 (3.2) | 4 (2.5) | 3 (5.0) | 1 (1.9) | 1 (3.2) |
| 50–59 | 461 (21.5) | 305 (24.2) | 102 (17.8) | 28 (17.3) | 14 (23.3) | 7 (13.2) | 5 (16.1) |
| 60–69 | 710 (33.2) | 406 (32.2) | 200 (35.0) | 63 (38.9) | 13 (21.7) | 15 (28.3) | 13 (41.9) |
| 70–79 | 613 (28.6) | 318 (25.2) | 190 (33.2) | 49 (30.3) | 23 (38.3) | 25 (47.2) | 8 (25.8) |
| ≥80 | 215 (10.1) | 119 (9.4) | 62 (10.8) | 18 (11.1) | 7 (11.7) | 5 (9.4) | 4 (12.9) |
| **Female, n (%)** | 1191 (55.6) | 750 (59.4) | 290 (50.7) | 80 (49.4) | 28 (46.7) | 28 (52.8) | 15 (48.4) |
| **Ethnicity, n (%)** | | | | | | | |
| European | 1350 (63.1) | 761 (60.3) | 364 (63.6) | 115 (71.0) | 45 (75.0) | 42 (79.3) | 23 (74.2) |
| Māori | 648 (30.3) | 417 (33.0) | 166 (29.0) | 40 (24.7) | 12 (20.0) | 8 (15.1) | 5 (16.1) |
| Pacific | 87 (4.1) | 56 (4.4) | 23 (4.0) | 3 (1.9) | 2 (3.3) | 2 (3.8) | 1 (3.2) |
| Asian | 36 (1.7) | 17 (1.4) | 15 (2.6) | 3 (1.9) | 1 (1.7) | 0 (0.0) | 0 (0.0) |
| Other | 19 (0.9) | 11 (0.9) | 4 (0.7) | 1 (0.6) | 0 (0.0) | 1 (1.9) | 2 (6.5) |
| **Smoking status, n (%)** | | | | | | | |
| Non-smoker | 213 (10.0) | 163 (12.9) | 37 (6.5) | 5 (3.1) | 6 (10.0) | 1 (1.9) | 1 (3.2) |
| Ex-smoker | 689 (32.2) | 377 (29.9) | 204 (35.7) | 55 (34.0) | 24 (40.0) | 14 (26.4) | 15 (48.4) |
| Smoker | 1235 (57.7) | 719 (57.0) | 331 (57.9) | 102 (63.0) | 30 (50.0) | 38 (71.7) | 15 (48.4) |
| Missing or unknown | 3 (0.1) | 3 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Prior exacerbations, n (%)** | | | | | | | |
| None | 738 (34.5) | 456 (36.1) | 145 (25.4) | 71 (43.8) | 28 (46.7) | 25 (47.2) | 13 (41.9) |
| 1 | 557 (26.0) | 342 (27.1) | 130 (22.7) | 43 (26.5) | 23 (38.3) | 11 (20.8) | 8 (25.8) |
| ≥2 | 845 (39.5) | 464 (36.8) | 297 (51.9) | 48 (29.6) | 9 (15.0) | 17 (32.1) | 10 (32.3) |
| **Mean (SD) number of exacerbations** | | | | | | | |
| All | 1.6 (1.8) | 1.4 (1.6) | 2.2 (2.1) | 1.1 (1.4) | 0.9 (1.3) | 1.4 (2.0) | 1.4 (1.8) |
| Moderate | 1.5 (1.7) | 1.4 (1.6) | 2.0 (2.0) | 1.1 (1.4) | 0.9 (1.3) | 1.3 (2.0) | 1.3 (1.6) |
| Severe | 0.1 (0.3) | 0.0 (0.2) | 0.1 (0.4) | 0.0 (0.2) | 0.0 (0.1) | 0.0 (0.2) | 0.1 (0.3) |
| **Median (IQR) number of exacerbations** | | | | | | | |
| All | 1.0 (2.0) | 1.0 (2.0) | 2.0 (3.0) | 1.0 (2.0) | 1.0 (1.0) | 1.0 (2.0) | 1.0 (2.0) |
| Moderate | 1.0 (2.0) | 1.0 (2.0) | 1.0 (3.0) | 1.0 (2.0) | 1.0 (1.0) | 1.0 (2.0) | 1.0 (2.0) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Comorbidities, n (%)[a]** | | | | | | | |
| Asthma | 1048 (49.0) | 684 (54.2) | 286 (50.0) | 44 (27.2) | 17 (28.3) | 12 (22.6) | 5 (16.1) |
| Ischemic heart disease | 450 (21.0) | 253 (20.0) | 129 (22.6) | 33 (20.4) | 16 (26.7) | 18 (34.0) | 1 (3.2) |
| Diabetes mellitus | 489 (22.9) | 280 (22.2) | 148 (25.9) | 37 (22.8) | 11 (18.3) | 9 (17.0) | 4 (12.9) |
| Heart failure | 317 (14.8) | 185 (14.7) | 95 (16.6) | 19 (11.7) | 8 (13.3) | 5 (9.4) | 5 (16.1) |
| Stroke | 222 (10.4) | 134 (10.6) | 53 (9.3) | 18 (11.1) | 5 (8.3) | 10 (18.9) | 2 (6.5) |
| Mental conditions | 797 (37.2) | 485 (38.4) | 201 (35.1) | 59 (36.4) | 21 (35.0) | 18 (34.0) | 13 (41.9) |
| **BMI, kg/m$^2$** | | | | | | | |
| Mean (SD) | 30.1 (8.7) | 31.0 (8.7) | 29.3 (8.6) | 28.3 (9.2) | 28.1 (7.5) | 27.1 (6.1) | 29.6 (7.7) |
| Median (IQR) | 28.5 (10.0) | 29.4 (10.4) | 27.8 (9.7) | 27.0 (9.1) | 27.6 (8.4) | 26.5 (7.6) | 29.5 (10.1) |

*(Continued)*

**Table 1** (Continued).

| | Total (N = 2140) | Index LABD Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | ICS/LABA (n = 1262) | Open Triple Therapy (n = 572) | LAMA Monotherapy (n = 162) | LABA Monotherapy (n = 60) | LAMA and ICS (n = 53) | LAMA/ LABA (n = 31) |
| **BMI category, n (%)** | | | | | | | |
| Underweight (<18.5) | 76 (3.7) | 30 (2.5) | 30 (5.2) | 13 (8.0) | 1 (1.7) | 2 (3.8) | 0 (0) |
| Normal (18.5–24.9) | 531 (24.8) | 269 (21.3) | 160 (28.0) | 50 (30.9) | 21 (35.0) | 20 (37.7) | 11 (35.5) |
| Overweight (25.0–29.9) | 566 (26.4) | 341 (27.0) | 147 (25.7) | 40 (24.7) | 19 (31.7) | 14 (26.4) | 5 (16.1) |
| Obese (≥30) | 903 (42.2) | 575 (45.6) | 222 (38.8) | 56 (34.6) | 19 (31.7) | 17 (32.1) | 14 (46.2) |

**Note:** [a]Recorded at any point during the study period.
**Abbreviations:** BMI, body mass index; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

overweight or obese compared with approximately 60% for all other treatments. Half of the patients receiving ICS/LABA (n = 684/1262, 54.2%) and open triple therapy (n = 286/572, 50.0%) had a comorbid diagnosis of asthma, compared with 16.1–28.3% of patients with comorbid asthma who received other treatments. One-third (n = 18/53, 34.0%) of patients receiving LAMA and ICS had ischemic heart disease (3.2–26.7% for other treatments),
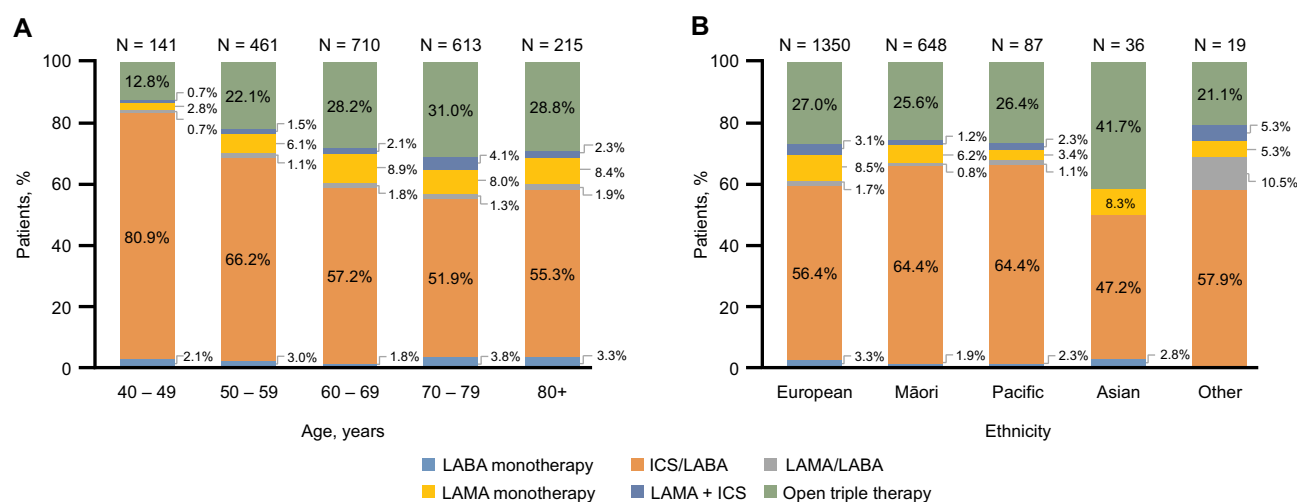


**Figure 3** LABD treatment for all LABD users, stratified by patient age at index (**A**) and ethnicity (**B**).
**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist.
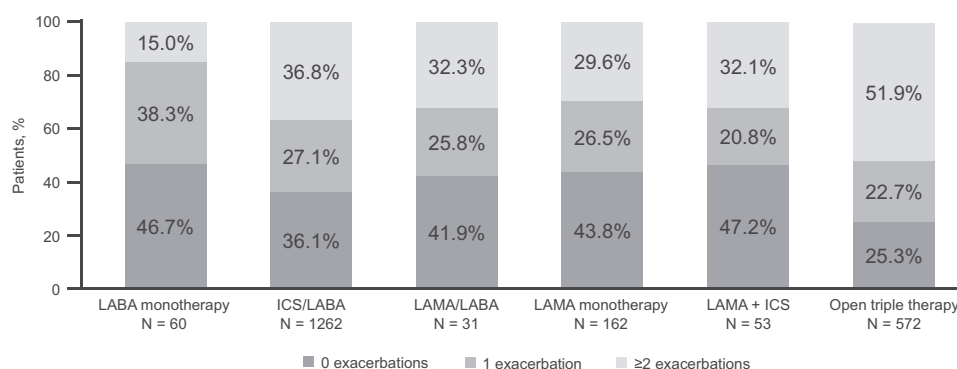


**Figure 4** Patient exacerbation history at index for all LABD users, stratified by type of LABD treatment.
**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist.

while one-quarter (n = 148/572, 25.9%) of patients on open triple therapy had diabetes (12.9–22.8% for other treatments).

## New LABD Users

### Treatment Patterns and Patient Characteristics

Of the 2140 patients receiving an LABD, 312 (14.6%) were new LABD users and had 24 months of follow-up. Overall, baseline characteristics for new LABD users were largely comparable with the overall population (Table 2). Over half (56.7%) were female, the mean (SD) age was 65.4 (10.7) years, and the mean (SD) BMI was 30.1 (9.0) kg/m$^2$ (69.9% were overweight or obese). Patients were mostly European (59.3%) or Māori (37.2%), and two-thirds were current smokers (65.4%). Asthma was present in one-third (33.3%) of patients, and mental conditions in over one-third (38.8%). The mean (SD) number of exacerbations in the year prior to index was 1.2 (1.3), notably lower than observed in the main cohort (1.6 [1.8]).

New LABD users most often started LABD treatment with ICS/LABA (n = 217/312, 69.6%), while 16.0% (n = 50/312) started LAMA monotherapy, and 14.4% (n = 45/312) other treatments (7.7% LABA monotherapy, 3.2% open triple therapy, 2.2% LAMA/LABA, and 1.3% LAMA and ICS). ICS/LABA was highest in younger patients (40–49 years of age; n = 19/23, 82.6%) and was similar across other age groups (decreasing from 69.7% [n = 53/76] in patients 50–59 years of age to 64.5% [n = 20/31] in patients ≥80 years of age). LAMA monotherapy generally increased with age, ranging from 4.3% (n = 1/23) in patients 40–49 years of age to 22.6% (n = 7/31) in patients ≥80 years of age (Figure 5). Among new LABD users, the majority of patients were either European (n = 185) or Māori (n = 116), and a greater proportion of Māori patients (75%) were found to initiate treatment with ICS/LABA compared with European patients (64.9%). Starting LABD treatment with ICS/LABA was also seen in all patients of Asian (n = 4) or other (n = 2) ethnic origin, and 80% of patients with a Pacific ethnic origin (n = 5), all of whom made up the minority of new LABD users.

Results after stratification according to treatment group are described only for the ICS/LABA and LAMA monotherapy groups (Table 2) due to small sample sizes for other treatments (and the heterogeneous nature of the combined group). The mean (SD) number of prior exacerbations was comparable for patients initiating ICS/LABA (1.3 [1.3]) and those initiating LAMA monotherapy (1.3 [1.6]). This pattern reflects prior moderate exacerbations

since only 5.8% (n = 22) of reported exacerbations were severe. Current or previous smoking was more common in patients initiating LAMA monotherapy (48/50, 96.0%) compared with ICS/LABA (191/217, 88.0%), while over twice as many patients initiating ICS/LABA (85/217, 39.2%) than LAMA monotherapy (8/50, 16.0%) had a prior asthma diagnosis. Patients initiating ICS/LABA also had a higher proportion of mental conditions (39.2% [n = 85/217] vs 28.0% [n = 14/50]), heart failure (16.1% [n = 35/217] vs 10.0% [n = 5/50]), and stroke (12.0% [n = 26/217] vs 4.0% [n = 2/50]), compared with those initiating LAMA monotherapy.

### Treatment Pathway Modifications

Of the 312 new LABD users, 31.1% (n = 97/312) continued (ie, had breaks of <60 days between prescriptions) with their index treatment after 12 months, while 68.9% (n = 215/312) modified their treatment; and 13.5% (n = 42/312) continued with their index treatment after 24 months compared with 86.5% (n = 270/312) who modified their treatment. Time to and type of treatment modification data – categorized as augmentation, direct switch, retreatment, or discontinuation/step down – are presented in Table 3. The mean (SD) duration of index LABD until first treatment modification was 175.5 (82.6) days during the first 12 months and 244.1 (163.2) days over 24 months. Patients who received LAMA monotherapy had a longer mean time to treatment modification over 24 months than patients receiving ICS/LABA or another treatment (265.8 days vs 243.9 days and 211.5 days, respectively).

Of those patients with a treatment modification during 24 months of follow-up, 23.0% of patients augmented their treatment (21.4% at 12 months), 7.0% had a direct switch of treatment (6.0% at 12 months), and 45.6% underwent retreatment (31.6% at 12 months). Overall, 24.4% of patients discontinued/stepped down their index treatment in the 24-month follow-up period. When assessing the type of modification stratified by index treatment group, augmentation was more frequent for patients receiving LAMA monotherapy compared with ICS/LABA (41.9% vs 16.6%, respectively, at 24 months) and a direct switch to another LABD was less frequent (2.3% vs 7.5%, respectively, at 24 months). A lower proportion of patients receiving LAMA monotherapy underwent retreatment versus patients who were receiving ICS/LABA (39.5% vs 53.6%, respectively, at 24 months). The proportion of patients who discontinued/stepped

**Table 2** Baseline Characteristics of New LABD Users, Stratified by Type of LABD Treatment

| | Total (N = 312) | Index LABD Treatment | | |
|---|---|---|---|---|
| | | ICS/LABA (n = 217) | LAMA Monotherapy (n = 50) | Other[a] (n = 45) |
| **Age, years** | | | | |
| Mean (SD) | 65.4 (10.7) | 64.9 (10.6) | 68.0 (10.5) | 65.3 (10.7) |
| Median (IQR) | 64.4 (16.5) | 64.4 (15.4) | 66.4 (14.8) | 63.4 (15.5) |
| **Age groups, n (%)** | | | | |
| 40–49 | 23 (7.4) | 19 (8.8) | 1 (2.0) | 3 (6.7) |
| 50–59 | 76 (24.4) | 53 (24.4) | 10 (20.0) | 13 (28.9) |
| 60–69 | 113 (36.2) | 78 (35.9) | 20 (40.0) | 15 (33.3) |
| 70–79 | 69 (22.1) | 47 (21.7) | 12 (24.0) | 10 (22.2) |
| ≥80 | 31 (9.9) | 20 (9.2) | 7 (14.0) | 4 (8.9) |
| **Female, n (%)** | 177 (56.7) | 135 (62.2) | 24 (48.0) | 18 (40.0) |
| **Ethnicity, n (%)** | | | | |
| European | 185 (59.3) | 120 (55.3) | 33 (66.0) | 32 (71.1) |
| Māori | 116 (37.2) | 87 (40.1) | 16 (32.0) | 13 (28.9) |
| Pacific | 5 (1.6) | 4 (1.8) | 1 (2.0) | 0 (0.0) |
| Asian | 4 (1.3) | 4 (1.8) | 0 (0.0) | 0 (0.0) |
| Other | 2 (0.6) | 2 (0.9) | 0 (0.0) | 0 (0.0) |
| **Smoking status, n (%)** | | | | |
| Non-smoker | 31 (9.9) | 26 (12.0) | 2 (4.0) | 3 (6.7) |
| Ex-smoker | 77 (24.7) | 46 (21.2) | 14 (28.0) | 17 (37.8) |
| Smoker | 204 (65.4) | 145 (66.8) | 34 (68.0) | 25 (55.6) |
| **Prior exacerbations, n (%)** | | | | |
| None | 112 (35.9) | 73 (33.6) | 20 (40.0) | 19 (42.2) |
| 1 | 97 (31.1) | 65 (30.0) | 14 (28.0) | 18 (40.0) |
| ≥2 | 103 (33.0) | 79 (36.4) | 16 (32.0) | 8 (17.8) |
| **Mean (SD) number of exacerbations** | | | | |
| All | 1.2 (1.3) | 1.3 (1.3) | 1.3 (1.6) | 1.0 (1.2) |
| Moderate | 1.2 (1.3) | 1.2 (1.3) | 1.3 (1.6) | 1.0 (1.2) |
| Severe | 0.1 (0.3) | 0.1 (0.3) | 0.0 (0.1) | 0.0 (0.0) |
| **Median (IQR) number of exacerbations** | | | | |
| All | 1.0 (2.0) | 1.0 (2.0) | 1.0 (2.0) | 1.0 (1.0) |
| Moderate | 1 (2.0) | 1 (2.0) | 1.0 (2.0) | 1.0 (1.0) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Comorbidities, n (%)[b]** | | | | |
| Asthma | 104 (33.3) | 85 (39.2) | 8 (16.0) | 11 (24.4) |
| Ischemic heart disease | 56 (17.9) | 40 (18.4) | 9 (18.0) | 7 (15.6) |
| Diabetes mellitus | 63 (20.2) | 42 (19.4) | 12 (24.0) | 9 (20.0) |
| Heart failure | 50 (16.0) | 35 (16.1) | 5 (10.0) | 10 (22.2) |
| Stroke | 32 (10.3) | 26 (12.0) | 2 (4.0) | 4 (8.9) |
| Mental conditions | 121 (38.8) | 85 (39.2) | 14 (28.0) | 22 (48.9) |
| **BMI, kg/m$^2$** | | | | |
| Mean (SD) | 30.1 (9.0) | 30.5 (9.0) | 29.2 (8.8) | 29.0 (8.8) |
| Median (IQR) | 28.2 (9.6) | 28.3 (9.4) | 28.6 (9.8) | 27.9 (11.0) |

(*Continued*)

Table 2 (Continued).

| | Total (N = 312) | Index LABD Treatment | | |
|---|---|---|---|---|
| | | ICS/LABA (n = 217) | LAMA Monotherapy (n = 50) | Other[a] (n = 45) |
| **BMI category, n (%)** | | | | |
| Underweight (<18.5) | 8 (2.6) | 4 (1.8) | 2 (4.4) | 2 (4.4) |
| Normal (18.5–24.9) | 81 (26.0) | 53 (24.4) | 13 (26.0) | 15 (33.3) |
| Overweight (25.0–29.9) | 87 (27.9) | 65 (30.0) | 13 (26.0) | 9 (20.0) |
| Obese (≥30) | 131 (42.0) | 93 (42.9) | 20 (40.0) | 18 (40.0) |

**Note:** [a]Includes pooled numbers from patients who were receiving LABA monotherapy (n = 24); open triple therapy with LABA+LAMA+ICS: (n = 10); LAMA/LABA (n = 7); and LAMA+ICS (n = 4). These subtypes are not reported individually due to small sample size. [b]Recorded at any point during the study period.
**Abbreviations:** BMI, body mass index; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

down treatment was also lower for LAMA monotherapy (16.3%) compared with ICS/LABA (22.5%). The same shift in patients who discontinued/stepped down treatment, or who were retreated, between 24 months and 12 months was observed in both groups. The results for a direct switch and augmentation at 24 months were similar to those at 12 months for each treatment group; the one exception was the proportion receiving LAMA monotherapy who augmented treatment, which increased from 12 months (31.3%) to 24 months (41.9%) (Table 3).

### LABD Treatment Evolution Across 2015–2017
The yearly rates of LABD initiation in COPD patients who were LABD initiators in 2015, 2016, and 2017 are presented in Figure 6. Initiation of LAMA (alone or in combination) increased from 16.6% (n = 56/337) in 2015 to 41.5% (n = 159/383) in 2016 and 45.8% (n = 211/461) in 2017. This increase was seemingly driven by an increase

in LAMA monotherapy – from 16.6% in 2015 to 40.1% in 2017 – and likely reflects access to new drugs, with a concurrent decline in the prescribing of tiotropium. Prescribing of ICS for LABD initiators remained stable at approximately 20% across the 3-year period.

## Discussion
Few data describe LABD treatment patterns in patients with COPD in New Zealand at the time of changes to the PHARMAC prescribing criteria and GOLD recommendations in 2016. There remains an opportunity to better optimize LABD treatments for patients with COPD. Utilizing comprehensive primary care data from the HealthStat general practice database in New Zealand, we performed a retrospective analysis of LABD use across 2015–2017. We found a predominant use of ICS/LABA (59% of all patients) at index that was apparent across all age groups surveyed. The use of ICS/LABA was, as
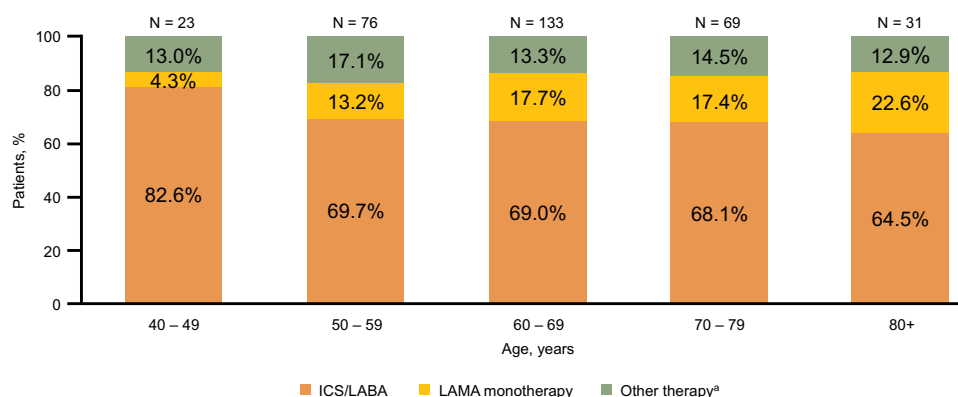


**Figure 5** LABD treatment in new LABD users, stratified by patient age at index.
**Note:** [a]LABA monotherapy, open triple therapy with LAMA+LABA+ICS, LAMA/LABA, or LAMA+ICS.
**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist.

**Table 3** Time to and Type of Treatment Modifications Over 12 and 24 Months in New LABD Users

| | Total (N = 312) | Index LABD Treatment | | |
|---|---|---|---|---|
| | | **ICS/LABA** (n = 217) | **LAMA Monotherapy** (n = 50) | **Other[a]** (n = 45) |
| **12-month period after initiation** | | | | |
| Patients with continuous use of index treatment, n (%) | 97 (31.1) | 67 (30.9) | 18 (36.0) | 12 (26.7) |
| Patients with modification of index treatment, n (%) | 215 (68.9) | 150 (69.1) | 32 (64.0) | 33 (73.3) |
| **Time to first treatment modification, days** | | | | |
| Mean ± SD | 175.5 ± 82.6 | 182.0 ± 82.1 | 175.6 ± 95.3 | 145.8 ± 65.9 |
| Median (IQR) | 150 (67.0) | 150 (101.0) | 150 (72.0) | 150.0 (0.0) |
| **Type of treatment modification, n (%)** | | | | |
| Augmentation | 46 (21.4) | 25 (16.7) | 10 (31.3) | 11 (33.3) |
| Direct switch | 13 (6.0) | 11 (7.3) | 1 (3.1) | 1 (3.0) |
| Retreatment | 68 (31.6) | 52 (34.7) | 12 (37.5) | 4 (12.1) |
| Discontinuation/step down | 88 (40.9) | 62 (41.3) | 9 (28.1) | 17 (51.5) |
| **24-month period after initiation** | | | | |
| Patients with continuous use of index treatment, n (%) | 42 (13.5) | 30 (13.8) | 7 (14.0) | 5 (11.1) |
| Patients with modification of index treatment, n (%) | 270 (86.5) | 187 (86.2) | 43 (86.0) | 40 (88.9) |
| **Time to first treatment modification, days** | | | | |
| Mean ± SD | 244.1 ± 163.2 | 243.9 ± 152.0 | 265.8 ± 189.4 | 221.5 ± 184.2 |
| Median (IQR) | 150 (182.0) | 150 (177.0) | 184 (222.0) | 150 (54.5) |
| **Type of treatment modification, n (%)** | | | | |
| Augmentation | 62 (23.0) | 31 (16.6) | 18 (41.9) | 13 (32.5) |
| Direct switch | 19 (7.0) | 14 (7.5) | 1 (2.3) | 4 (10.0) |
| Retreatment | 123 (45.6) | 100 (53.6) | 17 (39.5) | 6 (15.0) |
| Discontinuation/step down | 66 (24.4) | 42 (22.5) | 7 (16.3) | 17 (42.5) |

**Note:** [a]Includes pooled data from patients receiving LABA monotherapy (n = 24); open triple therapy with LABA+LAMA+ICS: (n = 10); LAMA/LABA (n = 7); and LAMA+ICS (n = 4). These subtypes are not reported individually due to small sample size.
**Abbreviations:** ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting $\beta_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

expected, slightly higher in those with prior asthma compared with those with COPD alone (65% vs 53%, respectively). Additionally, ICS/LABA was the most frequently prescribed treatment for new LABD users (70%). Although ICS/LABA use was highest in all age groups studied, more patients >80 years old (N = 31) were receiving LAMA monotherapy in this group compared to younger age groups. The potential risk of serious side effects associated with ICS treatment may be higher for older patients than younger patients[14,15] possibly explaining why more older patients were receiving LAMA monotherapy instead of ICS/LABA combination therapy; however, this result should be regarded with caution given the small sample size (N = 31). We found small differences in clinical characteristics, such as BMI,

comorbidities (eg, prior asthma history, ischemic heart disease, mental conditions), ethnicity, smoking, and exacerbation history, between LABD treatment groups. In new LABD users, continuous use was 31% and 13% after 12 and 24 months, respectively; retreatment was the most frequent treatment modification after 24 months, occurring in almost half of patients (46%), with treatment augmentation for 23% of patients. Among new LABD users between 2015 and 2017, we found increasing prescription of LAMA (alone or in combination; 17% to 46%), but stable use of ICS (approximately 20%).

Our finding of ICS/LABA as the predominant regimen prescribed for the treatment of COPD is consistent with a previous report in New Zealand. In a retrospective nationwide follow-up study of 83,435 patients initiating
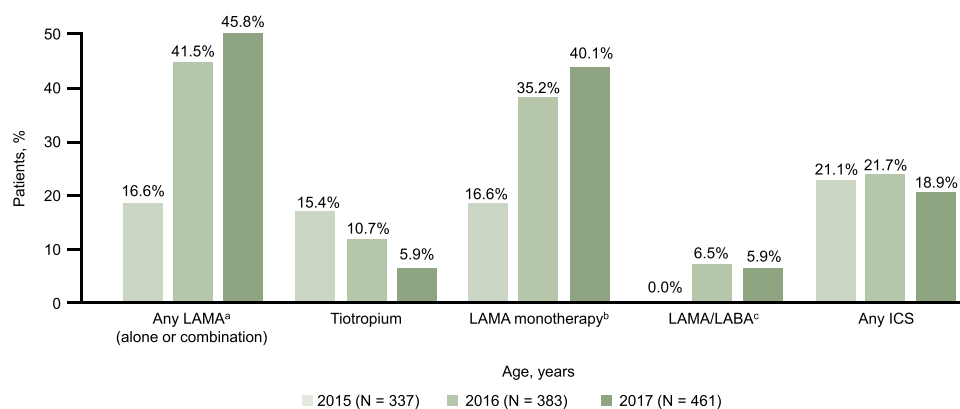
**Figure 6** Yearly rates of LABD initiation from 2015 to 2017.
**Notes:** Patients could have had multiple concurrent prescriptions for LABD, eg, for a LAMA and for a LAMA/LABA combination therapy. [a]LAMA monotherapy or LAMA +LABA combination therapy in two inhalers, including tiotropium. [b]LAMA monotherapy, including tiotropium. [c]LAMA/LABA combination therapy in one inhaler; includes glycopyrronium+indacterol, tiotropium+olodaterol, and umeclidinium+vilanterol.
**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting β$_2$-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist.

LABD therapy for COPD between 2006 and 2013, LABA in combination with an ICS was the most frequently dispensed regimen (64.8%), followed by LABA (21.4%) and LAMA (10.6%) monotherapies.[16] Initiation of a triple therapy regimen was not common, with only 201 patients (0.2%) initiating LABA+LAMA+ICS,[16] similar to the findings from our study where 3.2% of LABD users initiated on open triple therapy. This likely reflects more mild disease in patients newly starting LABD therapy, compared with long-term users, although data on COPD severity and/or spirometry would be needed to confirm this. More recently, in an Australian cohort study of 12,263 individuals ≥50 years of age receiving medications for COPD in April 2016, 41.7% were managed on monotherapy, 36.3% on dual therapy, and 20.5% on triple therapy.[17] Although we observed a comparable proportion (26.7%) receiving (open) triple therapy in our study as in the Australian cohort, our study conversely found almost twice as many patients (62.9%) were managed on dual therapy and significantly fewer (10.4%) were managed on monotherapy, which may reflect prescribing differences between countries. This is not something that was investigated in our study, but could be of interest in future research.

Previous work has shown that the patterns of LAMA, LABA, and ICS use for COPD in New Zealand often do not comply with clinical guidelines for treating COPD.[16] Similarly, the predominant use of ICS/LABA we observed during the 1-year index period (May 2015 to April 2016) may not necessarily be consistent with clinical guidelines for COPD treatment, which advocate dual bronchodilation

prior to ICS.[1] This finding, however, may in part reflect that half (49.0%) of our cohort had a history of asthma, the recommended treatment for which is an ICS-containing regimen.[18] Patients receiving ICS/LABA and open triple therapy had a higher rate of asthma diagnosis (54.2% and 50.0%, respectively) compared with those receiving non-ICS-containing treatments (16.1–28.3% across groups). The frequent use of ICS/LABA may also reflect patient exacerbation history, and previous studies have reported that patients with coexistent asthma have greater symptoms and exacerbations than those with COPD alone.[19–21] Ethnicity may also have influenced individual susceptibility to exacerbations; for example, it has been documented that Māori peoples have higher rates of chronic bronchitis (a diagnosis of which in our study was defined as a "moderate" COPD exacerbation), and suffer symptoms at a younger age than Europeans do.[21] Overall, approximately two-thirds of the patients receiving ICS/LABA had experienced one or more exacerbations in the previous 12 months (all LABD users: 63.9%; new LABD users: 66.4%).

Moreover, that ICS/LABA was the predominant treatment reflects clinical practice at the time related to the limited number and availability of other treatments (prior to March 2016). Notably, tiotropium was the only LAMA available up to November 2014, when glycopyrronium was introduced, with both requiring that patients satisfy PHARMAC Special Authority approval criteria to receive funding.[7] The increase in initiation of LAMA monotherapy from 16.6% in 2015 to 40.1% in 2017 suggests that both the introduction of a further LAMA (umeclidinium) and the removal of Special Authority approval criteria for

glycopyrronium in March 2016 impacted positively on patients at the primary care level. The requirement for prior stabilization of patients with LAMA alone before LAMA/LABA combination therapy may also have contributed. Conversely, use of tiotropium, which maintained its Special Authority approval criteria, showed a decline over the same period (15.4% in 2015 to 5.9% in 2017), while prescribing of ICS remained stable (approximately 20%). Overall, our findings suggest a change in prescribing practice associated with changing PHARMAC prescribing criteria, which could be of interest to policymakers when considering the impact of policy changes in general practice.

For the sub-cohort of new LABD users, continuous use with index treatment was low, approximately 30% at 12 months and less than half of this (13.5%) at 24 months. Modification of index treatment was thus common in our cohort, a finding consistent with previous studies of LABD initiation in patients with COPD.[16,22] The proportion of patients who augmented treatment or had a direct switch in our study was similar between 12 and 24 months, suggesting that such treatment changes occur in the first year following treatment initiation. The only exception to this was for LAMA monotherapy, for which augmentation increased between 12 and 24 months; however, LAMA had the longest overall mean time to treatment modification compared to any other LABDs, which may have been related to additional effects of LAMAs beyond improving bronchodilation – for example, a reduction in hyperinflammation of the lung versus ICS/LABA therapy.[23] A UK study that also analyzed COPD maintenance treatment changes found low direct switch rates of 4% for ICS/LABA therapy and 6% for LAMA monotherapy 24 months after starting LABD treatment (similar to our respective findings of 7.5% and 2.3%). However, while the proportion of patients augmenting treatment in both cohorts for that study was 36–37%, we found that 41% of patients starting LABD treatment with LAMA augmented treatment compared with 16.6% of patients starting on ICS/LABA treatment.[22] In our study, retreatment and discontinuation/step down were both types of treatment modification in which patients interrupted their index treatment. Both retreatment and discontinuation/step down were high after 12 and 24 months, occurring in a combined 73% and 70% of patients, respectively. Most of the patients who interrupted their index treatment during the 24-month follow-up underwent retreatment (likely from lapsed treatment), rather than discontinuing (either stepping down from, or completely stopping) treatment.

The high level of treatment re-initiation we observed may reflect irregular use of maintenance treatment by patients or the failure to capture some prescriptions in the database, either because a patient was hospitalized or was referred to another physician. The higher proportion of retreatment at 24 months (45.6%) versus 12 months (31.6%) may reflect censoring of data at 12 months when retreatment cannot be measured as accurately, while the longer 24-month time point allows this to be captured. A proportion of patients who did not re-initiate treatment at 24 months (ie, categorized as discontinued) might also have been categorized as re-initiating treatment if our observation period had been extended further to capture any subsequent prescriptions. The irregular use of treatment we observed, in particular, the high proportion of discontinuation/ step down and retreatment, may reflect well-known issues around patient treatment adherence. An estimated 50% or less of patients on long-term pharmacotherapy for chronic conditions are adherent to treatment,[24,25] with estimates for COPD showing an average of 40–60% of patients as adherent to prescribed medication regimens.[26] Improved adherence to inhaled therapies provides benefits in reducing symptom burden, hospitalization, and mortality.[27]

COPD places a large burden on the healthcare system in New Zealand. There is well established disparity, however, in the size of this burden in different ethnic groups, with a greater burden apparent in Māori.[3,4,28,29] In our study, in which approximately one-third (30.3%) of patients were Māori and most (63.1%) European, we did not observe major differences in the use of the different LABD treatments across ethnic groups, but there was a slightly higher use of ICS/LABA in Māori compared with European patients (all LABD users: 64.6% vs 56.4%; new LABD users: 75.0% vs 64.9%), which is consistent with previously reported findings in New Zealand.[29] It is possible that this reflects the reported higher incidence of severe disease in Māori over other ethnic groups.[4] Further study is needed to explore the reasons for the known disparity in the Māori population. Use of ICS/LABA was also greater in younger patients, both overall and in new LABD users, while open triple therapy use was more common in older patients, consistent with greater disease progression. Indeed, open triple therapy was the second most frequently used treatment in older patients with prior exacerbations, while the proportion of patients with one or more prior exacerbations was highest in those receiving triple therapy (74.6% had at least one, and 51.9% two or more, prior exacerbations). This is aligned with guidelines for the use of triple therapy. Similarly,

findings from a recent retrospective review of healthcare utilization in patients with severe COPD reported that triple therapy was the most common treatment regimen at admission.[30] Variations in asthma prevalence between discrete age groups and different ethnicities could also have affected the overall proportions of ICS/LABA users in these groups. We did not specifically stratify our results by COPD and/or asthma diagnosis, but this could be a factor of interest in future studies of prescription patterns among patients in New Zealand.

A strength of our study was that we based our analyses of LABD treatment patterns on data derived mainly from general practice, the clinical setting in which the management of COPD within the New Zealand healthcare system primarily takes place. For this purpose, we used the HealthStat general practice database, a comprehensive source of real-world primary care data for a large and well-characterized random sample of patients from approximately 10% of all general practices in New Zealand. Furthermore, these data are linked to hospital data from National Minimum Dataset. By also conducting a longitudinal analysis of treatment between 2015 and 2017, we were able to gain insight into the impact on LABD prescribing of changes in 2016 to the PHARMAC prescribing criteria and GOLD recommendations, and of the introduction of new treatments/inhalers (one ICS/LABA, two LAMA, and three LAMA/LABA) to the New Zealand market. We were able to capture this dynamic at the general practitioner level, which may inform on the implication of reimbursement restriction for management in COPD. Although the treatment patterns we describe may not necessarily be reflective of current-day trends in medication prescription, the identification of genuine treatment choices and patterns from a real-world setting may provide insight for both healthcare professionals and patients into optimizing LABD therapy prescription and persistence.

Our study has several limitations. While the study cohort was representative in terms of age and sex, the HealthStat database has a slight overrepresentation of Māori patients: 30.3%, compared with 16.5% (in 2018[31]) in the general population. This is due to higher response rates from practices with a higher than average number of Māori patients (who potentially have more severe disease). Moreover, of the eligible patients with COPD in HealthStat included in our study, 30.3% were Māori. There may thus be an element of imprecision in our data. The extent to which the higher proportion of Māori we

observed reflects over-representation in HealthStat or the higher prevalence of COPD in Māori[4] requires further study with larger datasets. Common to database studies, we made methodological estimates/assumptions, which may have led to bias. These included using data for prescriptions written as a proxy for LABD treatment use and deriving treatment patterns from prescription data. It is possible that prescriptions may have been missed for hospitalized patients (who may have received treatments while admitted), or those referred to a respiratory specialist. Moreover, whether patients actually administered their prescribed treatment may differ from prescription data.

It was also necessary to make assumptions regarding the duration of prescribed LABD medications and ICS products. Such assumptions were thought out to reflect clinical practice, such as a 90-day duration for LABD prescriptions based on prescriptions for chronic conditions in New Zealand typically lasting 3 months. Other potential limitations include the absence of data on COPD severity, the extent of smoking (pack-years), and from spirometry testing. Spirometry testing is generally under-performed in New Zealand: although the majority of practices had recorded pulmonary function test data in the HealthStat database, these data had not been recorded in a consistent or structured manner across practices and so their electronic extraction/subsequent inclusion in the final analysis was not feasible. The requirement for new LABD users to have 24 months of follow-up, which thereby excluded from all analyses the patients with the most severe disease who died during the study, is also a potential limitation. While not excluding patients with a prior asthma diagnosis may possibly have influenced the observed treatment patterns (such as the high use of ICS), our study cohort does reflect the situation commonly observed in everyday clinical practice. Future studies that stratify patients by asthma and/or COPD diagnosis would be useful for investigating treatment patterns between these groups, and in further helping to aid healthcare professionals with delivering the most appropriate care to patients.

## Conclusions

This retrospective analysis of LABD use among patients with COPD in New Zealand shows a high use of ICS/LABA across all age groups that may not necessarily be consistent with clinical guidelines for COPD, which recommend dual bronchodilation prior to addition of ICS in the absence of comorbid asthma. This finding, however, may reflect several factors, including an underlying prevalence of asthma, patient exacerbation history, and

unique local factors and culture. Moreover, this higher than expected use of ICS/LABA between May 2015 and April 2016 likely reflects LABDs available at the time and previous restrictions on the use of different LAMA, as set out by PHARMAC Special Authority criteria. Easing of these restrictions may have allowed treatment more closely aligned with clinical guidelines, a view supported by the observed increase in LAMA use across 2015–2017 (although not at the cost of ICS use). This increase may also have been influenced by PHARMAC criteria requiring stabilization with LAMA monotherapy prior to escalation to LAMA/LABA. Further studies in New Zealand are needed to better understand the impact of evolving treatment patterns and the low rate of continuous use with first prescribed LABD. Overall, our findings could be a useful reference for healthcare providers in optimizing LABD use among patients with COPD.

## Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from www. clinicalstudydatarequest.com.

## Acknowledgments

## Author Contributions

All authors made a significant contribution to the work reported (whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas); took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

## Disclosure

## References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report); 2021. Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT -2021-v1.1-25Nov20_WMV.pdf. Accessed February 4, 2021.

2. Cazzola M, Page C. Long-acting bronchodilators in COPD: where are we now and where are we going? *Breath*. 2014;10(2):111–120. doi:10.1183/20734735.014813

3. Shirtcliffe P, Weatherall M, Marsh S, et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J*. 2007;30(2):232–239. doi:10.1183/09031936.00157906

4. Barnard L, Zhang J. The impact of respiratory disease in New Zealand: 2018 update. Asthma + Respiratory Foundation NZ; 2019.

5. Yang IA, Brown JL, George J, et al. The COPD-X plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease; 2020. Available from: https://copdx.org.au/ copd-x-plan/Last. Accessed February 4, 2021.

6. Pharmaceutical Management Agency (PHARMAC). Medicine targeting: how do we target medicines? Available from: https://pharmac. govt.nz/medicine-funding-and-supply/the-funding-process/from-appli cation-to-funded-medicine-how-we-fund-a-medicine/medicine-target ing/. Accessed April 1, 2021.

7. Best Practice Advocacy Centre New Zealand (BPACnz). Newly-subsidised medicines for the treatment of patients with COPD. *Best Pract J*. 2016;74:7–13.

8. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S34–48. doi:10.1016/j.jaci.2011.12.983

9. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease (2017 report). GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195(5):557–582. doi:10.1164/rccm.201701-0218PP

10. Ministry of Health – Manatū Hauora (New Zealand Government). Enrolment in a primary health organisation; 2020. Available from: https://www.health.govt.nz/our-work/primary-health-care/about-primary-health-organisations/enrolment-primary-health-organisation. Accessed April 1, 2021.

11. HealthStat Primary Health Care Intelligence. HealthStat general practice database. http://www.healthstat.co.nz/Login.aspx?ReturnUrl=% 2fdefault.aspx. Accessed April 1, 2021.

12. Bogart M, Stanford RH, Laliberte F, et al. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *Int J Chron Obstruct Pulmon Dis*. 2019;14:343–352. doi:10.2147/ COPD.S184653

13. Palli SR, Frazer M, DuCharme M, et al. Differences in real-world health and economic outcomes among patients with COPD treated with combination tiotropium/olodaterol versus triple therapy. *J Manag Care Spec Pharm*. 2020;26(10):1363–1374. doi:10.18553/jmcp.2020.2015

14. Janson C, Johansson G, Ställberg B, et al. Identifying the associated risks of pneumonia in COPD patients: ARCTIC an observational study. *Respir Res*. 2018;19(1):172. doi:10.1186/s12931-018-0868-y

15. Price D, Yawn B, Brusselle G, et al. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J*. 2013;22 (1):92–100. doi:10.4104/pcrj.2012.00092

16. Parkin L, Barson D, Zeng J, et al. Patterns of use of long-acting bronchodilators in patients with COPD: a nationwide follow-up study of new users in New Zealand. *Respirology*. 2018;23(6):583–592. doi:10.1111/resp.13235

17. Lim R, Kerr M, Roughead EE. Use of medicines and health services for chronic obstructive pulmonary disease among a cohort of Australians over 50 years. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3085–3093. doi:10.2147/COPD.S172495

18. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention (2020 report); 2020. Available from: https:// ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04 -1-wms.pdf. Accessed April 1, 2021.

19. Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi SM, et al. Identification and definition of asthma-COPD overlap: the CanCOLD study. *Respirology*. 2020;25(8):836–849. doi:10.1111/resp.13780

20. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. *Respir Res*. 2011;12(1):127. doi:10.1186/1465-9921-12-127

21. Menezes AMB, Montes de Oca M, Pérez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest*. 2014;145(2):297–304. doi:10.1 378/chest.13-0622

22. Landis SH, Wurst K, Le HV, et al. Can assessment of disease burden prior to changes in initial COPD maintenance treatment provide insight into remaining unmet needs? A retrospective database study in UK primary care. *COPD*. 2017;14(1):80–85. doi:10.1080/ 15412555.2016.1240159

23. Santus P, Centanni S, Verga M, et al. Comparison of the acute effect of tiotropium versus a combination therapy with single inhaler budesonide/ formoterol on the degree of resting pulmonary hyperinflation. *Respir Med*. 2006;100(7):1277–1281. doi:10.1016/j.rmed.2005.10.008

24. World Health Organization (WHO). Adherence to long-term therapies: evidence for action; 2003. Available from: https://www.who. int/chp/knowledge/publications/adherence_full_report.pdf?ua=1. Accessed April 1, 2021.

25. Haynes RB, McDonald H, Garg AX, et al.Interventions for helping patients to follow prescriptions for medications. *Cochrane Database Syst Rev*. 2002;(2):Cd000011. doi:10.1002/14651858.CD000011

26. Restrepo RD, Alvarez MT, Wittnebel LD, et al. Medication adherence issues in patients treated for COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(3):371–384. doi:10.2147/COPD.S3036

27. Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*. 2009;64 (11):939–943. doi:10.1136/thx.2009.113662

28. Best Practice Advocacy Centre New Zealand (BPACnz). Diagnosis and management of COPD in Māori and Pacific peoples. *Best Pract J*. 2012;43:14–25.

29. Milne RJ, Beasley R. Hospital admissions for chronic obstructive pulmonary disease in New Zealand. *N Z Med J*. 2015;128 (1408):23–35.

30. Dummer J, Tumilty E, Hannah D, et al. Health care utilisation and health needs of people with severe COPD in the southern region of New Zealand: a retrospective case note review. *COPD*. 2020;17 (2):136–142. doi:10.1080/15412555.2020.1724275

31. Stats NZ Tatauranga Aotearoa (New Zealand Government). New Zealand's population reflects growing diversity. Ethnicity as a proportion of the population; 2019. Available from: https://www. stats.govt.nz/news/new-zealands-population-reflects-growing-diversity. Accessed August 1, 2020.