CHEST

Single-Inhaler Triple vs Long-Acting Beta$_2$-Agonist-Inhaled Corticosteroid Therapy for COPD

Comparative Safety in Real-World Clinical Practice

Samy Suissa, PhD; Sophie Dell'Aniello, MSc; and Pierre Ernst, MD

BACKGROUND: Recent treatment guidelines for COPD have replaced the long-acting beta$_2$-agonist (LABA) and inhaled corticosteroid (ICS) combination with single-inhaler triple therapy that adds a long-acting muscarinic antagonist (LAMA). However, the corresponding trials reported numerically higher incidences of cardiovascular adverse events with triple therapy compared with LABA-ICS.

RESEARCH QUESTION: Does single-inhaler triple therapy increase the incidence of major adverse cardiovascular events, compared with LABA-ICS, in a real-world clinical practice setting?

STUDY DESIGN AND METHODS: We identified a cohort of patients with COPD aged ≥ 40 years treated during 2017-2021 from the UK's Clinical Practice Research Datalink. Among LAMA-naive patients, initiators of single-inhaler triple therapy were matched 1:1 to LABA-ICS users on time-conditional propensity scores. They were compared on the incidence of major adverse cardiovascular events (MACEs), defined as hospitalization for myocardial infarction or stroke, or all-cause-mortality, over 1 year.

RESULTS: The cohort included 10,255 initiators of triple therapy and 10,255 matched users of LABA-ICS. The incidence rate of MACEs was 11.3 per 100 per year with triple therapy compared with 8.8 per 100 per year for LABA-ICS. The corresponding adjusted hazard ratio (HR) of MACEs with triple therapy was 1.28 (95% CI, 1.05-1.55), relative to LABA-ICS; however, the increase was mainly in the first 4 months (HR, 1.41; 95% CI, 1.14-1.74). The HR of all-cause death was 1.31 (95% CI, 1.06-1.62), whereas for acute myocardial infarction and stroke hospitalization it was 1.00 (95% CI, 0.56-1.79) and 1.06 (95% CI, 0.48-2.36), respectively, with triple therapy, relative to LABA-ICS.

INTERPRETATION: In a real-world setting of COPD treatment, patients who initiated single-inhaler triple therapy had an increased incidence of MACEs compared with similar patients treated with an LABA-ICS inhaler. This small increase was due to the all-cause mortality component, occurring mainly in the first 4 months after treatment initiation.

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KEY WORDS: cohort studies; major adverse cardiovascular events (MACE); mortality; new-user design; real-world evidence

ABBREVIATIONS: CPRD = Clinical Practice Research Datalink; ETHOS = Efficacy and Safety of Triple Therapy in Obstructive Lung Disease; HES = Hospital Episodes Statistics; HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th Revision; ICS = inhaled corticosteroid; IMPACT = Informing the Pathway of COPD Treatment; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; MACE = major adverse cardiovascular event

AFFILIATIONS: From the Centre for Clinical Epidemiology (S. S., S. D., and P. E.), Lady Davis Institute-Jewish General Hospital; Montreal, QC; and the Departments of Epidemiology, Biostatistics and Occupational Health (S. S.) and Medicine (S. S. and P. E.), McGill University, Montreal, QC, Canada.

CORRESPONDENCE TO: Samy Suissa, PhD; email: samy.suissa@mcgill.ca

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Take-home Points

Study Question: Is single-inhaler triple therapy for COPD associated with higher incidence of cardiovascular adverse events than a long-acting beta$_2$-agonist (LABA)-inhaled corticosteroid (ICS) combination, as suggested by the Informing the Pathway of COPD Treatment (IMPACT) and Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trials that reported numerically higher incidences of cardiovascular adverse events with triple therapy compared with LABA-ICS?

Results: In a large real-world clinical practice setting cohort of 10,255 initiators of triple therapy and 10,255 matched users of LABA-ICS, the hazard ratio of a major adverse cardiovascular event (MACE) with triple therapy was 1.28 (95% CI, 1.05-1.55), relative to LABA-ICS, mainly driven by the all-cause death component of MACE.

Interpretation: Patients with COPD who initiate single-inhaler triple therapy may have a small increase in the incidence of MACE, driven mainly by all-cause mortality, over the first year of use, when compared with similar patients treated with an LABA-ICS inhaler. A confirmation of this potential risk could be investigated by reanalysis of the IMPACT and ETHOS trials, stratified by prior long-acting muscarinic antagonist use. Cautious use of single-inhaler triple therapy in clinical practice could involve restricting it to the patient profile studied in the trials of these inhalers.

COPD is a leading cause of morbidity and mortality throughout the world.[1] Its treatment is based primarily on long-acting bronchodilator medications, including long-acting beta$_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), and antiinflammatory inhaled corticosteroids (ICSs).[2] There are now several dual and triple combinations of these drugs that are formulated in single inhalers.

Although the 2019 Global Initiative for Chronic Obstructive Lung Disease recommendations for the pharmacologic treatment of COPD included the LABA-ICS inhaler as a therapeutic choice, the more recent 2023 Global Initiative for Chronic Obstructive Lung Disease report has eliminated this option.[3,4] Thus, for example, the 2019 recommendation to use an LABA-ICS inhaler as initial therapy in patients with a history of exacerbations and high blood eosinophil count (> 300 cells/uL) was replaced by the 2023 recommendation to consider instead a triple LAMA-LABA-ICS combination, preferably in a single inhaler.[4] This elimination of the LABA-ICS treatment option was also evident in the 2023 Canadian Thoracic Society guideline.[5,6] The decision was mainly based on the results of two trials, Informing the Pathway of COPD Treatment (IMPACT) and Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS), that reported greater effectiveness with single-inhaler triple therapy compared with an LABA-ICS inhaler.[7,8]

On the other hand, the patients on triple therapy in IMPACT and ETHOS had a numerically higher incidence of cardiovascular adverse events than those receiving LABA-ICS.[7,8] Indeed, the hazard ratio (HR) of a confirmed major adverse cardiovascular event (MACE), reported in ETHOS, was 1.25 (95% CI, 0.73-2.15) with triple therapy compared with budesonide/formoterol.[8] In IMPACT, triple therapy had a numerically higher incidence than LABA-ICS for ischemic heart disease (26.1 vs 18.5 per 1,000 per year) and cerebrovascular events (12.1 vs 9.3 per 1,000 per year).[7]

We assessed the cardiovascular safety of a single-inhaler triple combination LAMA-LABA-ICS compared with LABA-ICS on the incidence of major cardiovascular events using a large population-based cohort formed from a real-world clinical practice setting. We used a new-user design to emulate a randomized trial.

Study Design and Methods

Data Source

The study cohort was identified from the Clinical Practice Research Datalink (CPRD), a primary care database from the United Kingdom that contains primary care medical records for > 50 million people enrolled in > 1,800 general practices. Participating general practitioners in the Aurum network record medical information as part of the routine care of patients, including demographic data, lifestyle factors, medical diagnoses recorded using Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) codes, and prescriptions. Over 85% of the CPRD practices can be linked to the Hospital Episodes Statistics (HES) database. The CPRD population is representative of the overall population, and these data sources have been validated.[9-11] The information

on medications and diagnoses has been validated and shown to be of high quality, particularly for studies of COPD.[10-14]

Study Design

The base cohort included all patients with a physician diagnosis of COPD who received a single-inhaler triple or a LABA-ICS combination after September 15, 2017, the date the first single-inhaler triple agent became available in the United Kingdom. All patients had to be aged ≥ 40 years on the date of their first COPD diagnosis. The study was restricted to patients linkable to the HES database.

From this base cohort, we used a prevalent new-user design to identify initiators of triple therapy and their matched users of LABA-ICS in a chronologic manner that attempts to mimic a randomized clinical trial (e-Fig 1).[15] By this design, each patient initiating triple therapy after September 15, 2017, generated a time-based exposure set, according to calendar time. Thus, an exposure set included all patients in the base cohort who had an LABA-ICS prescription within ± 1 month of the triple therapy initiator's date, and with the same duration (± 6 months) since their first LABA-ICS prescription, including the prescriptions received prior to September 15, 2017. Thus, patients who initiated triple therapy with no prior use of LABA-ICS were matched to patients who were new users of LABA-ICS (incident new users) at the same calendar time, whereas those who initiated triple therapy after switching from an LABA-ICS were matched to patients who also had been using LABA-ICS (prevalent new users) previously for the same duration. The members of the exposure set required at least 1 year of medical history before the exposure set time point to allow a baseline period to measure the covariates and to identify new and prevalent users. In addition, to avoid bias from prior exposure and in accordance with an adaptive selection strategy when comparing LAMA-LABA-ICS with LABA-ICS, a comparison to assess the addition of the LAMA component, we excluded patients who were previously treated with LAMAs, alone or in combination, during the baseline year.[16]

Time-conditional propensity scores were computed by conditional logistic regression as a function of covariates measured prior to the date of the time-based exposure set, separately for the incident and prevalent new-user strata defined by prior LABA-ICS treatment. Starting chronologically with the first patient initiating triple therapy, we selected as the matched LABA-ICS comparator the patient within the exposure set with the closest propensity score to the triple therapy initiator, after verifying the positivity assumption. The date of the triple therapy prescription and the corresponding date of the matched LABA-ICS prescription defined study cohort entry for the 1:1 matched pair. Patients were followed for up to 1 year from cohort entry, with follow-up ending at death, March 31, 2021, or the end of the patient's registration in the practice, whichever occurred first.

Outcome Events

The main safety outcome was a 3-point MACE that included hospitalization for acute myocardial infarction (International Classification of Diseases, 10th Revision [ICD-10]: I21.x), ischemic stroke (ICD-10: I63.x and I64.x), in primary or secondary position, and all-cause death. The former two cardiovascular events have been validated and shown to have high accuracy in the CPRD.[17,18]

Covariates

The time-conditional propensity score of triple therapy initiation was based on lifestyle, clinical diagnoses, and prescriptions from CPRD and HES data. Age, sex, region of practice, BMI, tobacco use, and alcohol misuse disorder were measured at or before cohort entry. The severity of COPD at treatment initiation was assessed by the number of prior moderate and severe COPD exacerbations and the frequency of use of other respiratory drugs, all measured during the baseline period. A moderate exacerbation was defined by a new prescription for prednisolone, and a severe exacerbation was defined as a hospitalization for COPD (ICD-10: J41, J42, J43, J44). Other respiratory drugs included short-acting inhaled beta-agonists and anticholinergics, methylxanthines, and antibiotics used for respiratory conditions. The most recent measures of dyspnea, FEV_1, and blood eosinophil count before cohort entry were identified. Dyspnea was measured by modified Medical Research Council Dyspnea Scale score, COPD Assessment Test score, or presence of dyspnea symptoms.[19] The % predicted FEV_1 measurement, generally postbronchodilator,[20] was calculated from the absolute FEV_1 value using age, sex, and height, with race imputed as White for all.[21] The 20% and 13% of patients who were missing data on FEV_1 and eosinophil count were included in the propensity score calculation by an indicator for missing. Baseline comorbidity, including from cardiovascular conditions, in the year before cohort entry was measured using clinical diagnoses, hospitalizations, and prescriptions (Table 1).

TABLE 1] Baseline Characteristics of the Study Cohort

Characteristic	Single-Inhaler Triple Therapy (n = 10,255)	Single-Inhaler LABA-ICS (n = 10,255)	Standardized Mean Difference
Age at cohort entry, y	70.5 [11.3]	70.6 [11.4]	0.0096
Female sex	5,351 (52.2)	5,430 (52.9)	0.0154
Active tobacco use	5,055 (49.3)	5,035 (49.1)	0.0039
Obesity status			
Obese	3,340 (32.6)	3,319 (32.4)	0.0044
Nonobese	6,473 (63.1)	6,479 (63.2)	0.0012
Missing	442 (4.3)	457 (4.5)	0.0071
Alcohol-related conditions	849 (8.3)	841 (8.2)	0.0028
FEV_1 % predicted[a]	57.2 [18.9]	57.9 [18.7]	0.0340
Blood eosinophil count, cells/μL[b]	244.7 [201.7]	248.5 [232.7]	0.0171
Severity of dyspnea			
None to mild	2,981 (29.1)	2,989 (29.1)	0.0017
Moderate to severe	6,335 (61.8)	6,360 (62.0)	0.0050
Missing	939 (9.2)	906 (8.8)	0.0112
Respiratory events and medications in year before cohort entry			
Hospitalization for COPD	1,346 (13.1)	1,219 (11.9)	0.0374
Moderate/severe COPD exacerbation			
0	4,285 (41.8)	4,316 (42.1)	0.0061
1	2,351 (22.9)	2,395 (23.4)	0.0102
≥ 2	3,619 (35.3)	3,544 (34.6)	0.0153
Asthma diagnosis	3,689 (36.0)	3,776 (36.8)	0.0176
Pneumonia hospitalization	938 (9.1)	893 (8.7)	0.0154
LABA only	370 (3.6)	370 (3.6)	0.0000
ICS only	938 (9.1)	946 (9.2)	0.0027
LABA-ICS[c]	7,806 (76.1)	7,806 (76.1)	0.0000
Short-acting beta-agonists	9,249 (90.2)	9,323 (90.9)	0.0247
Short-acting antimuscarinic	1,111 (10.8)	994 (9.7)	0.0376
Prednisolone	5,773 (56.3)	5,651 (55.1)	0.0240
Methylxanthines	326 (3.2)	311 (3.0)	0.0084
Leukotriene antagonists	530 (5.2)	570 (5.6)	0.0173
Respiratory antibiotics	7,627 (74.4)	7,660 (74.7)	0.0074
Comorbidity in year before cohort entry			
Hypertension	3,545 (34.6)	3,500 (34.1)	0.0092
Diabetes	2,248 (21.9)	2,195 (21.4)	0.0125
Ischemic heart disease	1,506 (14.7)	1,442 (14.1)	0.0178
Stroke (hospitalized)	311 (3.0)	287 (2.8)	0.0139
Heart failure	969 (9.4)	928 (9.0)	0.0138
Cancer	688 (6.7)	679 (6.6)	0.0035
Chronic kidney disease	1,207 (11.8)	1,255 (12.2)	0.0144
Other medication use in year before cohort entry			
ACE-inhibitors	2,562 (25.0)	2,517 (24.5)	0.0102
Angiotensin receptor blockers	1,286 (12.5)	1,286 (12.5)	0.0000
Beta-blockers	2,273 (22.2)	2,272 (22.2)	0.0002

(Continued)

TABLE 1] *(Continued)*

Characteristic	Single-Inhaler Triple Therapy (n = 10,255)	Single-Inhaler LABA-ICS (n = 10,255)	Standardized Mean Difference
Calcium channel blockers	2,841 (27.7)	2,823 (27.5)	0.0039
Thiazides diuretics	899 (8.8)	882 (8.6)	0.0059
Loop diuretics	2,159 (21.1)	2,118 (20.7)	0.0098
Antidiabetics	1,577 (15.4)	1,542 (15.0)	0.0095
Statins	4,969 (48.5)	4,927 (48.0)	0.0082
Antiplatelets	2,851 (27.8)	2,818 (27.5)	0.0072
Oral anticoagulants	1,468 (14.3)	1,430 (13.9)	0.0106
Antiarrhythmics	236 (2.3)	220 (2.1)	0.0106
NSAIDs	1,034 (10.1)	1,036 (10.1)	0.0006
Opioids	4,505 (43.9)	4,367 (42.6)	0.0272
Antidepressants	3,873 (37.8)	3,841 (37.5)	0.0064
PPIs	5,357 (52.2)	5,321 (51.9)	0.0070

Values are mean [SD], No. (%), or as otherwise indicated. ACE = angiotensin-converting enzyme; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.
[a]Based on available data from 80% of patients.
[b]Based on available data from 87% of patients.
[c]Stratification factor; time-conditional propensity scores computed separately for each stratum.

Data Analysis

Standardized mean differences of covariates were computed to assess the comparability of the two matched treatment groups. Rates of outcomes were computed pooled and stratified by prior LABA-ICS treatment. Cox proportional hazard regression, with stratification by prior LABA-ICS treatment, was used in an as-treated analysis to compare triple with LABA-ICS inhalers on the risks of MACEs and its components during the first year after treatment initiation. The as-treated analysis was based on continuous treatment, defined by successive prescriptions of the initial single-inhaler treatment between the end and start of prescription dates, with exposure discontinuation defined as the end of the last continuous prescription.

The data analysis for the primary MACE outcome was stratified by the number of exacerbations during the baseline year, by prior asthma diagnosis, and by prior LABA-ICS treatment, using the regression model with an interaction term between these factors and the treatment. In addition, to account for the variations in inhaler formulations and dosing, we estimated separate effects for the two triple inhaler formulations vs all LABA-ICS and vs the respective LABA-ICS agents used in the triple inhaler.[22,23] Thus, we compared glycopyrronium-formoterol-beclomethasone dipropionate vs formoterol-beclomethasone dipropionate and umeclidinium-vilanterol-fluticasone furoate vs vilanterol-fluticasone furoate.

Sensitivity analyses included an intention-to-treat analysis over the 1-year follow-up. The definition of continuous use for the as-treated analyses was evaluated by adding gaps of 15 and 30 days between prescriptions. To address potential confounding by indication among the prevalent new users, in whom the switch to triple therapy may have been triggered by a recent severe exacerbation, analyses were repeated after excluding patients with a COPD hospitalization in the 30 days before study cohort entry. Finally, we considered the effect of censoring due to switching or treatment discontinuation using inverse probability of censoring weights applied to the analysis of the primary MACE outcome. All analyses were conducted using SAS version 9.4 (SAS Institute). The study protocol was approved by CPRD's research data governance committee (protocol No. 23_002846) and the research ethics board of the Jewish General Hospital (protocol No. JGH-2024-3847), Montreal, QC, Canada.

Results

The base cohort included 298,190 patients who were users of LABA-ICS or triple inhalers in CPRD between September 2017 and March 2021, with a diagnosis of COPD, of which 226,001 were in practices with linkage to HES (Fig 1). The study cohort included 10,255 new users of triple therapy and 10,255 matched users of LABA-ICS with a diagnosis of

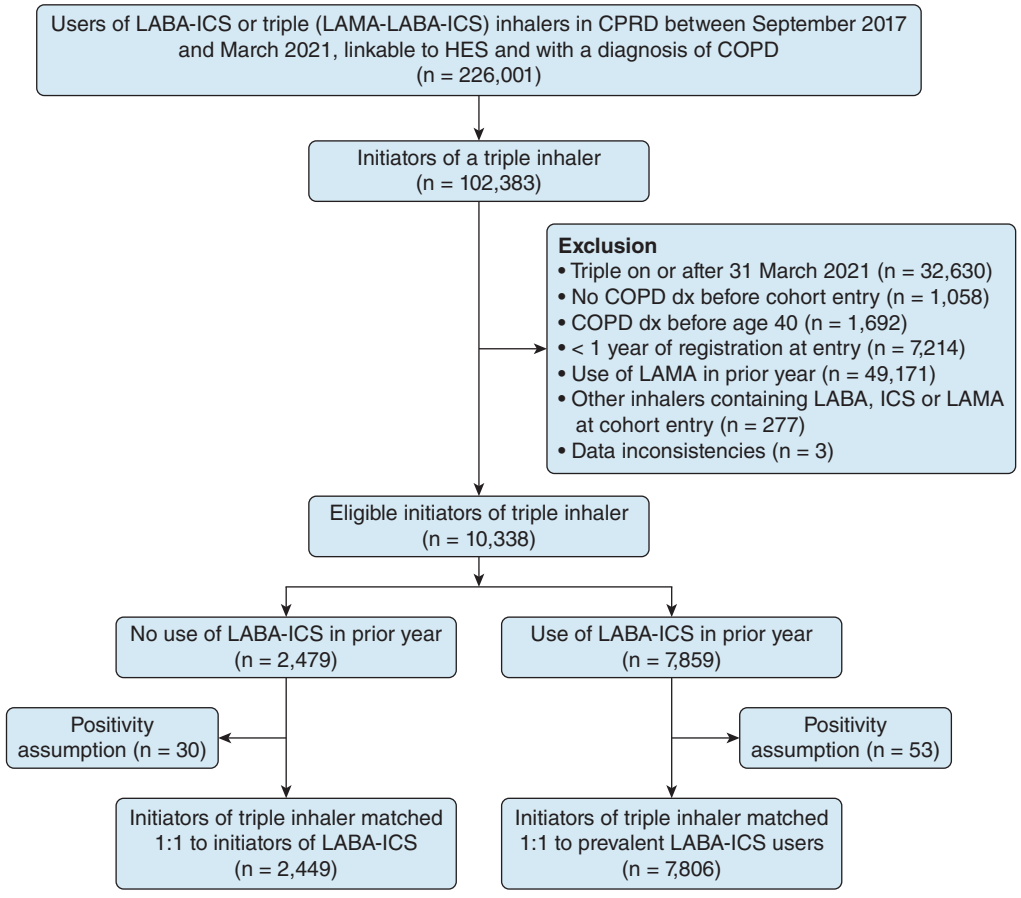

Figure 1 – *Flowchart of cohort selection for the prevalent new-user design to compare initiators of triple inhalers with LABA-ICS users. CPRD = Clinical Practice Research Datalink; dx = diagnosis; HES = Hospital Episodes Statistics; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist.*

COPD, after excluding users of LAMAs prior to treatment initiation. Of the new users of triple therapy, 24% were incident users not previously treated with LABA-ICS in the baseline year, whereas the remaining 76% were new users who switched from an LABA-ICS to a triple inhaler. The baseline characteristics comparing initiators of single-inhaler triple therapy with users of LABA-ICS show the two groups to be well balanced (Table 1). The baseline characteristics, stratified by prior LABA-ICS treatment, are provided in e-Tables 1 and 2. Among those with a prior LABA-ICS, the duration since LABA-ICS initial treatment was 6.9 years for both the triple and comparator groups who, respectively, received an average 50.0 and 52.6 prescriptions of LABA-ICS during this period. The single-inhaler triple therapy group included glycopyrronium-formoterol-beclomethasone dipropionate (61%) and umeclidinium-vilanterol-fluticasone furoate (39%), whereas the single-inhaler LABA-ICS agents included formoterol-beclomethasone dipropionate (50%), salmeterol-fluticasone propionate (20%), formoterol-budesonide (18%), vilanterol-fluticasone furoate (10%), and formoterol-fluticasone (2%). The doses of ICS in the different inhalers are reported in e-Table 3.

Over the 1-year follow-up, patients in each treatment arm received an average of eight prescriptions of their study treatment. The mean duration of continuous treatment from the time of initiation was 2.1 months in each of the two arms, with 78% of the triple arm patients censored for discontinuation within the year, and 11% for switching to an LABA-ICS, whereas 80% of the LABA-ICS arm patients were censored for discontinuation, and 6.7% for switching to a triple or adding an LAMA.

The cumulative incidence of a first MACE event over 1 year was approximately 8% for the two treatment groups; however, it was higher for the triple therapy arm during the first 6 months (Fig 2). The incidence rate of MACE was 11.3 per 100 per year with triple therapy compared with 8.8 per 100 per year for LABA-

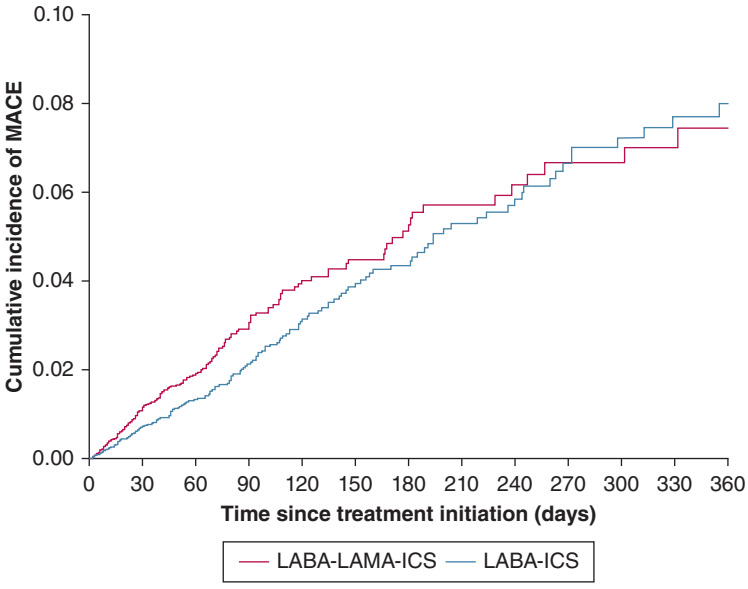

Figure 2 – *One-year as-treated cumulative incidence of MACE for the triple therapy and LABA-ICS matched groups, estimated using the Kaplan-Meier method. ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist; MACE = major adverse cardiovascular event.*

ICS (Table 2). The resulting adjusted HR of MACE associated with triple therapy relative to LABA-ICS was 1.28 (95% CI, 1.05-1.55) (Table 2).

All-cause mortality was the dominant component of MACE, with incidence rates of 9.8 and 7.4 per 100 per year with triple therapy and LABA-ICS, respectively, resulting in an adjusted HR of 1.31 (95% CI, 1.06-1.62) with triple therapy (Table 2). Figure 3 displays the cumulative incidence of all-cause death over 1 year. The incidence rates of acute myocardial infarction hospitalization were much lower at 1.1 per 100 per year in both groups, resulting in an adjusted HR of 1.00 (95% CI, 0.56-1.79) with triple therapy (Table 2). For stroke, the incidence rates were 0.65 and 0.61 per 100 per year with triple therapy and LABA-ICS, respectively, resulting in an adjusted HR of 1.06 (95% CI, 0.48-2.36) with triple therapy, relative to LABA-ICS (Table 2).

Stratification by the number of moderate or severe exacerbations in the year prior to treatment initiation and by asthma comorbidity shows that the results remain consistent across the groups (e-Table 4). Additional analyses, resulting from the differences over time of the cumulative incidence curves that suggest nonproportionality of hazards, find that the

TABLE 2] Incidence Rates and Adjusted HRs of MACE

Treatment Group	No. of Patients	No. of Events	Person- Years	Rate[a] Per 100 Per Year	Adjusted[a] HR (95% CI)
MACE					
Triple inhaler	10,255	212	1,831	11.29	1.28 (1.05-1.55)
LABA-ICS	10,255	189	2,142	8.75	1.00 (reference)
All-cause mortality					
Triple inhaler	10,255	186	1,834	9.83	1.31 (1.06-1.62)
LABA-ICS	10,255	161	2,147	7.41	1.00 (reference)
Acute myocardial infarction hospitalization					
Triple inhaler	10,255	20	1,831	1.09	1.00 (0.56-1.79)
LABA-ICS	10,255	23	2,144	1.08	1.00 (reference)
Stroke hospitalization					
Triple inhaler	10,255	12	1,833	0.65	1.06 (0.48-2.36)
LABA-ICS	10,255	13	2,145	0.61	1.00 (reference)

HR = hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; MACE = major adverse cardiovascular event.
[a]After matching on time-conditional propensity scores and prior use of LABA-ICS.

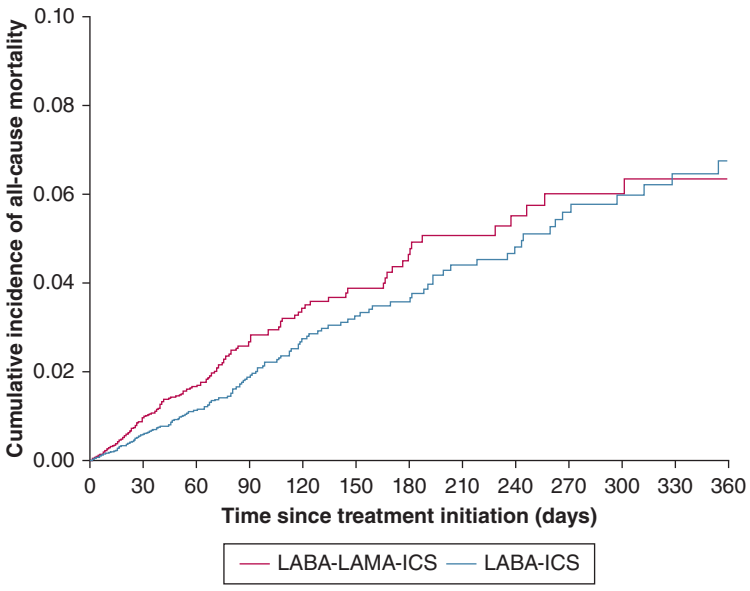

Figure 3 – *One-year as-treated cumulative incidence of all-cause death for the triple therapy and LABA-ICS matched groups, estimated using the Kaplan-Meier method. ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LAMA = long-acting muscarinic antagonist.*

HR of MACE is 1.41 (95% CI, 1.14-1.74) over the first 120 days, 0.77 (95% CI, 0.42-1.40) over the 120- to 240-day period, and 0.59 (95% CI, 0.19-1.84) after 240 days, comparing triple therapy with LABA-ICS.

With respect to the effects of specific agents, the HR of MACE with the glycopyrronium-formoterol-beclomethasone dipropionate triple inhaler was 1.44 (95% CI, 1.16-1.78), whereas for umeclidinium-vilanterol-fluticasone furoate it was 0.94 (95% CI, 0.70-1.26), vs all LABA-ICS combined (Table 3). However, when compared with the same LABA-ICS agents used in the respective triple inhaler, the HR of MACE with glycopyrronium-formoterol-beclomethasone dipropionate vs formoterol-beclomethasone dipropionate was 1.45 (95% CI, 1.13-1.86); with umeclidinium-vilanterol-fluticasone furoate vs vilanterol-fluticasone furoate, it was 1.44 (95% CI, 0.76-2.59), but with a smaller numbers of patients (Table 3).

TABLE 3] HRs of MACE Comparing Triple Inhaler Initiators With LABA-ICS Users

Treatment Group	No. of Patients	No. of Events	Person-Years	Rate[a] Per 100 Per Year	Adjusted[a] HR (95% CI)
Primary as-treated analysis					
Triple inhaler	10,255	212	1,831	11.29	1.28 (1.05-1.55)
Any LABA-ICS	10,255	189	2,142	8.75	1.00 (reference)
Each triple inhaler vs any LABA-ICS					
Glyco-formo-beclo	6,285	152	1,145	12.96	1.44 (1.16-1.78)
Umec-vilan-flutic	3,958	59	684	8.38	0.94 (0.70-1.26)
Any LABA-ICS	10,237	189	2,138	8.77	1.00 (reference)
Each triple inhaler vs same LABA-ICS formulation					
Glyco-formo-beclo	6,285	152	1,145	12.94	1.45 (1.13-1.86)
Formo-beclo	5,120	102	1,112	8.81	1.00 (reference)
Umec-vilan-flutic	3,958	59	684	8.37	1.44 (0.76-2.59)
Vilan-flutic	1,060	14	227	6.03	1.00 (reference)

Glyco-formo-beclo = glycopyrronium-formoterol-beclomethasone; HR = hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; MACE = major adverse cardiovascular event; Umec-vilan-flutic = umeclidinium-vilanterol-fluticasone furoate; Formo-beclo = formoterol-beclomethasone dipropionate; Vilan-flutic = vilanterol-fluticasone furoate.

[a]After matching on time-conditional propensity scores and prior use of LABA-ICS.

TABLE 4] Sensitivity Analyses for the Adjusted HRs of MACE Comparing Triple Inhaler Initiators With LABA-ICS Users

Treatment Group	No. of Patients	No. of Events	Person-Years	Rate[a] Per 100 Per Year	Adjusted[a] HR (95% CI)
Primary as-treated analysis					
Triple inhaler	10,255	212	1,831	11.29	1.28 (1.05-1.55)
LABA-ICS	10,255	189	2,142	8.75	1.00 (reference)
Intent-to-treat analysis (1 y)					
Triple inhaler	10,255	892	8,118	10.90	1.12 (1.02-1.23)
LABA-ICS	10,255	802	8,157	9.75	1.00 (reference)
Weighted by inverse probability of censoring					
Triple inhaler	10,255	212	1,831	11.29	1.26 (1.04-1.54)
LABA-ICS	10,255	189	2,142	8.75	1.00 (reference)
Continuous use defined by 15-d gap					
Triple inhaler	10,255	406	3,859	10.39	1.11 (0.97-1.28)
LABA-ICS	10,255	365	3,885	9.42	1.00 (reference)
Continuous use defined by 30-d gap					
Triple inhaler	10,255	506	4,884	10.25	1.14 (1.01-1.30)
LABA-ICS	10,255	449	4,979	9.06	1.00 (reference)
Initial treatment, no prior LABA-ICS					
Triple inhaler	2,449	73	425	17.17	1.31 (0.92-1.84)
LABA-ICS	2,449	57	437	13.03	1.00 (reference)
Treatment after prior LABA-ICS					
Triple inhaler	7,806	139	1,406	9.88	1.26 (1.00-1.60)
LABA-ICS	7,806	132	1,705	7.74	1.00 (reference)

HR = hazard ratio; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; MACE = major adverse cardiovascular event.
[a]After matching on time-conditional propensity scores and prior use of LABA-ICS.

Sensitivity analyses on the HR of MACE with triple therapy also confirm the robustness of the results (Table 4). The HR was slightly attenuated in the intention-to-treat analysis over the 1-year follow-up (HR, 1.12; 95% CI, 1.02-1.23). The HR was also attenuated when gaps of 15 and 30 days between prescriptions to define continuous treatment were introduced. Accounting for the effects of censoring by a weighted analysis did not change the results. The stratified analysis by whether the patients used the triple therapy de novo or switched from an LABA-ICS did not affect the findings. Finally, among prevalent new users and after excluding those with a COPD hospitalization within 30 days prior to study cohort entry, the HR of MACE with triple therapy was 1.18 (95% CI, 0.92-1.51) and it was 1.39 (95% CI, 1.05-1.83) in the first 4 months after treatment initiation.

Discussion

This real-world observational study suggests that patients who initiate single-inhaler triple therapy in COPD have a slightly increased incidence of MACE over the first year of use compared with similar patients treated with an LABA-ICS inhaler. This small increase in risk is dominated by the all-cause mortality component of MACE, which accounts for > 80% of the MACE events. The Kaplan-Meier curves and Cox model analyses suggest that the higher risk of these outcomes is mainly in the first 4 months of use of the triple inhaler. No increase in risk was observed for hospitalization for acute myocardial infarction and stroke; however, the number of events was small and resulted in wide CIs.

Our observational study was motivated by signals from the large IMPACT and ETHOS randomized trials that found a numerically higher incidence of cardiovascular

adverse events compared with those receiving LABA-ICS.[7,8] For example, the ETHOS trial's reported HR of confirmed MACE (HR, 1.25; 95% CI, 0.73-2.15) with triple therapy compared with LABA-ICS is similar to the estimate from our study (HR, 1.28; 95% CI, 1.05-1.55).[8] However, unlike the signals in the IMPACT trial, we did not find higher risks of hospitalization for acute myocardial infarction and stroke with triple therapy. However, the IMPACT trial did not necessitate hospitalization in defining the ischemic heart disease and cerebrovascular adverse events, which our observational study did, resulting in a lower incidence of these events and insufficient precision in the effects.

The increased risk of MACE with triple therapy in our study is dominated by the all-cause mortality component of MACE, accounting for > 80% of these events, with an HR of 1.31 (95% CI, 1.06-1.62) for all-cause death. This finding diverges from those of the IMPACT trial's rate ratio (our calculation) of all-cause death of 0.95 (95% CI, 0.64-1.41) and the ETHOS trial's HR of 0.82 (95% CI, 0.47-1.41), comparing triple therapy with LABA-ICS. Besides the nonrandomized nature of our observational study, some methodologic aspects can explain this discrepancy. Mainly, 55% of the patients enrolled in IMPACT and ETHOS were treated with a LAMA at the time of enrollment. In IMPACT, these patients were forced to discontinue all their medications, including LAMAs, at the time of randomization. In ETHOS, they had to discontinue LAMAs which were replaced by regular ipratropium during a 1- to 4-week run-in period, which was stopped at randomization. The forced withdrawal of maintenance therapy at randomization imposed by the trial design can introduce bias, as was shown with the withdrawal of ICS in IMPACT and ETHOS.[24-26] The bias can also occur if the withdrawal is not abrupt and involves a run-in period.[27] Our real-world study, on the other hand, was restricted to LAMA-naive patients, thus avoiding the potential confounding effects of withdrawing prior LAMAs in the trials.

Unlike the effects of withdrawing ICSs for which data have been reported for these trials, the data stratified by LAMA withdrawal at randomization were not reported. It is thus unclear whether and to what extent LAMA withdrawal could have adversely affected mortality in the patients allocated to the LABA-ICS arm. We would expect that LAMA withdrawal at randomization would result in higher mortality at the beginning of follow-up, with a subsequent attenuation of the effect. The IMPACT trial provides some partial insight into this question, with an analysis according to the prior use of triple therapy, thus including LAMA, withdrawn at randomization. It finds that, among the 40% of all patients previously on triple therapy, the HR of all-cause death was 0.71 (95% CI, 0.46-1.10) with triple therapy vs LABA-ICS, whereas among those not previously on triple therapy, the corresponding HR was 1.03 (95% CI, 0.72-1.47). Repeating this analysis according to prior LAMA use (55% of patients rather than only the 40% previously on triple therapy) and presenting the cumulative incidence curves by prior LAMA use would provide the more accurate effect of triple therapy on mortality among those naive to LAMAs, thus unconfounded by the effect of LAMA withdrawal.

It is notable that 65% of the patients who initiated single-inhaler triple therapy had < 2 exacerbations in the year before initiating this treatment, including 42% who had none. Moreover, among those who did not switch from an LABA-ICS inhaler, 50% had no exacerbation in the year prior to initiating triple therapy. However, treatment guidelines recommend triple therapy only for exacerbating patients, namely the type studied in the randomized trials of triple therapy, but not the nonexacerbators for whom no data are available.[2] Moreover, besides the absence the prior exacerbation indication, many of the patients starting triple therapy in our study had no or mild dyspnea, and 78% had a blood eosinophil count < 300 cells/μL, another criterion for its use.

Our study has several strengths. First, the prevalent new-user design identified study patients at the time of initiation of the single-inhaler triple agent and a corresponding time for the LABA-ICS comparators, emulating the randomized trial approach in an observational setting. Second, our design excluded patients previously treated with LAMAs and thus avoided the confounding effect of prior and discontinued LAMA use that affected the IMPACT and ETHOS trials. Third, our observational study was performed in a setting of general clinical practice which provides real-world evidence on these treatments. Limitations include, first, the treatment exposure which is based on written prescriptions, with uncertainty on whether they are dispensed, resulting in some exposure misclassification. Furthermore, the different inhalers could introduce variations in exposure and outcomes in the real-world setting. Indeed, we found that the risk varied substantially among the different agents, such that our regrouping of exposures by drug class (triple, LABA-ICS) obscured these differences.[22,23] Results were more consistent when triple inhalers were compared with the same LABA-ICS

agents used in the respective triple inhaler, suggesting that future observational studies should consider such variations. Second, the continuous treatment duration of triple therapy on which the as-treated analysis was done was relatively short (mean, 2.1 months), which could reflect the real-world clinical situation. However, the patients used an average of eight prescriptions of the study treatment during the 1-year follow-up so that using individual prescription durations may have misclassified the as-treated exposure. Nonetheless, the 1-year intent-to-treat analysis, unrelated to continuous use, supported the findings of the as-treated analysis, albeit somewhat attenuated. Third, although large, the study size did not provide sufficient numbers of acute myocardial infarction and stroke events, which required hospitalization, resulting in wide CIs for the comparison between the two treatments. Finally, residual confounding cannot be ruled out in any observational study, despite the use of time-conditional propensity scores which provided an LABA-ICS comparator group highly comparable on all available measures of patient characteristics to the triple inhaler group. Nonetheless, our analysis among prevalent new users, after excluding those without a COPD hospitalization within 30 days and thus less subject to confounding by indication, found a similar result, particularly in the first 4 months after treatment initiation.

Interpretation

In this real-world observational study, we found that patients with COPD who initiate single-inhaler triple therapy have a small increase in the incidence of MACE, driven mainly by all-cause mortality and occurring primarily in the first 4 months after treatment initiation, when compared with similar patients treated with an LABA-ICS inhaler. No increase in risk was observed for hospitalization for acute myocardial infarction and stroke; however, the number of events was small and resulted in wide CIs. A confirmation of the potential risk of these adverse events with triple therapy can be assessed from a reanalysis of the IMPACT and ETHOS trials, stratified by prior LAMA use. In the meantime, cautious use of single-inhaler triple therapy in the real-world clinical practice setting of COPD treatment could first involve restricting it to the patient profile studied in the trials of these inhalers.

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