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BRIEF REPORT

EVELUT®: A Real-World, Observational Study Assessing Dyspnoea and Symptom Burden in COPD Patients Switched from LABA/ICS to LAMA/LABA or LAMA/LABA/ICS

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ABSTRACT

Introduction: The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023) no longer recommends a long-acting β_2-agonist (LABA) plus inhaled corticosteroid (ICS) combination for the treatment of chronic obstructive pulmonary disease (COPD). In patients treated with LABA/ICS, who continue to experience symptoms without frequent or severe exacerbations, GOLD now recommends switching to long-acting muscarinic antagonist (LAMA)/LABA instead of escalating to triple therapy (TT; LAMA/LABA/ICS), which previously was also a recommended option. EVELUT®, a real-life, observational study, compared these two treatment strategies in terms of symptom relief and health status improvement.
Methods: Patients with symptomatic COPD at low exacerbation risk (GOLD B) were switched, at their physicians' discretion, from LABA/ICS to either fixed-dose LAMA/LABA (tiotropium/olodaterol, Respimat® [Tio/Olo]) or fixed or free TT. Primary endpoints were change in modified Medical Research Council (mMRC) and COPD Assessment Test™ (CAT™) scores after 12 weeks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-023-02524-y.

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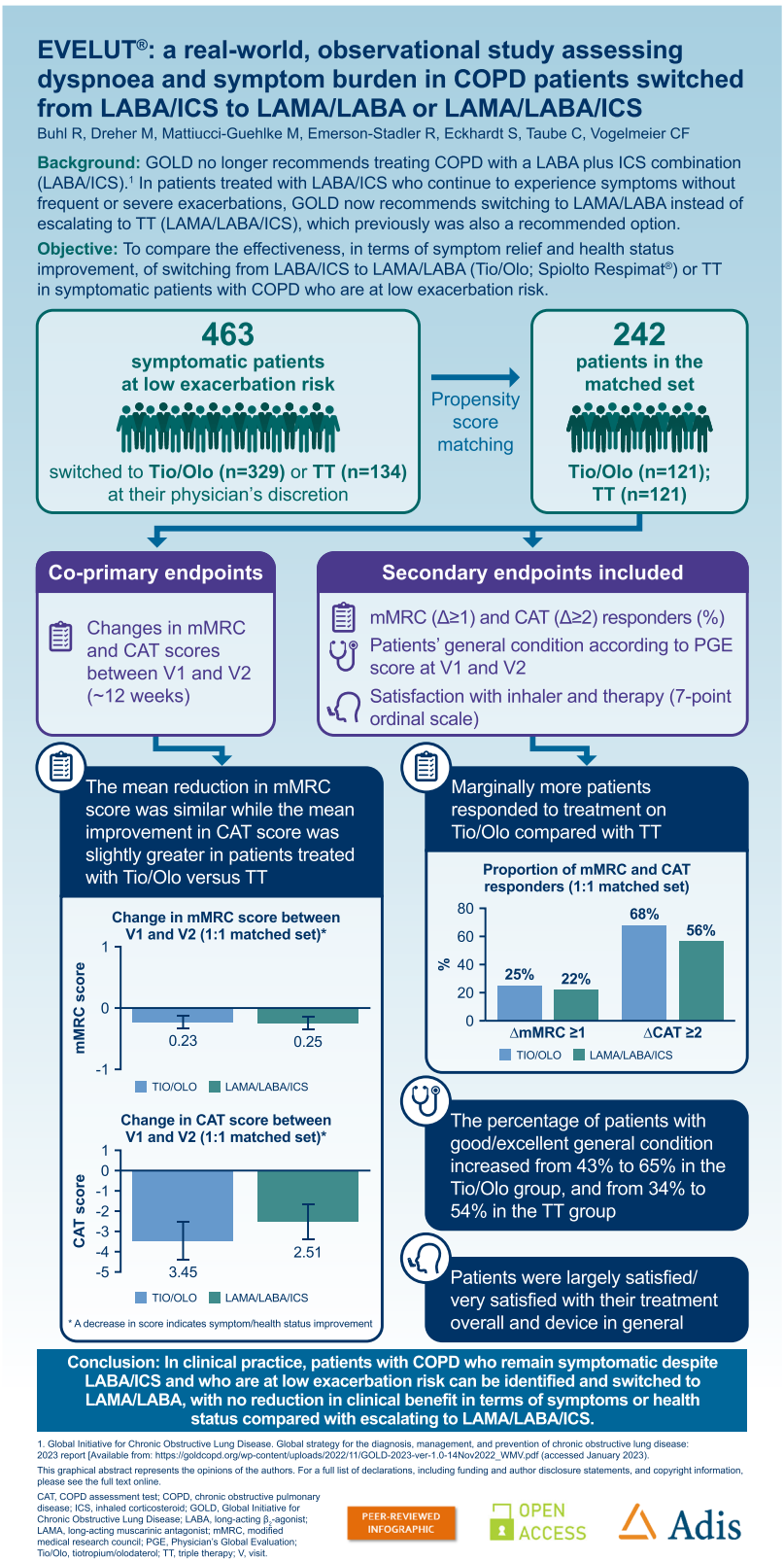
Results: The safety set contained 463 patients (Tio/Olo, $n = 329$; TT, $n = 134$). In a propensity score-matched set (Tio/Olo, $n = 121$; TT, $n = 121$), improvement in mMRC score was similar in patients on Tio/Olo (–0.23; 95% confidence interval [CI] –0.11, –0.36) and TT (–0.25; 95% CI –0.13, –0.38). Improvement in total CAT score was slightly larger in patients on Tio/Olo (–3.45; 95% CI –2.45, –4.45) versus TT (–2.51; 95% CI –1.62, –3.40). In both groups, Physician's Global Evaluation scores increased, with 69–89% of patients satisfied with their treatment overall. Marginally more patients on Tio/Olo responded to treatment versus TT (Δ mMRC score ≥ 1; 25% vs. 22%; Δ CAT score ≥ 2, 68% vs. 56%).

Conclusion: In patients with symptomatic COPD at low exacerbation risk, treatment can be switched from LABA/ICS to LAMA/LABA without compromising clinical benefit, compared with escalating to LAMA/LABA/ICS. Switching from LABA/ICS to LAMA/LABA can provide symptom relief and improve health status without exposure to the risks associated with ICS.

Clinical Trial Registration: ClinicalTrials.gov: NCT03954132.

Keywords: COPD; EVELUT; LABA/ICS; LAMA/LABA; LAMA/LABA/ICS; Observational; Triple therapy

Graphical Abstract



Key Summary Points

Why carry out this study?

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) no longer recommends a long-acting β_2-agonist (LABA) plus inhaled corticosteroid (ICS) combination for the treatment of COPD, recommending that symptomatic patients at low exacerbation risk be switched from LABA/ICS to long-acting muscarinic antagonist (LAMA)/LABA.

Previously, GOLD had included escalation to triple therapy (LAMA/LABA/ICS) as an alternative follow-up option for this group of patients.

The EVELUT® study compared the effectiveness of these two treatment strategies, evaluating the switch to fixed-dose LAMA/LABA (tiotropium/olodaterol; Spiolto Respimat®) versus any triple therapy (fixed or free) in terms of symptom relief and health status improvement, in patients on LABA/ICS without frequent or severe exacerbations who continued to experience symptoms (GOLD B)

What was learned from the study?

This real-world observational study shows that (1) physicians in routine clinical practice can identify patients with COPD who can be switched from LABA/ICS to LAMA/LABA, and (2) this switch is possible without compromising symptom relief and health status improvement compared with switching to triple therapy.

These findings will help to inform prescribing decisions regarding follow-up therapy for patients with COPD who are symptomatic on LABA/ICS maintenance therapy.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.22633756.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterised by dyspnoea, cough and/or sputum production [1, 2]. Long-term maintenance treatment is recommended for symptom relief and to reduce the risk of exacerbations (acute worsening of symptoms) [2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends dual bronchodilation with a long-acting muscarinic antagonist (LAMA) combined with a long-acting β_2-agonist (LABA) as the preferred treatment option for patients with symptomatic COPD, independent of their exacerbation history/risk [2]. Addition of inhaled corticosteroid (ICS) to LAMA/LABA is recommended only for patients with frequent or severe exacerbations and blood eosinophils $\geq$ 300 cells/μL (as initial therapy), and for those with blood eosinophils $\geq$ 100 cells/μL who continue to exacerbate on LAMA/LABA (as follow-up therapy) [2]. GOLD no longer recommends a LABA/ICS combination for the treatment of COPD; for patients on LABA/ICS who have persistent symptoms and are at low exacerbation risk, treatment should be switched to LAMA/LABA [2]. Together, these recommendations ensure that addition of ICS is reserved for patients in whom the benefits of treatment are likely to outweigh the associated risks, such as pneumonia [3].

When the EVELUT® study was designed, GOLD recommended that patients who were not well controlled on LABA/ICS either escalate to LAMA/LABA/ICS (triple therapy; TT) or switch to LAMA/LABA (for those with pneumonia, an inappropriate original indication for ICS, or a lack of response to ICS) [4]. However, no prospective clinical evidence was available

supporting a direct switch from LABA/ICS to LAMA/LABA instead of LAMA/LABA/ICS.

The EVELUT study evaluated these two alternative treatment strategies. It compared the effectiveness, in terms of improvement in symptoms and health status, of fixed-dose LAMA/LABA (tiotropium/olodaterol; Spiolto Respimat®) versus any triple therapy (TT; fixed or free) in patients with COPD and a low exacerbation risk who continued to experience symptoms on LABA/ICS therapy.

METHODS

Study Design

EVELUT (NCT03954132) was an open-label, observational, multicentre study of ~ 12 weeks' duration conducted in Germany between June 2019 and June 2021. At Visit 1 (baseline), patients with COPD who were symptomatic on LABA/ICS and at low exacerbation risk were switched to Tio/Olo or TT at the discretion of their attending physician and treated until Visit 2 (~ Week 12). Full details of the study design have been published previously [5].

Patients

Male and female patients aged ≥ 40 years old with a diagnosis of COPD as determined by the treating physician were eligible for enrolment. Patients were symptomatic (modified Medical Research Council [mMRC] score ≥ 1 and COPD Assessment Test™ [CAT™] score ≥ 10) and receiving LABA/ICS maintenance therapy prior to study entry. All participants had to provide written informed consent prior to study participation and had to be willing and able to follow the procedures outlined in the protocol.

Key exclusion criteria included: contraindications to either treatment regimen according to the summary of product characteristics; an acute exacerbation of COPD within 4 weeks prior to Visit 1; acute respiratory failure (pH < 7.35 and/or respiratory rate > 30/min) within 3 months prior to Visit 1; a current diagnosis/history of asthma or asthma–COPD overlap; a current diagnosis/history of allergic rhinitis or lung cancer within the last 5 years; and a history of frequent or severe exacerbations (≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalisation within the previous 12 months).

Participating sites were all medical practices (general practitioners, internal specialists, and pulmonologists); no hospitals were involved in the study. The EVELUT study protocol was submitted to the ethics committee of the State Medical Association of Rhineland-Palatinate on 10 April 2019 and was approved on 29 May 2019 (reference number: 2019–14258). The study was performed in accordance with the Declaration of Helsinki of 1964 and its subsequent amendments. All patients provided written, informed consent prior to participation in the study.

Endpoints

The co-primary endpoints were changes in mMRC and CAT scores between baseline (Visit 1) and the end of observation after ~ 12 weeks of treatment (Visit 2). Secondary endpoints included the patients' general condition according to the Physician's Global Evaluation (PGE) score, proportion of mMRC and CAT responders (Δ mMRC score ≥ 1; Δ CAT score ≥ 2), and patient satisfaction with the inhaler and therapy according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied), both measured at Visit 2.

Safety

Adverse drug reactions, pregnancies and fatal adverse events were reported.

Statistical Analyses

All analyses were exploratory. The sample size was calculated to give a rough estimate of statistical power based on the assumption that Tio/Olo was at least non-inferior to any TT using two-sample t tests (alpha, 2.5%; power, 90%). Forty-four evaluable patients overall (22 per group) were needed to assess non-

inferiority between Tio/Olo and TT regarding mMRC score, and 518 evaluable patients overall (259 per group) were required to assess non-inferiority regarding CAT score [5]. The minimal clinically important differences in mMRC and CAT scores (1 point and 2 points, respectively) were treated as non-inferiority margins.

The safety set comprised all patients who completed Visit 1 and received at least one dose of study medication. Analysis of primary endpoints was based on propensity score matching, and sensitivity analyses were performed using propensity score weighting and multivariable regression modelling. The propensity score was estimated using a range of prespecified baseline variables [5], subject to data availability. Patient matching was then performed using greedy nearest-neighbour matching on the logit of the propensity score using caliper matching (caliper width, 0.2). Statistical analyses of baseline characteristics and treatment response were descriptive.

RESULTS

Patient Populations and Baseline Characteristics

The study was expected to enroll ~ 900 patients from ~ 150 sites across Germany; however, due to the COVID-19 pandemic, site and patient recruitment were slower than expected. After a 1-year recruitment extension, enrolment was discontinued after 469 patients were screened from 49 sites (Fig. 1). Six of these were not recruited/treated; therefore, the safety set comprised 463 patients (329 patients on Tio/Olo; 134 patients on TT). Prior to matching, a further 25 patients were excluded for protocol violations. In total, 432 patients (303 patients on Tio/Olo; 129 patients on TT) completed Visit 2, with 290 patients on Tio/Olo and 128 patients on TT completing the mMRC and CAT questionnaires. The drop-out rate for the Tio/Olo arm was 7.9% versus 3.7% for the TT arm.

Following propensity score matching, the matched set included 121 patients in each of the Tio/Olo and TT treatment arms. Of these, 111 (Tio/Olo) and 118 (TT) patients completed the mMRC and CAT questionnaires. Creation of a larger matched set retaining standardised difference ≤ 0.1 in matched variables was not possible. Matched variables included age, sex, mMRC score, CAT score, pack-years of smoking, and physician speciality. Matching could not be performed for exacerbation history, forced expiratory volume in 1 s (FEV_1) or eosinophil levels as data were not available for all patients. Based on the resulting sample size, it was possible to assess non-inferiority between Tio/Olo and TT in terms of mMRC score, but not for the CAT score.

Baseline characteristics for the safety and matched sets are shown in Table 1. After matching, the two treatment groups showed some residual differences in terms of duration of COPD, GOLD spirometric status and respiratory therapies other than LABA/ICS used within the previous 6 months (Table 1). The majority of participants had moderate COPD (FEV_1 50–79% [matched set: Tio/Olo 58.7%; TT 52.1%]) and all patients in the matched set were in GOLD group B.

Reasons for switching from LABA/ICS to Tio/Olo or TT could be selected from a drop-down menu with the prespecified causes "exacerbations", "adverse event" or "other" (Table 2). In the safety and matched sets, around 10% of patients were switched to the Tio/Olo group for "adverse event", compared with none for the TT group. More patients were switched to TT than Tio/Olo due to "exacerbations", with the biggest difference in the matched set (Tio/Olo group 9.9%, TT group 16.5%).

Primary Endpoints

For the matched set, the mean reduction in total mMRC score between Visit 1 and Visit 2 was similar in patients treated with Tio/Olo (0.23; 95% confidence interval [CI] 0.11, 0.36) and TT (0.25; 95% CI 0.13, 0.38) (Fig. 2A; Table 3). Regarding total CAT score, the mean improvement from Visit 1 to Visit 2 was slightly larger in patients treated with Tio/Olo (3.45; 95% CI 2.45, 4.45) versus TT (2.51; 95% CI 1.62, 3.40) in the matched set (Fig. 2B; Table 3). With both propensity score weighting and in the

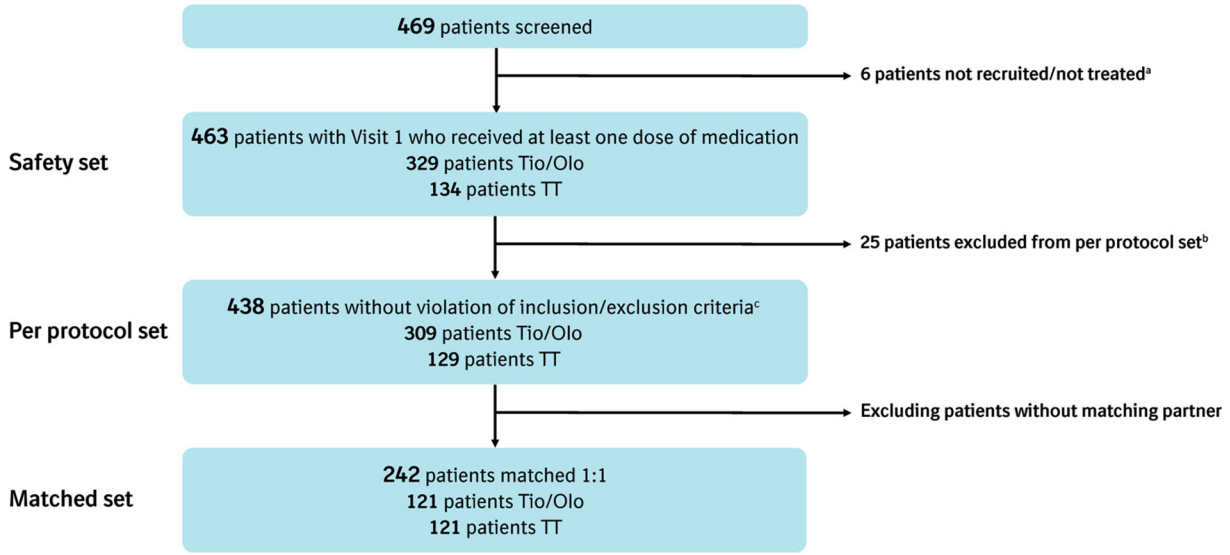


Fig. 1 Patient flow chart. [a]Four patients without documented reason, 2 patients with violation of inclusion/exclusion criteria. [b]Twenty-four patients with violation of inclusion/exclusion criteria, 1 patient with possible, unconfirmed protocol violation. [c]Of these, 6 patients in the Tio/Olo group had no documentation of Visit 2 and were thus excluded from the analysis. *Olo* olodaterol, *Tio* tiotropium, *TT* triple therapy

unmatched safety set, the mean improvements in both total mMRC and total CAT scores were greater for Tio/Olo versus TT (Table 3).

In the multivariable linear regression, patients with worse baseline mMRC and CAT scores, higher age at registration, lower number of pack-years of smoking and/or being a patient of a general practitioner (vs. speciality physician) tended to have greater improvements in mMRC score. For CAT score, patients with worse baseline CAT score, those who were patients of a general practitioner (vs. speciality physician) and those treated with Tio/Olo versus TT tended to show greater improvements. For further details, see Supplementary Material (Tables S1, S2).

Secondary Endpoints

The percentage of patients with good/excellent condition according to the PGE score increased from 42.9% at Visit 1 to 65.2% at Visit 2 in the Tio/Olo treatment group, and from 33.9% at Visit 1 to 53.8% at Visit 2 in the TT group in the matched set (Fig. 3). Data from the safety set are presented in the Supplementary Material (Figure S1).

Regarding patient satisfaction, most patients in each treatment group were at least satisfied ("very satisfied" or "satisfied") with their treatment overall (Tio/Olo 80%; fixed TT 69%; TT with ≥ 2 products 89%) (Fig. 4). In the matched set, $> 80\%$ of patients in both the Tio/Olo and the TT groups with ≥ 2 products, and almost 80% in the fixed TT group, were very satisfied or satisfied according to three satisfaction categories (patient satisfaction with the device in general, handling of the inhalation device, and inhaling from the device; Figs. 4, S2). Data from the safety set are presented in the Supplementary Material (Figures S3, S4).

In terms of responder analyses for the matched set (Fig. 5), the proportion of mMRC responders (Δ mMRC score ≥ 1) was slightly higher in the Tio/Olo group ($n = 28$ [25.0%]) compared with the TT group ($n = 26$ [21.8%]). The proportion of CAT responders (Δ CAT score ≥ 2) was also higher in the Tio/Olo group [$n = 76$ (67.9%)] than in the TT group ($n = 67$ [56.3%]). A greater benefit was seen in the safety set for patients on Tio/Olo, with the proportion of mMRC and CAT responders for Tio/Olo versus TT, respectively, being 40.6% versus 21.7% for mMRC and 70.6% versus

Table 1 Baseline characteristics of the safety and matched sets

	Safety set		Matched set	
	Tio/Olo ($n = 329$)	TT ($n = 134$)	Tio/Olo ($n = 121$)	TT ($n = 121$)
Age (years, mean, ± SD)	66.5 (± 10.7)	69.2 (± 8.9)	68.7 (± 9.3)	69.0 (± 9.1)
Gender (male, %)	51.7	58.2	60.3	59.5
Smoking status (smoker, %)	38.6	44.0	43.0	41.3
Pack-years (mean, ± SD)	35.1 (± 18.4)	42.7 (± 20.3)	41.0 (± 17.2)	40.5 (± 16.4)
COPD (years, mean, ± SD)	6.3 (± 5.9)	7.3 (± 5.6)	6.7 (± 6.3)	7.4 (± 5.9)
FEV_1 (target, %)				
≥ 80	7.9	4.5	5.8	5.0
50–79	52.3	53.0	58.7	52.1
30–49	22.5	35.8	24.8	36.4
< 30	4.3	6.7	5.8	6.6
Missing	13.1	0.0	5.0	0.0
GOLD group (%)				
A	0.0	0.7	0.0	0.0
B	99.4	98.5	100.0	100.0
C	0.0	0.0	0.0	0.0
D	0.3	0.7	0.0	0.0
Missing	0.3	0.0	0.0	0.0
Exacerbation rate (mean, SD)				
Mild exacerbations per patient	0.2 (0.6)	0.2 (0.7)	0.1 (0.3)	0.2 (0.7)
Moderate exacerbations per patient	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.1 (0.3)
mMRC score (mean, 95% CI)	2.03 (1.93, 2.12)	2.06 (1.92, 2.20)	2.07 (1.93, 2.22)	2.07 (1.93, 2.22)
CAT score (mean, 95% CI)	22.46 (21.71, 23.21)	21.99 (20.79, 23.18)	21.72 (20.59, 22.85)	21.79 (20.58, 23.00)
Prior respiratory therapies other than LABA/ICS[a] (%)				
SABA	19.8	14.2	14.0	14.9
LABA	0.9	0.0	0.0	0.0
SAMA	0.9	0.0	0.8	0.0
LAMA	1.2	0.0	2.5	0.0
LAMA/LABA FDC	0.0	0.7	0.0	0.8

Table 1 continued

	Safety set		Matched set	
	Tio/Olo ($n = 329$)	TT ($n = 134$)	Tio/Olo ($n = 121$)	TT ($n = 121$)
SAMA/SABA FDC	7.3	4.5	9.1	3.3
ICS	0.6	0.7	0.8	0.8
Systemic corticosteroid	0.3	1.5	0.0	0.8
Theophylline	0.6	1.5	0.8	1.7
Roflumilast	0.6	0.0	0.8	0.0
Other	0.3	0.0	0.0	0.0
Concomitant diseases (yes, %)	78.7	72.4	74.4	73.6
Allergic	1.5	0.7	2.5	0.8
Cardiovascular	60.2	60.4	60.3	61.2
Gastrointestinal/hepatobiliary	13.4	11.2	10.7	11.6
Metabolic/endocrine	34.3	29.9	29.8	33.1
Muscular-skeletal/dermatological	10.9	9.0	10.7	9.1
Neurological	6.1	6.0	4.1	6.6
Psychiatric	4.3	7.5	1.7	7.4
Pulmonary (except COPD)	2.1	6.7	2.5	7.4
Renal/urogenital	5.8	5.2	5.8	5.8
Reproductive	0.3	0.0	0.0	0.0
Other	12.2	10.4	9.9	9.9

Matching based on age, sex, mMRC score, CAT score, pack-years of smoking and physician speciality

CAT COPD Assessment Test™, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *FDC* fixed-dose combination, *FEV_1* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *mMRC* modified Medical Research Council, *Olo* olodaterol, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist, *SD* standard deviation, *Tio* tiotropium, *TT* triple therapy

[a]Within 6 months prior to start of study treatment

57.4% for CAT. For further details, see the Supplementary Material (Tables S3, S4).

Safety

Seven adverse drug reactions (ADRs) were reported in the Tio/Olo treatment group, with each patient reporting one ADR (sinus tachycardia [$n = 1$; Grade 1]; angina pectoris [$n = 2$; Grade 1]; dyspnoea [$n = 1$, Grade 1; $n = 2$, Grade 3] and hypertension [$n = 1$, Grade 1]). One of these ADRs (hypertension) required or prolonged hospitalisation, thus fulfilling the criteria for a serious ADR. No ADRs were reported in the TT group. Additionally, no adverse events with fatal outcomes were reported in either treatment group.

Table 2 Physician-reported reason for changing patient prescription from LABA/ICS to either Tio/Olo or TT

Reason for change in therapy, *n* (%)	Safety set		Matched set	
	Tio/Olo (*n* = 329)	TT (*n* = 134)	Tio/Olo (*n* = 121)	TT (*n* = 121)
Adverse event	33 (10.0)	0 (0.0)	11 (9.1)	0 (0.0)
Exacerbation	47 (14.3)	22 (16.4)	12 (9.9)	20 (16.5)
Other	246 (74.8)	111 (82.8)	98 (81.0)	101 (83.5)
Missing	3 (0.9)	1 (0.7)	0 (0.0)	0 (0.0)

ICS inhaled corticosteroid, *LABA* long-acting β_2-agonist, *Olo* olodaterol, *Tio* tiotropium, *TT* triple therapy

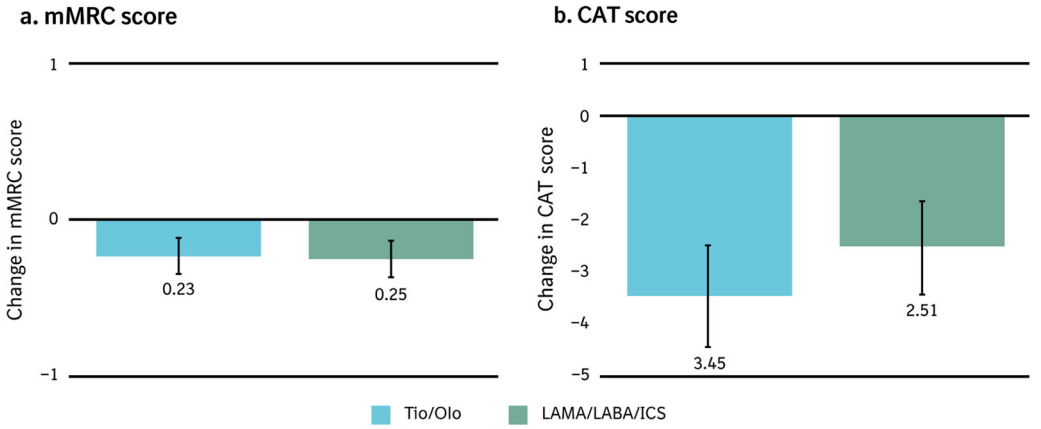


Fig. 2 Change in mMRC (a) and CAT (b) scores following switch from LABA/ICS (matched set). Error bar represents 95% CI. A decrease in score indicates symptom improvement. *CAT* COPD Assessment Test™, *CI* confidence interval, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *mMRC* modified Medical Research Council, *Olo* olodaterol, *Tio* tiotropium

Table 3 Primary endpoints: change in mMRC and CAT scores following switch from LABA/ICS

	Mean mMRC change (95% CI)		Mean CAT change (95% CI)	
	Tio/Olo	TT	Tio/Olo	TT
Propensity score matching	*n* = 111	*n* = 118	*n* = 111	*n* = 118
	0.23 (0.11, 0.36)	0.25 (0.13, 0.38)	3.45 (2.45, 4.45)	2.51 (1.62, 3.40)
Propensity score weighting	*n* = 290	*n* = 128	*n* = 290	*n* = 128
	0.53 (0.43, 0.64)	0.45 (0.31, 0.59)	6.10 (5.25, 6.95)	4.57 (3.39, 5.74)
Safety set (unmatched)	*n* = 290	*n* = 128	*n* = 290	*n* = 128
	0.53 (0.43, 0.64)	0.25 (0.14, 0.36)	6.10 (5.25, 6.95)	2.54 (1.70, 3.37)

CAT COPD Assessment Test™, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *mMRC* modified Medical Research Council, *Olo* olodaterol, *Tio* tiotropium, *TT* triple therapy

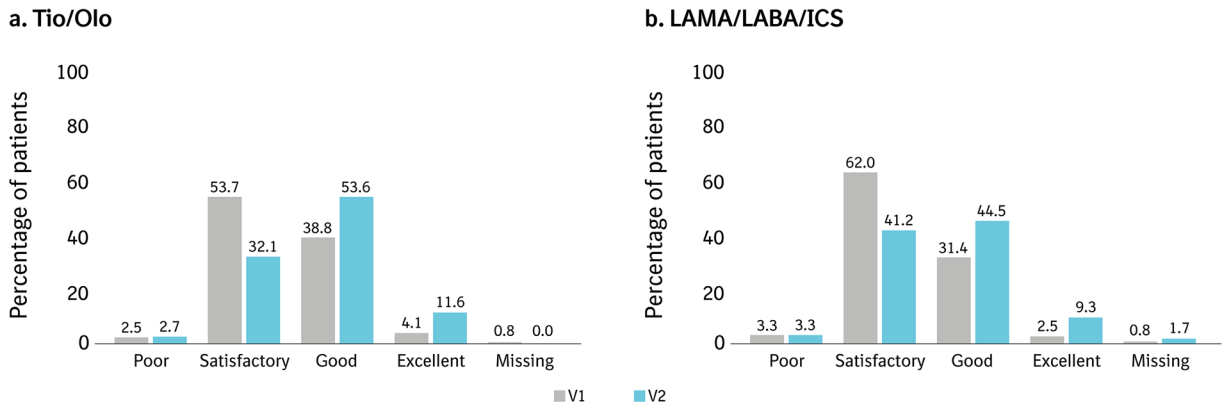


Fig. 3 General condition of the patient according to PGE score at Visit 1 and Visit 2 for the matched set. PGE score: 1–2 (Poor); 3–4 (Satisfactory); 5–6 (Good); 7–8 (Excellent). *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *Olo* olodaterol, *PGE* Physician's Global Evaluation, *Tio* tiotropium; *V* Visit

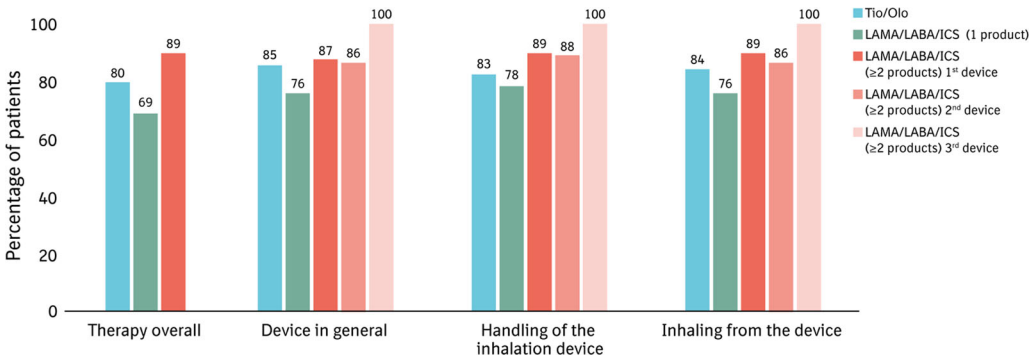


Fig. 4 Proportion of patients at least satisfied with therapy overall, the device in general, handling of the inhalation device and inhaling from the device at the end of the observation period for the matched set. [a]At least satisfied includes "very satisfied" and "satisfied". *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *Olo* olodaterol, *Tio* tiotropium

DISCUSSION

This study shows that, in routine clinical practice, physicians can identify patients with COPD who can be switched from LABA/ICS to LAMA/LABA, and that this switch is possible without compromising symptom relief and health status improvement compared with switching to TT. The study therefore supports the GOLD recommendation that symptomatic patients at low exacerbation risk without an indication for ICS should be switched from LABA/ICS to LAMA/LABA, ideally delivered in a single inhaler [2]. This is important given the need to limit ICS use to patients for whom the treatment effects are likely to outweigh the risks of adverse effects and complications of long-term ICS therapy [3], and to identify patients for whom safe ICS withdrawal can be achieved [6]. The results from EVELUT are in line with findings from another real-world study, the DACCORD study, in which physicians identified patients on TT who were eligible for withdrawal of ICS [7]. For these patients, there was no overall decline in COPD following step-down from TT to LAMA/LABA, and, in some cases, patients had better outcomes [7]. Both studies also support European Respiratory Society

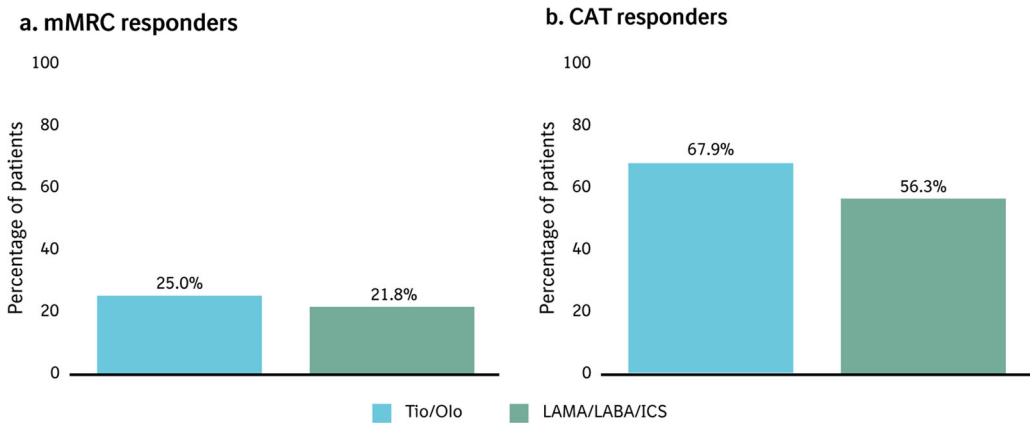


Fig. 5 Percentage of mMRC (a) and CAT (b) responders (matched set). *CAT* COPD Assessment Test™, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *mMRC* modified Medical Research Council, *Olo* olodaterol, *Tio* tiotropium

guidelines for ICS withdrawal, which recommend withdrawing ICS and replacing with LAMA and/or LABA in patients without frequent exacerbations [8].

After ~ 12 weeks of treatment, a slightly greater improvement in CAT score was seen for patients treated with Tio/Olo compared with those treated with TT; the percentage of CAT responders (Δ CAT score ≥ 2) was also slightly higher in the Tio/Olo versus TT group. For the change in mMRC score, results were similar: the proportion of responders (Δ mMRC score ≥ 1) was also slightly higher in the Tio/Olo group compared with the TT group. Together, these findings show that switching to Tio/Olo did not compromise clinical benefit versus switching to TT in terms of providing symptom relief and improving health status.

Blood eosinophil counts were available for fewer than 10% of patients in EVELUT, suggesting that using blood eosinophils to guide prescribing is uncommon in routine clinical practice in Germany. Previous studies suggest that symptoms are a stronger predictor of future exacerbations compared with blood eosinophil levels. In a real-world analysis of GOLD A/B patients with no prior exacerbations, lower FEV_1 percent predicted and more severe dyspnoea were independently associated with an increased risk of first exacerbation and severe exacerbation over a 1-year period [9]. By contrast, no difference was found between eosinophil groups (< 150; 150–< 300; ≥ 300 cells/μL) in terms of predicting the absolute risk of moderate exacerbations [9]. Consistent with these findings, both real-world data [10] and a pooled analysis of 11 clinical trials [11] found that previous exacerbation history, but not eosinophil count, was associated with future exacerbation risk.

Improvement in the patients' condition, as measured by the PGE score, was in line with other non-interventional studies of Tio/Olo with a 6-week follow-up period [12–14]. The EVELUT study builds upon this evidence base by providing data from a longer follow-up period (~ 12 weeks). High levels of patient satisfaction with the inhaler device and with treatment overall were reported in both arms after 12 weeks, consistent with previous non-interventional studies reporting patient-reported outcomes for Tio/Olo [12, 13, 15, 16]. Patients using ≥ 2 products for TT had the highest levels of satisfaction, suggesting that, contrary to previous studies [17, 18], patients may not necessarily prefer to use a single device and may prefer to use devices that they are familiar with to manage their COPD.

Regarding safety, the ADRs reported in the Tio/Olo arm were mostly in line with the known safety profile, as listed in the Summary of Product Characteristics for Spiolto Respimat

[19]. The percentage of ADRs in the Tio/Olo arm was slightly higher than in other non-interventional studies of Tio/Olo, in which ~ 1% of patients typically report ADRs [12, 13, 20], but was lower than in clinical trials (~ 6% treatment-related adverse events) [21, 22].

The EVELUT study population was representative of the broad majority of patients with COPD who are symptomatic infrequent/non-exacerbators without an indication for ICS [23, 24]. The inclusion of typical COPD patients adds strength to the generalisability of the findings; non-interventional real-world studies such as EVELUT include a broader cross-section of patients with COPD who are more representative of patients from routine clinical practice compared with those participating in randomised clinical trials. However, there are also some study limitations. Firstly, despite propensity score matching, imbalances in certain patient characteristics remained in the matched set used for the primary analysis. For example, comparison of spirometry status, exacerbation rates and COPD duration suggests that patients in the TT arm may have had marginally more severe COPD, potentially resulting in over-estimation of treatment effects in the Tio/Olo arm. However, this may equally reflect the fact that patients who in the opinion of the treating physician had no indication for ICS differ in some respects from patients who may benefit from ICS. Secondly, as more drop-outs occurred in the Tio/Olo arm, there is the potential for "survivor bias", which may have also led to over-estimation of treatment effects in the Tio/Olo arm. Thirdly, although patients were asked by the physician if they used medication regularly, treatment adherence was not verified by use of a patient diary. Lastly, it must be acknowledged that the patient population was smaller than initially planned due to the COVID-19 pandemic. It is possible that treatment outcomes may have differed for patients on fixed-dose TT compared with those on free TT, as reported in a recent publication by Huang et al. [25], but this was not explored in this study.

Overall, the results of the EVELUT study support the benefits of treatment with LAMA/LABA in patients with COPD, in line with the GOLD recommendations [2]. Switching patients with symptomatic COPD who were at low exacerbation risk from LABA/ICS to Tio/Olo resulted in an improvement in both symptoms and health status. Some patients experienced better outcomes on Tio/Olo versus TT, particularly as assessed using the CAT; this improvement could be related to the delivery device (increased lung deposition) [26, 27].

CONCLUSION

In clinical practice, patients with COPD who remain symptomatic despite LABA/ICS and who are at low exacerbation risk can be identified and switched to LAMA/LABA, with no reduction in clinical benefit in terms of symptoms or health status compared with escalating to LAMA/LABA/ICS. Withdrawing ICS and switching patients from LABA/ICS to LAMA/LABA can improve symptoms and health status without exposure to the associated risks of ICS.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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