Adv Ther (2021) 38:579–593
https://doi.org/10.1007/s12325-020-01528-2

ORIGINAL RESEARCH

Tiotropium/Olodaterol Delays Clinically Important Deterioration Compared with Tiotropium Monotherapy in Patients with Early COPD: a Post Hoc Analysis of the TONADO® Trials

Klaus F. Rabe · James D. Chalmers · Marc Miravitlles · Janwillem W. H. Kocks · Ioanna Tsiligianni · Alberto de la Hoz · Wenqiong Xue · Dave Singh · Gary T. Ferguson · Jadwiga Wedzicha

Received: August 13, 2020 / Accepted: October 8, 2020 / Published online: November 11, 2020

ABSTRACT

Introduction: Since chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, a composite endpoint of clinically important deterioration (CID) may provide a more holistic assessment of treatment efficacy. We compared long-acting muscarinic antagonist/long-acting β_2-agonist combination therapy with tiotropium/olodaterol versus tiotropium alone using a composite endpoint for CID. CID was evaluated overall and in patients with low exacerbation history (at most one moderate exacerbation in the past year [not leading to hospitalisation]), Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 patients and maintenance-naïve patients with COPD. We assessed whether early treatment optimisation is more effective with tiotropium/olodaterol versus tiotropium in delaying and reducing the risk of CID.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-020-01528-2) contains supplementary material, which is available to authorized users.

K. F. Rabe (✉)
LungenClinic Grosshansdorf, Airway Research Center North, German Center for Lung Research (DZL), Grosshansdorf, Germany
e-mail: k.f.rabe@lungenclinic.de

K. F. Rabe
Christian Albrechts University Kiel, Airway Research Center North, German Center for Lung Research (DZL), Kiel, Germany

J. D. Chalmers
Tayside Respiratory Research Group, University of Dundee, Dundee, UK

M. Miravitlles
Pneumology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain

M. Miravitlles
CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

J. W. H. Kocks
General Practitioners Research Institute, Groningen, The Netherlands

J. W. H. Kocks
Groningen Research Institute for Asthma and COPD (GRIAC), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

J. W. H. Kocks
Observational and Pragmatic Research Institute, Singapore, Singapore

I. Tsiligianni
Health Planning Unit, Department of Social Medicine, Faculty of Medicine, University of Crete, Crete, Greece

A. de la Hoz
Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

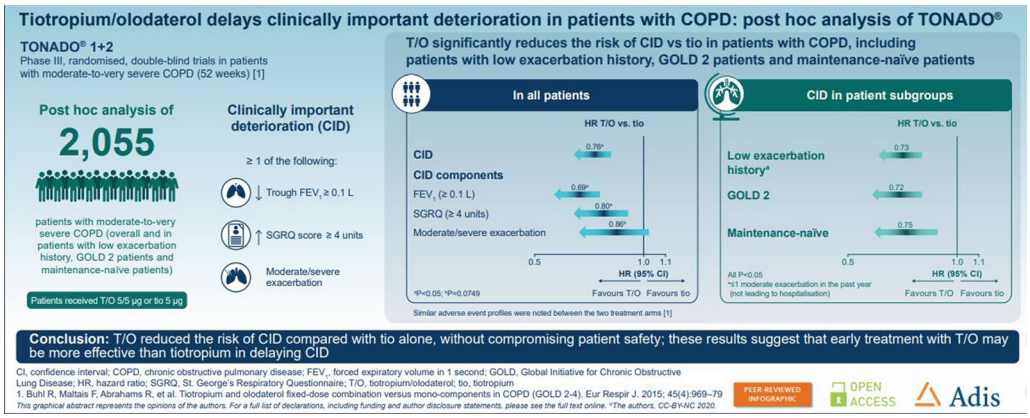
Methods: Data were analysed from 2055 patients treated with either tiotropium/olodaterol 5/5 μg or tiotropium 5 μg (delivered via Respimat®) in two replicate, 52-week, parallel-group, double-blind studies (TONADO® 1/2). CID was defined as a decline of at least 0.1 L from baseline in trough forced expiratory volume in 1 s, increase from baseline of at least 4 units in St. George's Respiratory Questionnaire score, or moderate/severe exacerbation. Time to first occurrence of one of these events was recorded as time to first CID.

Results: Overall, treatment with tiotropium/olodaterol significantly increased the time to, and reduced the risk of, CID versus tiotropium (median time to CID 226 versus 169 days; hazard ratio [HR] 0.76 [95% confidence interval 0.68, 0.85]; $P < 0.0001$). Significant reductions were also observed in patients with low exacerbation history (241 versus 170; HR 0.73 [0.64, 0.83]; $P < 0.0001$), GOLD 2 patients (241 versus 169; 0.72 [0.61, 0.84]; $P < 0.0001$) and maintenance-naïve patients (233 versus 171; 0.75 [0.62, 0.91]; $P = 0.0030$).

Conclusion: In patients with COPD, including patients with low exacerbation history, GOLD 2 patients and maintenance-naïve patients, tiotropium/olodaterol reduced the risk of CID versus tiotropium. These results demonstrate the advantages of treatment optimisation with tiotropium/olodaterol over tiotropium monotherapy.

Trial Registration: ClinicalTrials.gov identifier: TONADO® 1 and 2 (NCT01431274 and NCT01431287, registered 8 September 2011).

Graphic Abstract:



PLAIN LANGUAGE SUMMARY

COPD is a complicated disease that deteriorates over time. Worsening of COPD is associated with the lungs working less effectively, a fall in quality of life and a rise in sudden flare-ups of the disease. In this study, we looked at lung function, quality of life and flare-ups together using a measure called "clinically important deterioration" (CID). We looked at 2055 people with COPD to compare the effects of taking two bronchodilators (tiotropium and olodaterol) against taking one bronchodilator (tiotropium alone). Bronchodilators are a type of inhaled medication that relax the muscles in the lungs and widen airways, making it easier to breathe.

W. Xue
Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA

D. Singh
Medicines Evaluation Unit (MEU), University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK

G. T. Ferguson
Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA

J. Wedzicha
Respiratory Division, National Heart and Lung Institute, Imperial College London, London, UK

They have also been shown to reduce sudden flare-ups of COPD. Across a wide range of people with COPD, we found that treatment with tiotropium/olodaterol reduced the risk of a CID compared with tiotropium alone. This includes in those patients at an early stage of disease, who may benefit from finding the best treatment option for them as early as possible.

Keywords: Chronic obstructive pulmonary disease; Exacerbations; Health status; Lung function; Olodaterol; Tiotropium

Key Summary Points

Why carry out this study?

Since chronic obstructive pulmonary disease (COPD) is a heterogenous disease, using a composite endpoint that incorporates lung function, exacerbations and quality of life may provide a more holistic view of the potential benefits of a given therapy and increase our ability to detect differences between therapies.

Further studies are needed to ascertain whether more patients with COPD, including those with mild-to-moderate or few symptoms, could benefit from earlier treatment with long-acting muscarinic antagonist/long-acting β_2-agonist combination therapy.

In this post hoc analysis of data from the TONADO studies, we used a composite endpoint for clinically important deterioration (CID) that included assessments of lung function, health status and exacerbations to compare the effects of treatment with tiotropium/olodaterol versus tiotropium in patients with COPD.

What was learned from the study?

Overall, in 2055 patients with moderate-to-very severe COPD from the TONADO trials, tiotropium/olodaterol significantly reduced the risk of a CID compared with tiotropium alone.

Results were similar for patients considered to be at an earlier stage of COPD (patients with low exacerbation history [at most one moderate exacerbation], Global Initiative for Chronic Obstructive Lung Disease 2 patients and maintenance-naïve patients), suggesting that early treatment with tiotropium/olodaterol may be more effective in reducing the risk of a CID versus tiotropium.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, graphical abstract and plain language summary to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13061345.

INTRODUCTION

Whether more patients with chronic obstructive pulmonary disease (COPD), including those with mild-to-moderate disease or fewer symptoms, could benefit from earlier treatment with long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) combination therapy is a matter of debate [1, 2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report recommends LAMA or LABA monotherapy as initial pharmacological therapy for most patients [3]. Dual LAMA/LABA therapy is recommended for patients with COPD who remain symptomatic despite treatment with a single long-acting bronchodilator, or as initial therapy for patients who are highly symptomatic (COPD Assessment Test™ [CAT] > 20) and classified as

being in GOLD group D (at least two moderate exacerbations or at least one leading to hospitalisation, modified British Medical Research Council questionnaire [mMRC] grade $\geq$ 2 and CAT $\geq$ 10) or for patients in GOLD group B (at most one moderate exacerbation, mMRC grade $\geq$ 2 and CAT $\geq$ 10) with severe breathlessness [3]. The report does, however, acknowledge the lack of high-quality evidence to support initial pharmacological treatment strategies in patients with newly diagnosed COPD [3]. In contrast, the American Thoracic Society 2020 clinical practice guidelines recommend LAMA/LABA combination therapy over LABA or LAMA monotherapy for patients with COPD with dyspnoea or exercise intolerance [4]. Additionally, the National Institute for Health and Care Excellence recommends dual LAMA/LABA therapy for patients with no indication of asthmatic features or corticosteroid responsiveness who remain breathless or have exacerbations despite optimised non-pharmacological management and use of short-acting bronchodilators [5].

The benefits of LAMA/LABA combination therapy versus LAMA or LABA monotherapies have consistently been demonstrated in patients with COPD, including improvements in lung function, health status and symptoms [3, 6–9]. This was exemplified by Oba et al. [9] in a recent network analysis of more than 100,000 patients with moderate-to-very severe COPD from 99 studies. The results showed that LAMA/LABA reduced COPD exacerbations compared with either LAMA or LABA monotherapy or a LABA/inhaled corticosteroid (ICS) combination; this finding was true for both patients with high or low exacerbation risk [9]. Greater improvements in symptom and quality-of-life scores, and similar safety outcomes, were also observed with combination therapy versus monotherapy [9]. In addition, post hoc analysis of data from the TONADO and OTEMTO trials showed significant improvements in lung function, health status and breathlessness with tiotropium/olodaterol versus tiotropium both in patients who were naïve to LAMA, LABA and ICS therapy at study entry [10] and in patients receiving only LAMA monotherapy at study entry [11].

Notably, the majority of studies comparing LAMA/LABA combination therapy with monotherapy have assessed lung function as a means of evaluating the effectiveness of treatment regimens [12]. In addition, reporting of exacerbation rates and time to first exacerbation are often regulatory requirements for drug registration, leading to their prominence over other endpoints [13]. However, the GOLD 2020 report advises that symptoms as well as exacerbations are taken into account when considering combination therapy as a treatment option [3], while many clinicians prioritise improvements in both symptoms and quality of life. Given the heterogeneous nature of COPD, using a composite endpoint that incorporates lung function, exacerbations and quality of life has the potential to provide a more holistic view of the potential benefits of a given therapy and increase the ability to detect differences between interventions.

Care must be taken in selecting the right composite endpoint components, which must be clinically meaningful and help to guide medical decision-making [14]. Clinically relevant thresholds for change have been established for several parameters that may be included in a composite endpoint, including forced expiratory volume in 1 s (FEV_1) [15] and the St. George's Respiratory Questionnaire (SGRQ) score [16]. These thresholds, termed the minimal clinically important difference (MCID), represent the smallest difference in score that patients perceive as beneficial and that would mandate a change in the patient's management [17].

In COPD, a number of recent studies have explored the use of composite endpoints [18–24], several of which include components with MCIDs [18–20]. Clinically important deterioration (CID) is one such composite measure that has been used to assess COPD worsening. Since preventing disease progression is a major goal of COPD [3], CID provides a valuable measure. Post hoc analysis of clinical trials has demonstrated that LAMA/LABA reduces the risk of CID (encompassing lung function, health status and the occurrence of moderate-to-severe exacerbations) compared with LAMA or LABA monotherapy, LABA/ICS or placebo [18, 19].

The aim of this post hoc analysis was to use a composite endpoint to assess whether tiotropium/olodaterol is more effective than tiotropium alone in delaying CID in patients from

the TONADO 1 and 2 trials, specifically in patients at an earlier stage of disease or with a lower disease burden. Patients were assessed overall and in the following subgroups: patients with low exacerbation history (at most one moderate exacerbation and no exacerbations leading to hospitalisation in the past year); patients with GOLD 2 COPD (moderate COPD); and patients who were naïve to COPD maintenance therapy (maintenance-naïve). In addition, this study will help to evaluate the utility of CID as a metric for monitoring COPD worsening in patients receiving different treatments.

METHODS

The TONADO trials have been described in detail previously [25] and are briefly summarised below. TONADO® 1 (NCT01431274)/ TONADO® 2 (NCT01431287) were two replicate, 52-week, parallel-group, double-blind studies. In total, 5162 patients were treated with either tiotropium/olodaterol 2.5/5 μg or 5/5 μg, tiotropium 2.5 μg or 5 μg, or olodaterol 5 μg (delivered once daily via Respimat®). Patients were aged at least 40 years, with a smoking history of more than 10 pack-years and moderate-to-very severe COPD (GOLD 2–4). For further details, see the Supplementary Methods. The primary endpoints assessed were FEV_1 area under the curve from 0 to 3 h response, trough FEV_1 response and SGRQ total score at 24 weeks [25].

The TONADO® studies were performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. The protocols were approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients.

Definition and Assessment of CID

In this post hoc analysis, we used a composite endpoint to evaluate the time to first CID. The composite endpoint was defined as a decline from baseline in trough FEV_1 of at least 0.1 L, increase from baseline of at least 4 units in SGRQ score, or moderate or severe exacerbation, as previously defined by Singh et al. [19]. The time to first occurrence of one of these events was recorded as the time to first CID.

Assessment of trough FEV_1 was performed on day 1 and at weeks 2, 6, 12, 18, 24, 32, 40 and 52. Assessment of SGRQ was completed on day 1 and after 12, 24 and 52 weeks [25]. Data are presented for comparisons of tiotropium/olodaterol 5/5 μg and tiotropium 5 μg.

Statistical Analysis

Time to first CID (composite endpoint) and time to first clinically significant event (individual components of the composite endpoint) were measured in days. The 25th percentiles for the individual components, and the medians for the composite endpoint (overall and for each patient subgroup), are reported for each treatment arm wherever estimable.

Hazard ratios (HRs) for treatment comparisons were obtained by fitting a Cox proportional hazard regression model, with study, ICS use at baseline, region, GOLD stage and smoking status as fixed categorical effects, and with baseline SGRQ score and the number of exacerbations in the previous year as fixed continuous covariates.

Kaplan–Meier estimates of the probability of CID based on the composite endpoint and for the individual components of the composite endpoint were generated for the total study population.

RESULTS

Baseline Characteristics in the TONADO® Studies

This post hoc analysis evaluated data from 2055 patients treated with either tiotropium/olodaterol 5/5 μg or tiotropium 5 μg in the TONADO® 1 and 2 trials. Baseline demographics were similar between the two treatment arms (Supplementary Table 1) and have been described previously [25]. The majority of patients were male (tiotropium/olodaterol, 71.2%;

tiotropium, 73.1%), with a mean age approx. 64 years (mean ± standard deviation 63.8 ± 8.3; 63.9 ± 8.6) and over one-third were current smokers (38.9%; 35.8%). The majority of patients were classified as GOLD stage 2 (tiotropium/olodaterol, 48.8%; tiotropium, 50.0%) or stage 3 (tiotropium/olodaterol, 39.7%; tiotropium, 37.5%); the remaining patients were classified as GOLD stage 4 (tiotropium/olodaterol, 11.6%; tiotropium, 12.4%). At baseline, pre- and post-bronchodilator screening for FEV_1 were similar in the tiotropium/olodaterol (1.180 ± 0.493 L and 1.344 ± 0.505 L, respectively) and tiotropium (1.200 ± 0.504 L and 1.370 ± 0.521 L) groups.

CID Composite Endpoint

When the CID composite endpoint was used, median time to event was delayed and the risk of CID was significantly reduced in patients treated with tiotropium/olodaterol compared with tiotropium in the total patient population (time to event 226 versus 169 days; HR 0.76 [95% CI 0.68, 0.85]; $P < 0.0001$) (Fig. 1). Kaplan–Meier estimates also show a reduced risk of CID and a longer time to event for patients treated with tiotropium/olodaterol versus tiotropium, and clear separation between the two treatment arms (Fig. 2).

A similar and significant delay in median time to CID and reduction in risk of CID with tiotropium/olodaterol versus tiotropium alone was also observed in the three subpopulations assessed: patients with low exacerbation history (241 versus 170; HR 0.73 [95% CI 0.64, 0.83]; $P < 0.0001$), GOLD 2 patients (241 versus 169; HR 0.72 [95% CI 0.61, 0.84]; $P < 0.0001$) and maintenance-naïve patients (233 versus 171; HR 0.75 [95% CI 0.62, 0.91]; $P = 0.0030$) (Fig. 1).

Individual Components of the Composite Endpoint

Overall Patient Population

Overall, there was a significant reduction in the risk of trough FEV_1 decline from baseline of at least 0.1 L (HR 0.69 [95% CI 0.59, 0.80]; $P < 0.0001$) and in the risk of SGRQ score increase from baseline of at least 4 units (HR 0.80 [95% CI 0.68, 0.93]; $P = 0.0046$) with tiotropium/olodaterol versus tiotropium (Table 1). There was also a reduction in the risk of moderate or severe exacerbations (HR 0.86 [95% CI 0.73, 1.02];

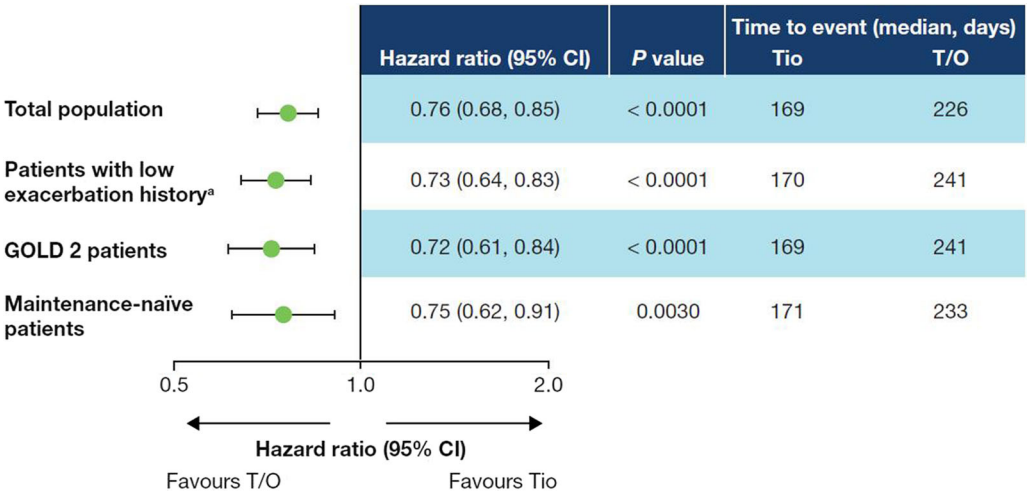


Fig. 1 Treatment comparison and time to event for tiotropium (5 µg) versus tiotropium/olodaterol (5/5 µg) using the CID composite endpoint score. [a]Low exacerbation history was defined as at most one moderate exacerbation in the past year (not leading to hospitalisation). CI confidence interval, CID clinically important deterioration, GOLD Global Initiative for Chronic Obstructive Lung Disease, T/O tiotropium/olodaterol, Tio tiotropium

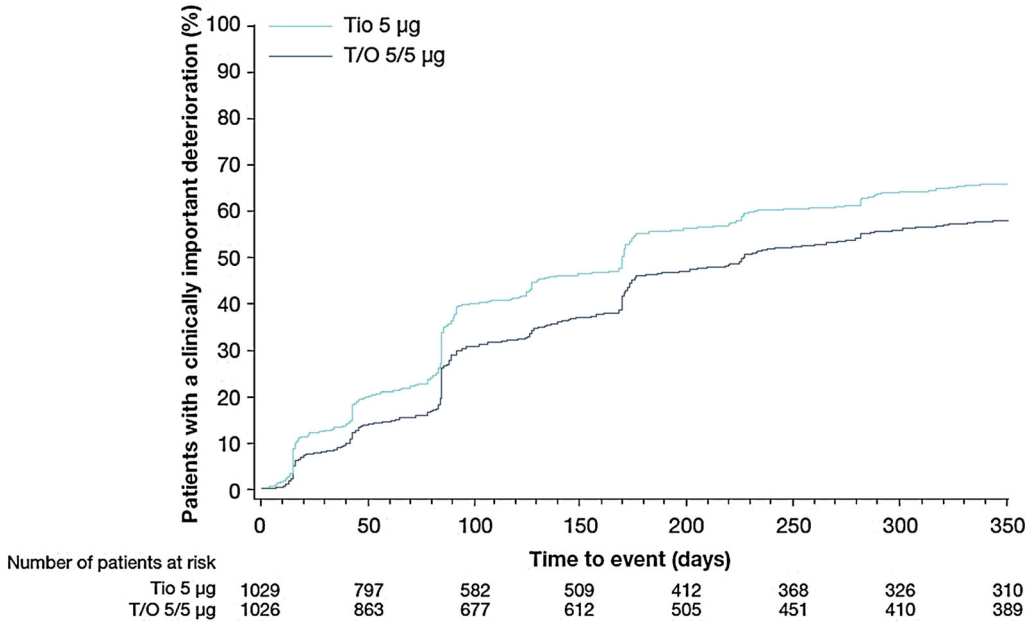


Fig. 2 Time to first CID in patients treated with tiotropium (5 µg) versus tiotropium/olodaterol (5/5 µg) in the overall patient population. CID clinically important deterioration, T/O tiotropium/olodaterol, Tio tiotropium

Table 1 Individual components of the composite endpoint: event rates and time to first event (25th percentile) in the total patient population

Endpoint	Tiotropium 5 µg		Tiotropium/olodaterol 5/5 µg		Time to first event treatment comparison (tiotropium–tiotropium/olodaterol)	
	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	HR (95% CI)	*P* value
Trough FEV_1 decline from baseline ≥ 0.1 L	386/1026 (37.6)	132	305/1023 (29.8)	279	0.69 (0.59, 0.80)	< 0.0001
SGRQ score increase from baseline ≥ 4 units	339/955 (35.5)	172	290/979 (29.6)	365	0.80 (0.68, 0.93)	0.0046
Moderate or severe exacerbation	297/1029 (28.9)	270	285/1026 (27.8)	293	0.86 (0.73, 1.02)	0.0749

CI confidence interval, *FEV_1* forced expiratory volume in 1 s, *HR* hazard ratio, *SGRQ* St. George's Respiratory Questionnaire

P = 0.0749) with tiotropium/olodaterol versus tiotropium.

In patients treated with tiotropium/olodaterol versus tiotropium, 29.8% versus 37.6% experienced a trough FEV_1 decline from

Table 2 Individual components of the composite endpoint: event rates and time to first event (25th percentile) in patients with low exacerbation history (≤ 1 moderate exacerbation in the past year)

Endpoint	Tiotropium 5 µg		Tiotropium/olodaterol 5/5 µg		Time to first event treatment comparison (tiotropium–tiotropium/olodaterol)	
	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	HR (95% CI)	*P* value
Trough FEV_1 decline from baseline ≥ 0.1 L	297/775 (38.3)	132	230/771 (29.8)	274	0.68 (0.57, 0.81)	< 0.0001
SGRQ score increase from baseline ≥ 4 units	266/720 (36.9)	170	215/739 (29.1)	365	0.74 (0.62, 0.89)	0.0011
Moderate or severe exacerbation	198/776 (25.5)	328	188/773 (24.3)	351	0.85 (0.70, 1.04)	0.1192

CI confidence interval, *FEV_1* forced expiratory volume in 1 s, *HR* hazard ratio, *SGRQ* St. George's Respiratory Questionnaire

baseline of at least 0.1 L, 29.6% versus 35.5% an SGRQ score increase from baseline of at least 4 units, and 27.8% versus 28.9% experienced moderate or severe exacerbations (Table 1).

Patients with Low Exacerbation History

For patients with low exacerbation history, there was a significant reduction in the risk of trough FEV_1 decline (HR 0.68 [95% CI 0.57, 0.81]; $P < 0.0001$) and in the risk of SGRQ score increase from baseline (HR 0.74 [95% CI 0.62, 0.89]; $P = 0.0011$) with tiotropium/olodaterol compared with tiotropium (Table 2). The risk was also reduced for moderate or severe exacerbations, but the reduction was not statistically significant between treatment groups (Table 2).

In patients with low exacerbation history who received treatment with tiotropium/olodaterol versus tiotropium, 29.8% versus 38.3% of patients experienced a trough FEV_1 decline from baseline of at least 0.1 L, 29.1% versus 36.9% experienced an SGRQ score increase from baseline of at least 4 units, and 24.3% versus 25.5% experienced moderate or severe exacerbations (Table 2).

GOLD 2 Patients

For GOLD 2 patients, there was a significant reduction in the risk of trough FEV_1 decline with tiotropium/olodaterol versus tiotropium (HR 0.67 [95% CI 0.55, 0.82]; $P < 0.0001$). There was a reduction of 14% in the risk of SGRQ score increase from baseline and 21% in the risk of moderate or severe exacerbations for patients treated with tiotropium/olodaterol versus tiotropium, although neither of these reductions were statistically significant (Table 3).

In GOLD 2 patients treated with tiotropium/olodaterol versus tiotropium, 34.1% versus 44.4% of patients experienced a trough FEV_1 decline from baseline of at least 0.1 L, 30.1% versus 34.3% experienced an SGRQ score increase from baseline of at least 4 units, and 20.6% versus 24.8% experienced moderate or severe exacerbations (Table 3).

Maintenance-Naïve Patients

In maintenance-naïve patients, there was a significant reduction in the risk of trough FEV_1 decline with tiotropium/olodaterol compared with tiotropium (HR 0.56 [95% CI 0.44, 0.72];

Table 3 Individual components of the composite endpoint: event rates and time to first event (25th percentile) in GOLD 2 patients

Endpoint	Tiotropium 5 µg		Tiotropium/olodaterol 5/5 µg		Time to first event treatment comparison (tiotropium–tiotropium/olodaterol)	
	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	HR (95% CI)	*P* value
Trough FEV_1 decline from baseline ≥ 0.1 L	228/514 (44.4)	92	170/499 (34.1)	225	0.67 (0.55, 0.82)	< 0.0001
SGRQ score increase from baseline ≥ 4 units	169/492 (34.3)	171	144/478 (30.1)	365	0.86 (0.69, 1.07)	0.1755
Moderate or severe exacerbation	128/516 (24.8)	338	103/501 (20.6)	–	0.79 (0.61, 1.03)	0.0804

CI confidence interval, *FEV_1* forced expiratory volume in 1 s, *HR* hazard ratio, *SGRQ* St. George's Respiratory Questionnaire

Table 4 Individual components of the composite endpoint: event rates and time to first event (25th percentile) in maintenance-naïve patients

Endpoint	Tiotropium 5 µg		Tiotropium/olodaterol 5/5 µg		Time to first event treatment comparison (tiotropium–tiotropium/olodaterol)	
	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	Event rate, *n*/*N* (%)	Time to first event (25th percentile), days	HR (95% CI)	*P* value
Trough FEV_1 decline from baseline ≥ 0.1 L	169/380 (44.5)	127	103/350 (29.4)	241	0.56 (0.44, 0.72)	< 0.0001
SGRQ score increase from baseline ≥ 4 units	113/357 (31.7)	174	89/328 (27.1)	365	0.84 (0.63, 1.11)	0.2136
Moderate or severe exacerbation	74/382 (19.4)	–	68/351 (19.4)	–	1.02 (0.73, 1.42)	0.9210

CI confidence interval, *FEV_1* forced expiratory volume in 1 s, *HR* hazard ratio, *SGRQ* St. George's Respiratory Questionnaire

$P < 0.0001$). No other components of the composite endpoint were statistically significant for comparison of tiotropium/olodaterol versus tiotropium (Table 4). Although the treatment comparison was not statistically significant for SGRQ score, a 16% reduction in the risk of SGRQ score increase from baseline was observed with tiotropium/olodaterol versus tiotropium (Table 4).

In maintenance-naïve patients treated with tiotropium/olodaterol versus tiotropium, 29.4% versus 44.5% of patients experienced a trough FEV_1 decline from baseline of at least 0.1 L, 27.1% versus 31.7% experienced an SGRQ score increase from baseline of at least 4 units, and 19.4% versus 19.4% experienced moderate or severe exacerbations (Table 4).

Safety

Safety data from the TONADO® trials have been published previously [25]. In brief, the proportion of patients with adverse events was similar in those treated with tiotropium/olodaterol versus tiotropium (74.0% versus 73.3%), as was the proportion of patients discontinuing treatment due to an adverse event (7.4% versus 9.0%). The most frequently reported adverse events were respiratory, thoracic and mediastinal disorders (39.4% for tiotropium/olodaterol versus 42.7% for tiotropium), COPD (32.3% versus 32.9%), and infections and infestations (36.3% versus 33.7%). The incidence of pneumonia was similar in those treated with tiotropium/olodaterol versus tiotropium (3.3% versus 2.5%).

DISCUSSION

Findings from the TONADO® 1 and 2 studies have previously shown that the once-daily LAMA/LABA combination of tiotropium and olodaterol improves lung function, breathlessness and quality of life in patients with moderate-to-very severe COPD compared with tiotropium alone [25–27]. This post hoc analysis of data from the two TONADO COPD trials further demonstrated that tiotropium/olodaterol significantly reduces the risk of a CID versus tiotropium alone.

The definition of CID assessed here has been described previously, and our findings are in line with recent studies by Singh et al. [19], Anzueto et al. [18] and Rabe et al. [20], all of whom used the same CID composite endpoint. Singh et al. [19] demonstrated that the risk of a first CID was reduced with LAMA/LABA (umeclidinium/vilanterol) versus monotherapy with either tiotropium, umeclidinium or vilanterol, or versus placebo in symptomatic patients with COPD. Similarly, Anzueto et al. showed that LAMA/LABA (indacaterol/glycopyrronium) had significant treatment benefits over tiotropium monotherapy in patients with moderate-to-severe COPD, as well as versus LABA/ICS [18].

Our findings for the risk of reaching a CID were remarkably similar in the overall patient population and among the three subpopulations assessed. The subpopulation analysis highlights the benefits of treatment with tiotropium/olodaterol versus tiotropium in patients with either less severely impaired lung function or a lower disease burden, i.e. GOLD 2 patients with moderate COPD, patients with symptomatic COPD and a low risk of exacerbations, and maintenance-naïve patients.

Maintenance-naïve patients starting on tiotropium/olodaterol showed a 25% reduction in the risk of a CID and a significant reduction (44%) in the risk of lung function decline versus those patients who initiated tiotropium. A decrease in the risk of health status decline was also observed with tiotropium/olodaterol versus tiotropium in these patients; however, this did not reach significance, likely because of the smaller sample sizes in these subgroup analyses. Overall, these observations suggest that starting treatment with a LAMA/LABA combination may be beneficial not only in improving COPD outcomes but also in preventing disease worsening. Current recommendations from GOLD suggest that a LAMA/LABA combination should only be used as initiation therapy in patients with group D COPD who are highly symptomatic or with group B COPD and severe breathlessness [3]. However, our findings suggest that patients with low exacerbation history could benefit from earlier treatment with

LAMA/LABA, and support the recent argument put forward by Cazzola et al. [1] that LAMA/LABA combination therapy could have benefits as initial maintenance therapy. These findings are supported by previous studies that have consistently demonstrated LAMA/LABA combination therapy to be more effective than LAMA or LABA monotherapy in improving lung function and health status [1, 6, 8], and in reducing the risk of exacerbations [1, 8, 9].

In addition to clinical evidence advocating the benefits of dual bronchodilation [1], there is a strong rationale for using LAMA/LABA as initial maintenance treatment. Pharmacologically, the use of a LAMA/LABA combination exploits both the adrenergic and cholinergic pathways in the airway smooth muscle (ASM) to maximise bronchodilation. While LAMAs block the effect of bronchoconstriction by blocking acetylcholine binding to M3 muscarinic receptors in ASM, activation of β_2-adrenoreceptors by LABAs induces ASM relaxation [1, 28]. In addition to controlling ASM constriction and relaxation, muscarinic and adrenergic receptors are located on inflammatory cells, and drugs that target these receptors might also reduce inflammation in COPD [1, 28]. Additionally, LAMA/LABA is reported to have a good cardiovascular safety profile and does not increase severe cardiovascular adverse events versus monotherapy [1, 6, 29].

Analysis of the risk associated with the individual components of the composite endpoint clearly indicated that lung function was the strongest driver of CID, both in the overall patient population and in all three patient subgroups. Given that this study evaluates different bronchodilator treatments, where the most prominent effect is inevitably on lung function, this finding is not surprising. Other individual components also contributed to the risk of CID observed, with the risk of health status decline (as defined by the risk of SGRQ score increase from baseline of at least 4 units), showing a significant reduction with tiotropium/olodaterol versus tiotropium in the total patient population and in patients with low exacerbation history; this likely reflects the benefits of improved lung function on overall health, daily life and perceived well-being in patients with COPD. In support of this, a recent pooled analysis of 23 randomised controlled COPD studies reported a correlation between lung function and health status, with greater improvements in trough FEV_1 reported in patients with better SGRQ scores [30]. Notably, there was more variation observed between the different patient subpopulations for moderate-to-severe exacerbations.

Previous studies have demonstrated the suitability of various composite endpoints to predict long-term outcomes in patients with COPD [21–24], including for CID [18–20]. Given that COPD is a progressive disease, the use of CID as a composite endpoint provides a valuable measure to monitor patients who do not respond well to treatment but whose treatments may prevent deterioration or disease worsening—a major treatment goal for patients with COPD [3]. The value of the composite endpoint assessed here has previously been demonstrated in a post hoc analysis of the UPLIFT® study, in which CID events at 6 months were shown to be a good predictor of both future moderate or severe exacerbations and severe exacerbations, as well as mortality (albeit to a weaker extent) [20]. Using the same definition of CID, data from two 3-year studies (TORCH and ECLIPSE) reported similar findings; patients who had an early CID (i.e. within 6–12 months of follow-up) consistently experienced an increased long-term risk of lung function and health status decline, exacerbation and mortality [31].

General limitations associated with post hoc analyses include the non-randomised nature of the study and the lack of prespecified subgroups [32]. Another limitation of this analysis was that clinically significant events did not have to be confirmed at a second clinic visit as an inclusion criterion. This was a consequence of the length of the TONADO studies (52 weeks) and the number of assessments occurring during this period (only three SGRQ assessments). A further limitation is that the timings between clinically significant events are not known, as only the time to the first individual event was included in the analysis. Instances where subsequent clinically significant events occurred after the first event were therefore not captured, nor was

the order in which events occurred. In addition, as described previously for similar CID analyses [33], the most frequent events were those that were recorded at distinct time points; since FEV_1 and SGRQ were only assessed at the set study visit dates, this limits the precision of the Kaplan–Meier plots and HRs. Nonetheless, this also reflects the manner in which assessments would be conducted in clinical practice, where physicians assess disease progression or treatment failure at scheduled visits or based on major events, such as exacerbations, which can occur at any time.

CONCLUSION

In this post hoc analysis of data from the TONADO studies, tiotropium/olodaterol delayed the time to, and reduced the risk of, CID compared with tiotropium alone in the overall trial population, in patients with low exacerbation history, patients with GOLD 2 COPD and in maintenance-naïve patients. Taken together with previous studies on tiotropium/olodaterol, LAMA/LABA combination therapy versus monotherapy, these results suggest that early treatment with tiotropium/olodaterol may be more effective than tiotropium in reducing the risk of CID in these important patient populations. In addition, the data reported here support the use of CID endpoints to monitor COPD disease progression, and suggest that this could be a valuable metric to assess in future randomised COPD trials.

ACKNOWLEDGEMENTS

We thank the participants included in these studies. Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

Funding. Support for this project and the journal's Open Access Fee were funded by Boehringer Ingelheim International GmbH. No Rapid Service Fee was received by the journal for the publication of this article.

Authorship. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript, were involved at all stages of development and have approved the submitted manuscript. The authors received no compensation related to the development of the manuscript.

Disclosures. Klaus F. Rabe reports personal fees from Boehringer Ingelheim, AstraZeneca, Novartis and Chiesi, and grants from Boehringer Ingelheim, AstraZeneca and Takeda, outside the submitted work. James D. Chalmers has received grants and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Grifols, Insmed, Novartis and Zambon, grants from Gilead and personal fees from Napp, outside the submitted work. Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, TEVA, Spin Therapeutics, pH Pharma, Novartis, Sanofi and Grifols and research grants from GlaxoSmithKline and Grifols, outside the submitted work. Janwillem W.H. Kocks has received grants and personal fees from AstraZeneca, Boehringer Ingelheim and GSK, grants from Chiesi, and personal fees from Mundipharma and Teva, outside the submitted work. Ioanna Tsiligianni has received grants and personal fees from GSK, grants from ELPEN and personal fees from Boehringer Ingelheim, Menarini and Novartis, outside the submitted work. Alberto de la Hoz and Wenqiong Xue are employees of Boehringer Ingelheim. Dave Singh reports personal fees from Apellis, Cipla, Genentech, Peptinnovate and Skyepharma, and grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Merck, Mundipharma, Novartis, Pfizer, Pulmatrix, Teva, Theravance and Verona, outside the submitted work. Gary T. Ferguson has received grants, personal fees and non-

financial support from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Pearl Therapeutics, Sunovion and Theravance, and personal fees from Circassia, Innoviva, Mylan and Verona, outside the submitted work. Jadwiga Wedzicha has received grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Johnson and Johnson, and Novartis, and meeting expenses from AstraZeneca, Boehringer Ingelheim, GSK and Novartis, outside the submitted work.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance, in the form of the preparation and revision of the manuscript, was supported financially by Boehringer Ingelheim and provided by Vicki Cronin, PhD, at MediTech Media, under the authors' conceptual direction and based on feedback from the authors.

Compliance with Ethics Guidelines. The TONADO® studies were performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. The protocols were approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients.

Data Availability. The data sets used and analysed during the current study are available from the corresponding author on reasonable request. Before this request, users should get permission from the local ethics committee.

REFERENCES

1. Cazzola M, Matera MG. POINT: should LAMA/LABA combination therapy be used as initial maintenance treatment for COPD? Yes. Chest. 2018;154(4):746–8.

2. Barrecheguren M, Miravitlles M. COUNTERPOINT: should LAMA/LABA combination therapy be used as initial maintenance treatment for COPD? No. Chest. 2018;154(4):749–51.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2020 report). 2019. https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf. Accessed 15 Jun 2020.

4. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of COPD: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;201(9):e56–69.

5. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2019. https://www.nice.org.uk/guidance/ng115/chapter/Recommendations#ftn.footnote_3. Accessed 15 Jun 2020.

6. Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilation with LAMA/LABA for the treatment of stable COPD. Chest. 2016;149(5):1181–96.

7. Calzetta L, Ora J, Cavalli F, Rogliani P, O'Donnell DE, Cazzola M. Impact of LABA/LAMA combination on exercise endurance and lung hyperinflation in COPD: a pair-wise and network meta-analysis. Respir Med. 2017;129:189–98.

8. Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. Thorax. 2016;71(1):15–25.

9. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2018;12:CD012620.

10. Buhl R, de la Hoz A, Xue W, Singh D, Ferguson GT. Efficacy of tiotropium/olodaterol compared with tiotropium as a first-line maintenance treatment in patients with COPD who are naïve to LAMA, LABA and ICS: pooled analysis of four clinical trials. Adv Ther. 2020;37:4175–89.

11. Buhl R, Singh D, de la Hoz A, Xue W, Ferguson GT. Benefits of tiotropium/olodaterol compared with tiotropium in patients with COPD receiving only LAMA at baseline: pooled analysis of the TONADO® and OTEMTO® studies. Adv Ther. 2020;37:3485–99.

12. van der Molen T, Cazzola M. Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. Prim Care Respir J. 2012;21(1):101–8.

13. De Soyza A, Calverley PM. Large trials, new knowledge: the changing face of COPD management. Eur Respir J. 2015;45(6):1692–703.

14. McCoy CE. Understanding the use of composite endpoints in clinical trials. West J Emerg Med. 2018;19(4):631–4.

15. Donohue JF. Minimal clinically important differences in COPD lung function. COPD. 2005;2(1):111–24.

16. Alma HJ, de Jong C, Jelusic D, et al. Thresholds for clinically important deterioration versus improvement in COPD health status: results from a randomised controlled trial in pulmonary rehabilitation and an observational study during routine clinical practice. BMJ Open. 2019;9(6):e025776.

17. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407–15.

18. Anzueto AR, Vogelmeier CF, Kostikas K, et al. The effect of indacaterol/glycopyrronium versus tiotropium or salmeterol/fluticasone on the prevention of clinically important deterioration in COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:1325–37.

19. Singh D, Maleki-Yazdi MR, Tombs L, Iqbal A, Fahy WA, Naya I. Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol. Int J Chron Obstruct Pulmon Dis. 2016;11:1413–24.

20. Rabe KF, Halpin DMG, Han MK, et al. Composite endpoints in COPD: clinically important deterioration in the UPLIFT trial. Respir Res. 2020;21(1):177.

21. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12.

22. Celli BR, Decramer M, Liu D, Metzdorf N, Asijee GM, Tashkin DP. Defining a COPD composite safety endpoint for demonstrating efficacy in clinical trials: results from the randomized, placebo-controlled UPLIFT® trial. Respir Res. 2016;17(1):48.

23. Briggs A, Spencer M, Wang H, Mannino D, Sin DD. Development and validation of a prognostic index for health outcomes in chronic obstructive pulmonary disease. JAMA Intern Med. 2008;168(1):71–9.

24. Jones RC, Donaldson GC, Chavannes NH, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(12):1189–95.

25. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). Eur Respir J. 2015;45(4):969–79.

26. Maltais F, Beck E, Webster D, et al. Four weeks once daily treatment with tiotropium+olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients [abstract P5557]. Eur Respir J. 2010;36(suppl 54):1014s.

27. Buhl R, de la Hoz A, Voss F, Singh D, Ferguson GT. Efficacy of tiotropium/olodaterol compared with tiotropium in patients naïve to LAMA, LABA and ICS: pooled analysis of four clinical trials. Am J Respir Crit Care Med. 2019;199:A7098.

28. Panettieri RA Jr. Bronchodilators, receptors and cross-talk: together is better? Postgrad Med. 2015;127(7):771–80.

29. Rogliani P, Matera MG, Ora J, Cazzola M, Calzetta L. The impact of dual bronchodilation on cardiovascular serious adverse events and mortality in COPD: a quantitative synthesis. Int J Chron Obstruct Pulmon Dis. 2017;12:3469–85.

30. Donohue JF, Jones PW, Bartels C, et al. Correlations between FEV1 and patient-reported outcomes: a pooled analysis of 23 clinical trials in patients with chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2018;49:11–9.

31. Naya IP, Tombs L, Muellerova H, Compton C, Jones PW. Long-term outcomes following first short-term

clinically important deterioration in COPD. Respir Res. 2018;19(1):222.

32. Curran-Everett D, Milgrom H. Post-hoc data analysis: benefits and limitations. Curr Opin Allergy Clin Immunol. 2013;13(3):223–4.

33. Singh D, Fabbri LM, Vezzoli S, Petruzzelli S, Papi A. Extrafine triple therapy delays COPD clinically important deterioration vs ICS/LABA, LAMA, or LABA/LAMA. Int J Chron Obstruct Pulmon Dis. 2019;14:531–46.