Prognostic value of clinically important deterioration in COPD: IMPACT trial analysis

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ABSTRACT

Introduction: Clinically important deterioration (CID) is a multicomponent measure for assessing disease worsening in chronic obstructive pulmonary disease (COPD). This analysis investigated the prognostic value of a CID event on future clinical outcomes and the effect of single-inhaler triple versus dual therapy on reducing CID risk in patients in the IMPACT trial.

Methods: IMPACT was a phase III, double-blind, 52-week, multicentre trial. Patients with symptomatic COPD and at least one moderate/severe exacerbation in the prior year were randomised 2:2:1 to fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 µg, FF/VI 100/25 µg or UMEC/VI 62.5/25 µg. CID at the time-point of interest was defined as a moderate/severe exacerbation, ≥100 mL decrease in trough forced expiratory volume in 1 s or deterioration in health status (increase of ≥4.0 units in St George’s Respiratory Questionnaire total score or increase of ≥2.0 units in COPD Assessment Test score) from baseline. A treatment-independent post hoc prognostic analysis compared clinical outcomes up to week 52 in patients with/without a CID by week 28. A prospective analysis evaluated time to first CID with each treatment.

Results: Patients with a CID by week 28 had significantly increased exacerbation rates after week 28, smaller improvements in lung function and health status at week 52 (all p<0.001), and increased risk of all-cause mortality after week 28 versus patients who were CID-free. FF/UMEC/VI significantly reduced CID risk versus dual therapies (all p<0.001).

Conclusions: Prevention of short-term disease worsening was associated with better long-term clinical outcomes. FF/UMEC/VI reduced CID risk versus dual therapies; this effect may improve long-term prognosis in this population.

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Preventing short-term clinically important deterioration (CID) is associated with better long-term clinical outcomes in patients with COPD. FF/UMEC/VI reduces CID risk versus FF/VI and UMEC/VI therapy, and this may improve patients’ long-term prognosis. https://bit.ly/3gP1KJu

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous and frequently progressive disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 report advocates routine monitoring of disease progression using measurements of change in an individual’s symptoms, exacerbation risk and lung function [1, 2].

Clinically important deterioration (CID) is a multicomponent measure of worsening COPD that mirrors these recommendations to assess suboptimal treatment responses and disease instability using widely accepted thresholds of change in lung function and/or health status or a first acute moderate-to-severe COPD exacerbation as a measure of important deterioration [3]. Post hoc analyses have consistently shown that short-term worsening identified by these three individual CID measures can be reduced through treatment escalation with long-acting bronchodilator versus placebo, dual bronchodilator versus monotherapy, or triple therapy versus inhaled corticosteroid (ICS)/long-acting β₂-agonist (LABA) or long-acting muscarinic antagonist (LAMA)/LABA therapy [3–7]. These positive findings for intensification of bronchodilatation have also been confirmed prospectively with triple therapy versus ICS/LABA [5] and LAMA/LABA versus LAMA or LABA monotherapy [8].

Preventing short-term CID events (defined by worsening in lung function, health status or exacerbations) has also been associated with sustained treatment benefits [5, 9], and a reduced risk of all-cause mortality in up to 3 years of follow-up in the ECLIPSE and TORCH studies [9]. In TORCH, all CID components contributed to mortality risk and freedom from all event types was associated with the greatest survival benefit [9]. In the UPLIFT study patients with a CID were more likely to experience subsequent exacerbation and death [6]. However, data in COPD populations at high exacerbation risk are needed to further understand the contribution of each component to clinical outcomes.

Recently, the InforMing the PAthway of COPD Treatment (IMPACT) trial demonstrated that single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) significantly reduced moderate/severe exacerbation rates versus FF/VI or UMEC/VI, and significantly reduced severe exacerbation rates and all-cause mortality versus UMEC/VI in symptomatic COPD patients with a history of exacerbations [10]. Based on 1-year data from IMPACT, we conducted a treatment-independent post hoc analysis of the prognostic value of a CID event (deterioration on any of the CID components) within the first 28 weeks on moderate/severe exacerbation occurrence and mortality risk after week 28, and worsening of lung function and health status over 52 weeks. Additional analyses included the effect of FF/UMEC/VI versus FF/VI and UMEC/VI on reducing the risk of a first CID.

Methods

Study design

IMPACT (European Union Clinical Trials Register: CTT116855 and ClinicalTrials.gov: NCT02164513) was a phase III, double-blind, parallel-group, 52-week, multicentre study in patients ≥40 years of age with symptomatic COPD and at least one moderate/severe exacerbation in the prior year. Patients were randomised 2:2:1 to FF/UMEC/VI 100/62.5/25 µg, FF/VI 100/25 µg or UMEC/VI 62.5/25 µg once daily via a single dry-power inhaler (ELLIPTA; GlaxoSmithKline, Brentford, UK) [10]. The study design and primary results have been previously published [10].

End-points

CID was defined as any of the following on-treatment events: moderate/severe exacerbation, deterioration in lung function (≥100 mL decrease from baseline in trough forced expiratory volume in 1 s (FEV₁)) [11]

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or deterioration in health status (increase from baseline of \(≥4.0\) units in St George’s Respiratory Questionnaire (SGRQ) total score [11] or \(≥2.0\) units in COPD Assessment Test (CAT) score [12]) (table 1). Moderate exacerbations were those requiring treatment with antibiotics and/or oral/systemic corticosteroids; severe exacerbations were those resulting in hospitalisation or death.

The post hoc prognostic analysis, independent of treatment, investigated whether short-term worsening by week 28 in any component (CID-positive), compared with freedom from all worsening types (CID-negative), led to worse longer-term outcomes. Outcomes of interest included annual moderate/severe or severe exacerbation rates, time to first moderate/severe or severe exacerbation and all-cause mortality during weeks 29–52, and change from baseline in trough FEV\(_1\), SGRQ total score and CAT score at week 52.

All-cause mortality incorporated on- and off-treatment deaths, and included 99.6% of the study population’s vital status at week 52. On- and off-treatment deaths were those that occurred between study treatment start and 7 days after stopping study treatment (inclusive) for patients who completed the study or up to the projected week 52 date plus 7 days for patients who prematurely discontinued study treatment. As the IMPACT trial was enriched for a population at risk of exacerbations, the effect of CID status by week 28 on all-cause mortality was also examined using a single-component definition based solely on first moderate/severe exacerbation; this was compared with the full three-component CID definitions (using either SGRQ total score (CID\(_{SGRQ}\)) or CAT score (CID\(_{CAT}\)) for assessing health status) (table 1) and two-component definitions that excluded exacerbations to understand the relative importance of exacerbation events in the composite definitions.

The prospective analysis evaluated between-treatment comparisons of CID risk (time to first event) with FF/UMEC/VI versus FF/VI and UMEC/VI at weeks 28 and 52. Pre-specified subgroup analyses assessed treatment effect on CID\(_{SGRQ}\) and CID\(_{CAT}\) risk by baseline CAT score (<20 or \(≥20\) units) [1], baseline medication use, baseline ICS use, smoking status, age, body mass index and sex. Post hoc subgroup analyses by exacerbation history in the prior year (<2 or \(≥2\) moderate/severe and 0 or \(≥1\) severe) and blood eosinophil count (<150 or \(≥150\) cells\(\cdot\)\(µL\)^\(-1\) were also conducted. A further post hoc analysis evaluated the risk of CID\(_{SGRQ}\), CID\(_{CAT}\) or any CID component by continuous baseline eosinophil counts. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and are described in the supplementary material. No imputations for missing data were performed.

**Results**

**Patients**

The IMPACT intent-to-treat population included 10 355 patients (FF/UMEC/VI \(n=4151\); FF/VI \(n=4134\); UMEC/VI \(n=2070\). Baseline demographics and clinical characteristics were similar between treatment arms (table 2).

**Non-treatment-related prognostic outcomes by CID status by week 28**

Using the CID\(_{SGRQ}\) definition, CID-positive patients by week 28 had a 75% increase in annual moderate/severe exacerbation rate (rate ratio (RR) 1.75 (95% CI 1.60–1.92); \(p<0.001\)) and a 96% increase in severe exacerbation rate.

### TABLE 1 Clinically important deterioration (CID) and mortality sensitivity analysis definitions used in this analysis

| CID component | Exacerbation | Lung function | Health status |
|---------------|--------------|---------------|---------------|
| **Composite CID definitions** | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥4.0\) unit increase from baseline in SGRQ total score |
| CID\(_{SGRQ}\) | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥2.0\) unit increase from baseline in CAT score |
| CID\(_{CAT}\) | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥4.0\) unit increase from baseline in SGRQ total score |
| **Mortality sensitivity analysis definitions** | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥2.0\) unit increase from baseline in CAT score |
| Two-component including SGRQ | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥4.0\) unit increase from baseline in SGRQ total score |
| Two-component including CAT | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥2.0\) unit increase from baseline in CAT score |
| Single-component including exacerbation only | Moderate/severe exacerbation | \(≥100\) mL decrease from baseline in trough FEV\(_1\) | \(≥4.0\) unit increase from baseline in SGRQ total score |
| | | | \(≥2.0\) unit increase from baseline in CAT score |

SGRQ: St George’s Respiratory Questionnaire; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV\(_1\): forced expiratory volume in 1 s.
(RR 1.96 (95% CI 1.56–2.47); p<0.001) over weeks 29–52 versus CID-negative patients (table 3). Significant improvements in trough FEV₁ (difference 143 mL) and health status (SGRQ difference −7.5 units; CAT difference −2.1 units) at week 52 were seen in the CID-negative versus CID-positive subgroups (all p<0.001) (table 3).

Similar results were seen using the CID\textsuperscript{CAT} definition. Compared with CID-negative patients, by week 28, CID-positive patients had a 72% increase (RR 1.72 (95% CI 1.56–1.89); p<0.001) and 91% increase (RR 1.91 (95% CI 1.50–2.42); p<0.001) in the rate of moderate/severe and severe exacerbations, respectively, over weeks 29–52. Furthermore, CID-negative patients demonstrated improvements in week 52 FEV₁ (difference 142 mL) and health status (SGRQ difference −5.4 units; CAT difference −3.2 units) versus CID-positive patients (all p<0.001) (table 3).

Kaplan–Meier survival analysis indicated that CID-positive patients by week 28 (using CID\textsuperscript{SGRQ} and CID\textsuperscript{CAT} definitions) had a numerically higher mortality risk over weeks 29–52 compared with CID-negative patients (55% increased risk (p=0.069) for CID\textsuperscript{SGRQ} and 80% increased risk (p=0.025) for CID\textsuperscript{CAT} (Cox proportional hazard model)) (figure 1a and b and supplementary figure E1). The prognostic findings appeared to highlight increasing differences in mortality accumulated month-by-month of the follow-up period in the CID-positive versus CID-negative subgroups (figure 1).

In the sensitivity analysis, single-component CID assessed by exacerbation status alone at week 28 showed no separation in mortality risk during weeks 29–52 (p=0.402 (Cox proportional hazard model)) (figure 1c). Hazard ratio point estimates for CID-positive versus CID-negative patients for all-cause mortality were higher using the CID\textsuperscript{SGRQ} and CID\textsuperscript{CAT} definitions compared with two-component definitions (excluding exacerbations), and were lowest when using moderate/severe exacerbation only as a prognostic marker of short-term CID (supplementary figure E1).

**Effects of treatment on the incidence and risk (time to first) of CID**

Using the CID\textsuperscript{SGRQ} definition, the proportion of patients experiencing a CID was between 62% and 83% for all treatments by week 28 and 52, with a lower incidence seen with FF/UMEC/VI versus FF/VI or UMEC/VI (figure 2 and supplementary table E1). Results were similar for the CID\textsuperscript{CAT} definition, with between 67% and 85% of patients experiencing a composite CID for all treatments by week 28 and 52.
### TABLE 3 Outcomes post-week 28 by clinically important deterioration (CID) status at week 28 (definition including St George’s Respiratory Questionnaire (SGRQ) or COPD Assessment Test (CAT))

| Definition including SGRQ | CID-positive | CID-negative | Difference (CID-positive versus CID-negative) |
|---------------------------|-------------|--------------|---------------------------------------------|
|                           | N=7008\(^a\) | N=3055\(^a\) | % increase in rate (95% CI)                 |
| Rate of exacerbations     |             |              |                                             |
| Moderate/severe exacerbations after week 28 | n=5660\(^a-f\) | n=2729\(^a-f\) | 75 [60–92]\(^b\) |
| Severe exacerbations after week 28 | 0.94 (0.90–0.98) | 0.54 (0.49–0.58) |                                      |
|                           |             |              | % increase in risk (95% CI)                 |
| Time to first exacerbation |             |              |                                             |
| Moderate/severe exacerbations after week 28 | n=5643\(^a-f\) | n=2732\(^a-f\) | 72 [56–89]\(^b\) |
| Severe exacerbations after week 28 | 1900 [32] | 548 [20] |                                      |
|                           |             |              | % increase in risk (95% CI)                 |
| All-cause mortality       |             |              |                                             |
| All-cause mortality after week 28\(^\#\) | n=5887 | n=2732 | 55 [3–147]\(^b\) |
|                           | 77 [1] | 23 [-1] |                                      |
| Definition including CAT |             |              |                                             |
|                           | N=7304\(^a\) | N=2759\(^a\) | % increase in rate (95% CI)                 |
| Rate of exacerbations     |             |              |                                             |
| Moderate/severe exacerbations after week 28 | n=1650\(^a-f\) | n=2439\(^a-f\) | 72 [56–89]\(^b\) |
| Severe exacerbations after week 28 | 0.92 (0.88–0.96) | 0.54 (0.49–0.58) |                                      |
|                           |             |              | % increase in risk (95% CI)                 |
| Time to first exacerbation |             |              |                                             |
| Moderate/severe exacerbations after week 28 | n=1653\(^a-f\) | n=2643\(^a-f\) | 68 [52–86]\(^b\) |
| Severe exacerbations after week 28 | 1959 [32] | 489 [20] |                                      |
|                           |             |              | % increase in risk (95% CI)                 |
| All-cause mortality       |             |              |                                             |
| All-cause mortality after week 28\(^\#\) | n=6176 | n=2443 | 80 [8–200]\(^b\) |
|                           | 82 [1] | 18 [-1] |                                      |

| Definition including SGRQ | LS mean CFB (95% CI) | Difference (95% CI) |
|---------------------------|----------------------|---------------------|
|                           |                      |                     |
| Trough FEV\(_1\) at week 52 mL | n=5359 | 9 [2–15] | 152 [143–162] | −143 [−155–−132]\(^b\) |
| SGRQ total score at week 52 | n=529 | −2.4 [−2.7–−2.0] | −9.8 [−10.3–−9.3] | 7.5 [6.8–8.1]\(^b\) |
| CAT score at week 52 | n=5218 | −1.2 [−1.3–−1.0] | −3.3 [−3.5–−3.0] | 2.1 [1.8–2.4]\(^b\) |

| Definition including CAT | LS mean CFB (95% CI) | Difference (95% CI) |
|-------------------------|----------------------|---------------------|
|                           |                      |                     |
| Trough FEV\(_1\) at week 52 mL | n=5359 | 9 [2–15] | 152 [143–162] | −143 [−155–−132]\(^b\) |
| SGRQ total score at week 52 | n=529 | −2.4 [−2.7–−2.0] | −9.8 [−10.3–−9.3] | 7.5 [6.8–8.1]\(^b\) |
| CAT score at week 52 | n=5218 | −1.2 [−1.3–−1.0] | −3.3 [−3.5–−3.0] | 2.1 [1.8–2.4]\(^b\) |

COPD: chronic obstructive pulmonary disease; N: number of patients with CID status available at week 28; LS: least squares; CFB: change from baseline; FEV\(_1\): forced expiratory volume in 1 s. \(^a\): number of patients who deteriorated on any of the CID components up to week 28 (CID-positive) or who did not deteriorate on any of the CID components up to week 28 (CID-negative) (if a patient has all missing on-treatment assessments for an end-point (trough FEV\(_1\), SGRQ and CAT) up to the time-point of interest, CID status was considered as missing for that patient, end-point and time-point); \(^b\): seven patients were excluded from the analysis due to missing covariates (CID-positive n=4; CID-negative n=3); \(^c\): p<0.001; \(^d\): number of patients included in the Kaplan–Meier estimates; \(^\#\): post hoc analysis of all-cause mortality including off-treatment data following additional collection of vital status (providing data for 99.6% of the IMPACT trial population); \(^\|\): p>0.05; \(^f\): seven patients were excluded from the analysis due to missing covariates (CID-positive: n=3; CID-negative: n=4); \(^\|\|\): p<0.05. Positive differences in CAT score ≥2 units or SGRQ total score ≥4 units and negative differences in trough FEV\(_1\) ≥100 mL in magnitude indicate sustained clinically important worsening between the CID-positive and CID-negative subgroups (difference in change from baseline greater than the corresponding minimal clinically important differences [11, 12, 26]).

Kaplan–Meier plots of time to first CID event using CID\(_{SGRQ}\) or CID\(_{CAT}\) showed early separation in favour of FF/UMEC/VI versus both dual therapies (figure 3). This trend was also seen with each individual CID component (supplementary figure E2).

Using the CID\(_{SGRQ}\) definition, FF/UMEC/VI significantly reduced CID risk by 33% and 31% by week 28 and 52, respectively, versus FF/VI, and 26% and 24%, respectively, versus UMEC/VI (all p<0.001) (figures 2
FIGURE 1 Kaplan–Meier plots of time to on-/off-treatment all-cause mortality post-week 28 by clinically important deterioration (CID) or exacerbation status at week 28 using a) the three-component definition using the St George’s Respiratory Questionnaire (CIDSGRQ), b) the three-component definition using the COPD Assessment Test (CIDCAT) and c) moderate/severe exacerbation only. COPD: chronic obstructive pulmonary disease; HR: hazard ratio; CPH: Cox proportional hazard model. Post hoc analysis of all-cause mortality including off-treatment data following additional collection of vital status (providing data for 99.6% of the IMPACT trial population).
and 3. Similar results were seen using the CIDCAT definition, with FF/UMEC/VI significantly reducing CID risk by 28% and 27% at week 28 and 52, respectively, versus FF/VI, and by 23% and 22%, respectively, versus UMEC/VI (all p<0.001) (figures 2 and 3).

FF/UMEC/VI significantly reduced the risk of all individual CID components versus FF/VI and UMEC/VI, with the greatest reduction observed for the lung function component (56% and 52% by week 28 and 52, respectively, versus FF/VI; 34% by both week 28 and 52 versus UMEC/VI; all p<0.001) (figure 2).

There was no concordance (i.e. \( \kappa < 0.2 \)) between any of the three individual CID components at week 28 or 52 within both composite end-points in the overall study population or for any treatment arm.

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### FIGURE 2

Reduction in clinically important deterioration (CID) risk (time to first) with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus a) FF/VI and b) UMEC/VI. n: number of patients with events; N: number of patients with analysable data; CIDSGRQ: three-component definition using the St George’s Respiratory Questionnaire; CIDCAT: three-component definition using the COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 s; \( \geq 100 \text{ mL decrease from baseline in trough FEV1} \); \( \geq 4.0 \text{ unit increase from baseline in SGRQ total score} \); \( \geq 2.0 \text{ unit increase from baseline in CAT score} \). p<0.001 for all comparisons.
The comparison of health status deterioration using either SGRQ or CAT worsening showed only a weak level of concordance ($\kappa = 0.23$–0.27 and 0.29–0.30 at week 28 and 52, respectively) (supplementary table E2).

Subgroup analysis of CID risk by week 52

Across all subgroups analysed, including different exacerbation histories, and for both CID$^{\text{SGRQ}}$ and CID$^{\text{CAT}}$, FF/UMEC/VI demonstrated significant reductions in CID risk by week 52 versus FF/VI and UMEC/VI, with the exception of the small subgroup of patients on LAMA+LABA therapy prior to screening (8–9% of patients). In this subgroup, FF/UMEC/VI significantly reduced CID risk versus FF/VI but not UMEC/VI (CID$^{\text{SGRQ}}$ 36% (p<0.001) and 12% (p=0.203) risk reduction; CID$^{\text{CAT}}$ 28% (p<0.001) and 6% (p=0.529) risk reduction, respectively) (supplementary figure E3). In the small subgroup of patients who received LAMA monotherapy prior to screening (7–9% of patients), FF/UMEC/VI significantly reduced CID risk (CID$^{\text{SGRQ}}$ definition) by 39% (p<0.001) and 31% (p=0.003) versus FF/VI and UMEC/VI, respectively. Similar results were seen using the CID$^{\text{CAT}}$ definition, with FF/UMEC/VI significantly reducing the risk of a composite CID by 43% (p<0.001) and 30% (p=0.004) versus FF/VI and UMEC/VI, respectively (supplementary figure E3).
A reduction in CID risk (CIDSGRQ and CIDCAT definitions) by week 52 with FF/UMEC/VI versus both dual therapies was observed across the continuum of baseline blood eosinophil counts (figure 4). Treatment effect was greater at higher blood eosinophil counts for FF/UMEC/VI versus UMEC/VI. This relationship was driven by increased reduction in risk of moderate/severe exacerbation events with FF/UMEC/VI versus UMEC/VI at higher blood eosinophil counts, as there was no detectable relationship between blood eosinophil counts and reduction in the risk of lung function or health status deterioration with FF/UMEC/VI versus UMEC/VI (supplementary figure E4).

Safety
Safety data from IMPACT have been published previously [10]. The safety profile of FF/UMEC/VI was similar to FF/VI and UMEC/VI, with no new safety signals identified [10].

Discussion
This analysis of short-term disease worsening as a prognostic marker, assessed using CID status at week 28 independent of treatment, showed that patients who experience CID before week 28 have a near doubling in severe exacerbation rate during weeks 29–52 compared with CID-negative patients by week 28. Similarly, patients with greater disease stability (CID-negative by week 28) had sustained clinically relevant improvements in lung function and health status at 52 weeks compared with CID-positive patients by week 28, irrespective of CIDSGRQ or CIDCAT definition.

Statistical significance in the mortality analysis was only achieved for the CIDCAT definition and the number of deaths was small, limiting interpretation; nevertheless, analysis of outcomes by CID status by week 28 showed that the lowest probability of all-cause mortality was consistently observed in patients free from all CID types (including lung function and health status deterioration) rather than free from exacerbation events alone. Indeed, our analysis in this population enriched for exacerbations at study entry indicates that freedom from exacerbations alone in the first 28 weeks is not a useful prognostic marker for mortality when used in isolation.

This current analysis confirms previous evidence that lung function, health status or exacerbation deteriorations are not concordant events in patients with COPD [13]. Consequently, individual CID events likely measure different forms of deterioration and sustained suboptimal responses, highlighting the heterogeneity of multiple types of worsening that occur over relatively short time periods in COPD. Using a composite end-point to capture these events appears to increase prognostic capability.

These findings are in line with those seen in TORCH [14, 15], ECLIPSE [16, 17] and FULFIL [18]. In TORCH, patients experiencing an SGRQ-defined CID in the first 6 months had a significantly greater risk of moderate/severe or severe exacerbations and mortality, and experienced sustained clinically relevant deterioration in lung function and health status over the next 30 months, compared with CID-free patients in the first 6 months [9]. Similar results were seen in ECLIPSE when comparing 3-year outcomes based on 12-month CID status [17], and a prospective analysis of FULFIL highlighted that patients CID-free by
24 weeks had sustained improvement in lung function, health status and symptoms at 52 weeks compared with patients with a short-term CID [5]. Similarly, in the UPLIFT study comparing tiotropium versus placebo, a CID event by 6 months was associated with increased risk of subsequent exacerbation and death [6].

The prospective analysis, comparing composite worsening between treatment groups, highlighted that once-daily FF/UMEC/VI reduced the risk of composite CID and of all individual CID component events versus FF/VI and UMEC/VI. These benefits were fully apparent by week 28 for all analyses, with no increased impact at week 52. This suggests that the CID concept is well suited for detecting short-term deterioration or suboptimal treatment responses in COPD without needing a full 1-year follow-up. This is also in line with the FULFIL study results [5], demonstrating generalisability of the CID concept as a potential trial end-point. It also suggests that the benefits of optimising care with triple over dual therapy in advanced COPD occur early and go beyond exacerbation benefits. FF/UMEC/VI benefits were seen in nearly all subgroups, except in patients on LAMA+LABA therapy at baseline, where significant benefits were seen versus FF/VI but not UMEC/VI. Of interest, the greatest benefits of triple versus dual therapy were observed in patients on LAMA monotherapy at baseline. Although this finding should be investigated in further prospective studies, as only 7–9% of patients were on a LAMA at baseline, triple therapy may offer greater prevention against CID in patients with COPD who have no or limited prior exposure to combination therapies. The finding that both CIDSGROQ and CIDCAT definitions detected similar levels of deterioration and treatment benefits with FF/UMEC/VI versus FF/VI and UMEC/VI therapy highlights both to be potentially useful outcome measures in clinical practice. However, as the CAT instrument is easier to use and interpret than the SGRQ, this measure may have greater clinical utility in clinical practice [19]. Research into understanding the role of ICS in preventing CID event types other than exacerbations in COPD is currently limited [7, 20]. In this study, the ICS component (FF) provided short-term benefits on reducing deteriorations in lung function and health status independent of the benefit seen on preventing a first exacerbation. This finding is supported by the analysis showing each CID component was an independent marker of worsening based on $\kappa$ statistics. Surprisingly, the largest benefit of FF/UMEC/VI versus UMEC/VI was seen on reducing lung function deterioration rather than exacerbation prevention. Thus, at least in patients with symptomatic COPD and at risk of exacerbations, the ICS benefit may be broader than solely preventing exacerbations. Interestingly, in TRIBUTE, which compared the effects of alternative triple and dual regimens on CID outcomes, while significant extension in time to first composite CID with beclomethasone/glycopyrronium/formoterol versus indacaterol/glycopyrronium over 12 months was observed, when the individual components were investigated, only the SGRQ total score demonstrated significant improvement [7]. These differences seen between IMPACT and TRIBUTE may be due to a lower exacerbation risk of patients enrolled in TRIBUTE compared with IMPACT, or because the triple- and dual-therapy arms in TRIBUTE used different bronchodilator components, whereas the same LABA was used in IMPACT [10, 21].

The prevention of lung function or health status deterioration with FF/UMEC/VI versus UMEC/VI was of a similar magnitude across a range of blood eosinophil levels. In contrast, the reduction in exacerbation risk with FF/UMEC/VI versus UMEC/VI increased at higher eosinophil counts, a finding also supported by other recent trials [10, 21–25]. These data support that important effects of ICS therapy on reducing lung function and health status worsening were likely independent of the protective effects on exacerbations. However, it is worth noting that a recent analysis of budesonide/formoterol versus formoterol studies demonstrated an association between higher eosinophil counts and greater ICS benefit on lung function and health status. As IMPACT recruited a population at risk of exacerbations, it is unclear if a similar profile of protection from disease worsening would be seen in exacerbation-free patients.

IMPACT did not include CID as a primary end-point and the 5-month follow-up period is relatively short to properly assess the risk associated with CID status at week 28, especially regarding all-cause mortality. In line with other analyses of CID [3, 6], these analyses did not impute missing data. Furthermore, most of the CID components (FEV$_{1,}$ SGRQ and CAT) were only assessed at study visits. While this is a limitation of all CID analyses, it also reflects clinical practice as disease progression (or treatment failure) will usually be assessed by the treating physician at scheduled visits or when key deteriorations (i.e. exacerbations) occur. Finally, findings from this analysis are reflective of a population of symptomatic patients with established exacerbation risk rather than the general COPD population. Despite these limitations, given the broad range of benefits seen with FF/UMEC/VI compared with UMEC/VI in IMPACT, further studies may be warranted to examine the benefits of add-on ICS in preventing CID in patients with less advanced disease.

Conclusions

The benefits of treatment optimisation to prevent short-term CID events are likely to reduce future risks of exacerbations requiring hospitalisation and all-cause mortality. In addition, once-daily FF/UMEC/VI
reduced the risk of CID events versus FF/VI and UMEC/VI, demonstrating a consistent benefit across most patient types over short time periods for adding ICS or intensifying bronchodilation in the IMPACT trial population.

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