DElaying Disease Progression In COPD with Early Initiation of Dual Bronchodilator or Triple Inhaled PharmacoTherapy (DEPICT): A Predictive Modelling Approach

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ABSTRACT

Introduction: Clinical studies demonstrate an accelerated decline in lung function in patients with moderate chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 2) versus severe and very severe COPD (GOLD grades 3 and 4). This predictive modelling study assessed the impact of initiating pharmacotherapy earlier versus later on long-term disease progression in COPD.

Methods: The modelling approach used data on decline in forced expiratory volume in 1 s (FEV_1) extracted from published studies to develop a longitudinal non-parametric superposition model of lung function decline with progressive impact of exacerbations from 0 per year to 3 per year and no ongoing pharmacotherapy. The model simulated decline in FEV_1 and annual exacerbation rates from age 40 to

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75 years in COPD with initiation of long-acting anti-muscarinic antagonist (LAMA)/long-acting beta$_2$-agonist (LABA) (umeclidinium (UMEC)/ vilanterol (VI)) or triple (inhaled corticosteroid (ICS)/LAMA/LABA; fluticasone furoate (FF)/ UMEC/VI) therapy at 40, 55 or 65 years of age. *Results*: Model-predicted decline in FEV$_1$ showed that, compared with 'no ongoing' therapy, initiation of triple or LAMA/LABA therapy at age 40, 55 or 65 years preserved an additional 469.7 mL or 236.0 mL, 327.5 mL or 203.3 mL, or 213.5 mL or 137.5 mL of lung function, respectively, by the age of 75. The corresponding average annual exacerbation rates were reduced from 1.57 to 0.91, 1.06 or 1.23 with triple therapy or to 1.2, 1.26 and 1.4 with LAMA/LABA therapy when initiated at 40, 55 or 65 years of age, respectively. *Conclusions*: This modelling study suggests that earlier initiation of LAMA/LABA or triple therapy may have positive benefits in slowing disease progression in patients with COPD. Greater benefits were demonstrated with early initiation therapy with triple versus LAMA/ LABA.

Keywords: Chronic obstructive pulmonary disease (COPD); COPD exacerbation; Dual bronchodilator therapy (LAMA/LABA); GOLD grades; Lung function decline; Triple therapy (ICS/LAMA/LABA)

Key Summary Points

Why carry out this study?

There is often a progressive decline in lung function in COPD.

While life-long treatment for COPD is usually required, the long-term benefit on lung function decline of initiating a dual bronchodilator (LAMA/LABA) or triple therapy (ICS/LAMA/LABA) early in the natural history of COPD is not known.

Using a modelling approach, this study explored the benefits of dual bronchodilator or triple therapies on lung function decline when initiated at 40, 55 and 65 years of age.

What was learned from the study?

Triple therapy and dual LAMA/LABA therapy when initiated at age 40 years preserved an additional 469.7 mL and 236.0 mL of lung function, respectively, by the age of 75.

This modelling study suggests that initiation of pharmacotherapy at an early stage of COPD has the potential to slow disease progression.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by respiratory symptoms and persistent airflow obstruction [1]. There is often a progressive decline in lung function (forced expiratory volume in 1 s [FEV$_1$]) in COPD that is greater than the physiological decline observed with age [1, 2]. The rate of lung function decline varies between individual patients with COPD [3]. In studies of large COPD populations, the average rate of lung function decline is greater in patients with moderate COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 2 [1]) compared with severe and very severe COPD (GOLD grades 3 and 4, respectively), suggesting a more accelerated decline in the earlier phases of the disease [4].

One of the aims of COPD management is to reduce the risk of disease progression. While smoking cessation can modify the course of the disease [5], the evidence from randomized controlled trials (RCTs) concerning the effect of pharmacological interventions on lung function decline has been inconsistent [6–11]. These RCTs have often been conducted over relatively short time periods, with 4 years being the longest study. Furthermore, patients with mild COPD (GOLD grade 1) have often been excluded from these studies [12] which have included a high proportion of severe and very severe patients with COPD. Longer-term investigations are warranted in order to understand the impact of pharmacological interventions in

patients with COPD of younger age and with milder lung function impairment [13].

An exacerbation of COPD occurs when respiratory symptoms rapidly worsen, often associated with increased local and systemic inflammation, typically (but not always) due to an infection [1]. Exacerbations are a major contributor to impaired health status, lung function decline and mortality [14–17]. The recommended initial pharmacological therapy for patients with COPD is based on individual assessment of symptoms and exacerbation risk [1]. Patients with COPD with low exacerbation risk (GOLD groups A and B) are treated with bronchodilator(s) including long-acting antimuscarinic antagonists (LAMAs) and long-acting beta₂-agonists (LABAs). Patients with higher exacerbation risk (group E) and with higher blood eosinophil counts may also be considered for triple therapy (inhaled corticosteroid (ICS) + LAMA + LABA) as an initial therapy [1]. RCTs in patients with COPD and a history of exacerbations while taking maintenance inhaled therapy have shown considerable benefits of triple therapy over LAMA + LABA treatment for individuals with higher blood eosinophil counts, including prevention of exacerbations and risk of mortality [18–20]. This evidence underpins the GOLD recommendation to consider earlier intervention with triple therapy for patients with COPD with both high exacerbation risk and higher blood eosinophil counts.

The long-term benefit on lung function decline of initiating a dual bronchodilator or triple therapy early in the natural history of COPD is not known. This is practically difficult to assess in a clinical trial setting because of time and cost constraints. However, this can be investigated using a modelling and simulation approach based on existing data. Clinical prediction models are becoming more recognized as a tool for generating evidence to inform public health policy and to support clinical decision-making [21–23]. In the respiratory field, modelling studies have been used to predict factors associated with future exacerbation risk in COPD [24–26] and for comparing different ICS-based treatment regimens in asthma [27, 28].

In COPD, the rate of decline in lung function varies with time, disease severity and in response to exacerbations [1–3, 14, 15, 29, 30]. This modelling analysis investigated the impact of initiating pharmacotherapy earlier versus later on long-term disease progression (lung function decline) in COPD. Data from previously published studies on lung function decline in general population subjects (no known COPD) and in patients with COPD, including data on the impacts of disease severity, exacerbations and pharmacotherapy, were used to develop the model. Clinical trial data for the triple therapy fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) and LAMA/LABA therapy UMEC/VI were used for estimates of treatment effects in the model simulations.

METHODS

Model Overview and Structure

The modelling approach used data extracted from the published literature to develop a longitudinal non-parametric superposition model of lung function decline. In general population subjects without known lung disease, FEV_1 declines with age in adult life at a fairly constant rate and can easily be modelled [31], with the average rate of decline among smokers and non-smokers reported as approximately 36 mL/year (Fig. 1). As a result of the variable discontinuous process of lung function decline in COPD, a non-parametric model was considered appropriate. The additive and cumulative effects of exacerbations in accelerating lung function decline and of pharmacotherapy in reducing exacerbations and slowing lung function decline were modelled by superposition of these effects on the underlying loss of lung function with time (FEV_1, mL/year) related to the disease process. The FEV_1 decline simulation model included the following assumptions:

- Lung function decline in general population subjects (no known COPD and never/non-smokers) at a constant rate was used as a benchmark to assess percent decline in
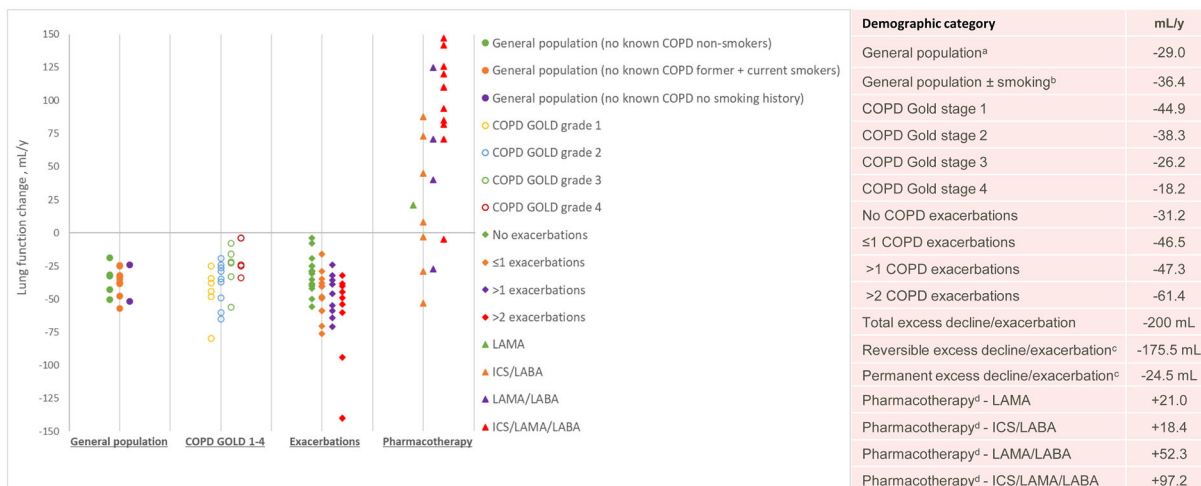
Demographic category	mL/y
General population[a]	-29.0
General population ± smoking[b]	-36.4
COPD Gold stage 1	-44.9
COPD Gold stage 2	-38.3
COPD Gold stage 3	-26.2
COPD Gold stage 4	-18.2
No COPD exacerbations	-31.2
≤1 COPD exacerbations	-46.5
>1 COPD exacerbations	-47.3
>2 COPD exacerbations	-61.4
Total excess decline/exacerbation	-200 mL
Reversible excess decline/exacerbation[c]	-175.5 mL
Permanent excess decline/exacerbation[c]	-24.5 mL
Pharmacotherapy[d] - LAMA	+21.0
Pharmacotherapy[d] - ICS/LABA	+18.4
Pharmacotherapy[d] - LAMA/LABA	+52.3
Pharmacotherapy[d] - ICS/LAMA/LABA	+97.2

Fig. 1 Summary of published lung function decline data in general population subjects with no known COPD and COPD populations with impact of disease severity, exacerbations and pharmacotherapy. [a]Refers to general population (no known COPD and never/non-smokers). [b]Refers to general population (no known COPD ± smoking). [c]Reversible excess decline is defined as decrease in lung function during an exacerbation that is recovered after an exacerbation; permanent excess decline is defined as decrease in lung function during an exacerbation that is not recovered after an exacerbation, based on average data in the literature [3, 14, 36, 37] (Supplementary Materials, Table S1). [d]Data from studies for pharmacotherapy refer to change in FEV_1 after 52 weeks of treatment with the exception of two sets of data where change in FEV_1 is reported after 26 weeks [38, 41]. These data do not take into account treatment at baseline. Data points on figure represent values from individual published studies [2, 3, 9, 10, 14, 15, 30, 33, 36–55, 57]; values in table represent average values from published data. Data from Kim et al. [47] includes data for FEV_1 decline by GOLD grade (1–4) and by GOLD group (A–D). Data from Pauwels 1999 [10] and Tashkin 2012 [50] includes data for FEV_1 decline in patients categorized as GOLD grade 1 or 2—on the figure these data points are shown under the grade 2 category. *COPD* chronic obstructive pulmonary disease, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *LAMA* long-acting antimuscarinic antagonist

COPD, where the lung function decline begins from about the age of 20–25 years [1, 31].

- The assumption was that lung function declines in patients with COPD at different rates as disease progresses; initial slow decline in GOLD grade 1, with more rapid decline in GOLD grade 2, and subsequent slowing of the rate of decline in GOLD grades 3 and 4 [4, 32].
- COPD lung function decline is accelerated by exacerbations. The impact of exacerbations was simulated where (a) the number of exacerbations per year increased progressively from 0 to 0.5, then 1, then 2 and eventually 3 exacerbations per year [33–35], and (b) each exacerbation caused an initial additional decline (− 200 mL) which was a partially reversible decline in lung function (− 175.5 mL) and which was reduced over 3 months to a smaller permanent decline (− 24.5 mL), based on average data in the literature [3, 14, 36, 37] (Supplementary Materials, Table S1).
- COPD lung function decline is modified by pharmacotherapy. The impacts of pharmacotherapy with ICS/LAMA/LABA (FF/UMEC/VI) and LAMA/LABA (UMEC/VI) were assessed as the effects in reducing the annual rate of exacerbations and in increasing lung function (see data in Fig. 1).

This article is not based on any new studies with human participants or animals performed by any of the authors.

Model Input

Targeted literature searches were conducted using PubMed and Google Scholar to identify studies presenting data on FEV_1 decline. Additional studies were identified through manual searches of reference lists of relevant articles and through checking papers known to the authors. Only articles published in English were considered and no date limits were set. The four search topics were (1) lung function decline with age in general population (no known COPD) subjects; (2) lung function decline in patients with COPD split by airflow limitation-defined severity (mild or GOLD grade 1, moderate or GOLD grade 2, severe or GOLD grade 3, very severe or GOLD grade 4); (3) impact of COPD exacerbations on lung function decline; (4) impact of pharmacotherapy on lung function decline in COPD. The pharmacotherapy studies considered RCTs that included any triple therapy administered by a single inhaler and included a comparator of dual (LAMA/LABA or ICS/LABA) and/or monotherapy [9, 18, 33, 38–42]. All pharmacotherapy trials were in patients with COPD and a current or recent smoking history, with the exception of one where a smoking history was not specified as an inclusion criterion [38].

Identified studies were screened and selected for inclusion by one reviewer and checked by a second reviewer. A data extraction template was used to extract and capture pre-defined data items, including study design, sample size and duration of follow-up period; baseline/demographic data; follow-up period data (FEV_1 decline expressed as mL/year, exacerbations number/rate per year). Data extraction was performed by one person and verified by a second person.

Data from the studies identified in the literature search were used to estimate the model inputs for lung function decline in COPD by age, severity, exacerbation frequency and impact of LAMA/LABA and triple therapy (Table 1). In the model, treatment effects based on data for FF/UMEC/VI and UMEC/VI from the IMPACT study were used for the model simulations [33]. The inputs for increase in FEV_1 with triple or dual therapy represent average values across COPD age groups as data split by age groups were not available. These data were regarded as representative of these treatment classes as illustrated by average values across studies for increase in FEV_1 (mL) at the end of treatment (Fig. 1).

No subgroups were evaluated, for example in terms of eosinophil counts or smoking status.

Model Outputs/Outcomes

The model output was decline in FEV_1 over the age range 40–75 years. This age range was chosen to reflect the greater prevalence of COPD in those ≥ 40 years of age compared with those < 40, and with the assumption that the disease severity increases as the age advances [1]. Data summaries, graphical output, calculations and simulations were produced in Microsoft Excel (Version 2208).

Base Case, Scenario and Sensitivity Analyses

The assumed base case was model-simulated decline in FEV_1 over 40–75 years with progressive impact of exacerbations from 0 per year to 3 per year and no ongoing pharmacotherapy. The scenarios of interest were simulated decline in FEV_1 when triple or LAMA/LABA therapy was initiated at either 40, 55 or 65 years of age.

A sensitivity analysis was conducted whereby the assumption on exacerbation rates was progression from 0 to 1 per year, and the same scenarios of interest were investigated.

RESULTS

Literature Search and Summary of Extracted Data

The studies identified by the literature research [2, 3, 9, 10, 14, 15, 18, 29, 30, 33, 36–57] and that were used to inform development of the model are summarized in the Online Data Supplement (Appendix 1). Figure 1 summarizes the published data on lung function decline for different populations. In general population

Table 1 Modelling methodology: values used for simulations

Subject	Age range (years)	FEV$_1$ lung function decline (mL/year)[a]	Moderate/severe exacerbation rate/year[b]	Months between exacerbations[b]	Months between exacerbations therapy with ICS/LAMA/LABA[c]	Months between exacerbations therapy with LAMA/LABA[c]	FEV$_1$ increase with ICS/LAMA/LABA at week 52 (mL)[c]	FEV$_1$ increase with LAMA/LABA at week 52 (mL)[c]
General population (no known COPD and never/non-smokers)	25–75	29	–	–	–	–	–	–
COPD	40–49	40	0.5	24	44	32	94	40
COPD	50–57	63	1	12	22	16	94	40
COPD	58–67	58	2	6	11	8	94	40
COPD	68–75	35	3	4	7	5	94	40

COPD chronic obstructive pulmonary disease, *FEV$_1$* forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *LAMA* long-acting anti-muscarinic antagonist

[a]Based on typical values and pattern of decline over time from the literature [2, 3, 9, 10, 14, 15, 30, 33, 36–55, 57]

[b]Based on assumption of increasing annual exacerbation frequency from 0.5 to 3 with age; frequency assigned to correspond with typical lifetime exacerbation frequency [33]

[c]Average values for magnitude of ICS/LAMA/LABA and LAMA/LABA treatment effects were used, corresponding with those seen in the IMPACT study [33]

subjects, lung function decline was similar among smokers and non-smokers. Lung function decline was numerically greater in patients with COPD with milder versus more severe disease (assessed by GOLD grade), and with increasing rate of exacerbations. However, these data are heterogeneous with large overlaps in average values. Pharmacotherapy had a positive impact on lung function, with greatest effects observed with triple therapy versus dual or monotherapy.

Model-Simulated Decline in Lung Function

Figure 2a shows that the model-simulated rate of decline in lung function (expressed as $FEV_1\%$ predicted) from age 40 to 75 years in a scenario of increasing exacerbations with disease progression (red line) was slowed with triple therapy, and larger effects were seen when therapy is initiated earlier versus later. The same pattern was observed when lung function decline was expressed as absolute volume (FEV_1 mL) (Fig. 2b). Compared with the baseline assumption of no ongoing pharmacological therapy, initiation of triple therapy at age 40 years preserved an additional 469.7 mL of lung function by the age of 75 and a delay in progress to GOLD grade 4 of 3.66 years (Table 2). If triple therapy was started at either 55 or 65 years, the potential preservation of lung function was 327.5 mL or 213.5 mL, and the delay to GOLD grade 4 was 3.16 years or 1.58 years, respectively. This was largely driven by the reductions in exacerbations rates, as defined in the model, which were reduced on average between 40 and 75 years from 1.57 (no ongoing therapy) to 0.91, 1.06 or 1.23 if triple therapy was initiated at 40, 55 or 65 years, respectively.

Simulated decline in lung function was also reduced by earlier versus later intervention with LAMA/LABA therapy (Fig. 3a, b). Initiation of LAMA/LABA therapy at ages 40, 55 or 65 years preserved an additional 236.0 mL, 203.3 mL or 137.5 mL of lung function, respectively, by the age of 75; delayed progression to GOLD grade 4 by 1.5, 1.16 and 0.33 years, respectively; and reduced average annual exacerbation rates from

1.57 to 1.20, 1.26 and 1.40, respectively (Table 2).

Triple therapy had a greater benefit on lung function decline compared to LAMA/LABA treatment (Table 2). The numerical difference between treatments (triple versus no therapy and LABA/LAMA versus no therapy) in additional lung function remaining at 75 years was 233.7 mL, 124.2 mL and 76.0 mL greater with triple therapy, following initiation of therapy at ages 40, 55 or 65 years, respectively. The simulation of lung function decline when initiating triple or LABA/LAMA treatment starting at age 40 is illustrated in Supplementary Materials, Fig. S1.

The sensitivity analysis, which modelled the exacerbation rate as progressing from 0 to 0.5 to 1 per year, showed a similar pattern of results to the baseline model with FEV_1 decline slowed with earlier versus later intervention with triple therapy (Supplementary Materials, Fig. S2), and to a lesser magnitude with LAMA/LABA therapy (Supplementary Materials, Fig. S3).

DISCUSSION

This modelling analysis shows that starting pharmacotherapy at an earlier versus later stage in patients with COPD has the potential for long-term benefits in terms of lung function preservation, delaying progression to GOLD grade 4. Pharmacological treatment reduces the average annual rate of exacerbations, which is a mechanism by which the delay in FEV_1 decline can be achieved. These benefits were greater with triple therapy FF/UMEC/VI versus dual bronchodilator treatment with UMEC/VI. The greatest overall benefit in delaying disease progression was observed with initiation of triple therapy at 40 years. This simulation model provides new information on the potential long-term benefits on lung function decline of initiating LABA/LAMA or triple pharmacotherapy, at an earlier versus later stage of disease.

This FEV_1 decline model made several assumptions with respect to the occurrence and patterns of exacerbation rates. The model assumed that exacerbations of COPD accelerate the decline of FEV_1 and this was supported by
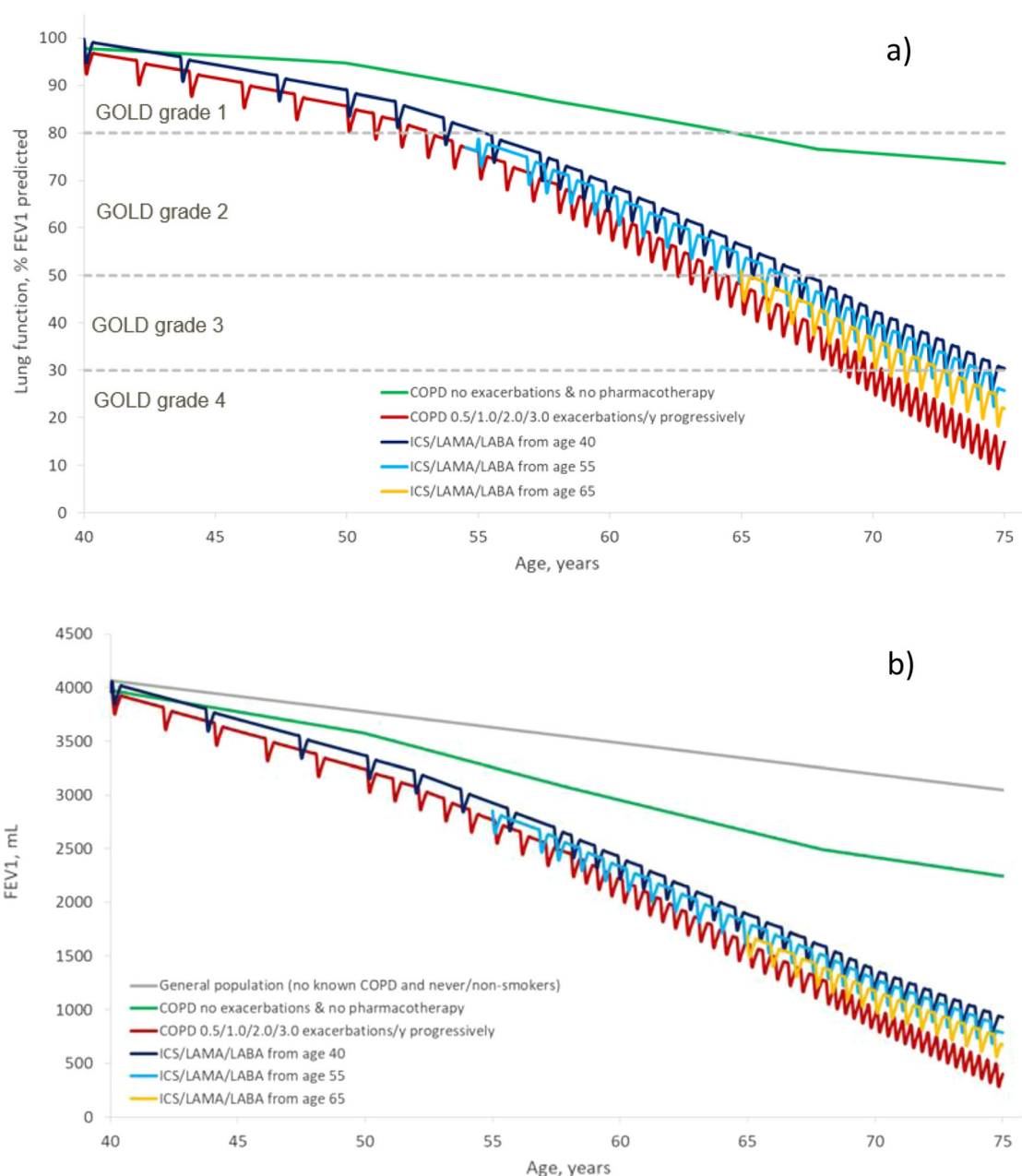
Fig. 2 COPD lung function decline and impact of commencing ICS/LAMA/LABA triple therapy at age 40, 55 or 65 years, measured as **a** FEV$_1$ percent of predicted and **b** FEV$_1$ mL. *COPD* chronic obstructive pulmonary disease, *FEV$_1$* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *LAMA* long-acting anti-muscarinic antagonist

the data from studies identified in the literature search that show an increasing impact on loss of lung function with increased exacerbation frequency [3, 14, 15, 36, 37, 51, 53–55]. Exacerbation rates (number per patient per year) were modelled to progressively worsen over time from 0 to 3 exacerbations per year. Real-life patterns of exacerbation frequency vary among individuals [58] and the results of the sensitivity analysis which modelled exacerbation rates

Table 2 Summary of modelling simulation outputs

Start of therapy	Age at which lung function first drops below FEV_1 pred 30%		Time delay in progress to COPD Gold stage 4 (< 30% FEV_1 pred)		Lung function remaining at age 75 (FEV_1 mL)		Additional lung function remaining at age 75 (FEV_1 mL)		Exacerbations total between 40 and 75 (average/year)	
	Triple	LAMA/LABA	Triple	LAMA/LABA	Triple	LAMA/LABA	Triple	LAMA/LABA	Triple	LAMA/LABA
None	69.0 years 829 months	69.0 years 829 months	– –	– –	456.5 mL	456.5 mL	–	–	55 (1.57)	55 (1.57)
From age 40	72.5 years 873 months	70.58 years 847 months	3.66 years 44 months	1.5 years 18 months	926.2 mL	692.5 mL	469.7 mL	236.0 mL	32 (0.91)	42 (1.20)
From age 55	72.25 years 867 months	70.25 years 843 months	3.16 years 38 months	1.16 years 14 months	784.0 mL	659.8 mL	327.5 mL	203.3 mL	37 (1.06)	44 (1.26)
From age 65	70.66 years 848 months	69.4 years 833 months	1.58 years 19 months	0.33 years 4 months	670.0 mL	594.0 mL	213.5 mL	137.5 mL	43 (1.23)	49 (1.40)

FEV_1 forced expiratory volume in 1 s, *LABA* long-acting beta$_2$-agonist, *LAMA* long-acting anti-muscarinic antagonist
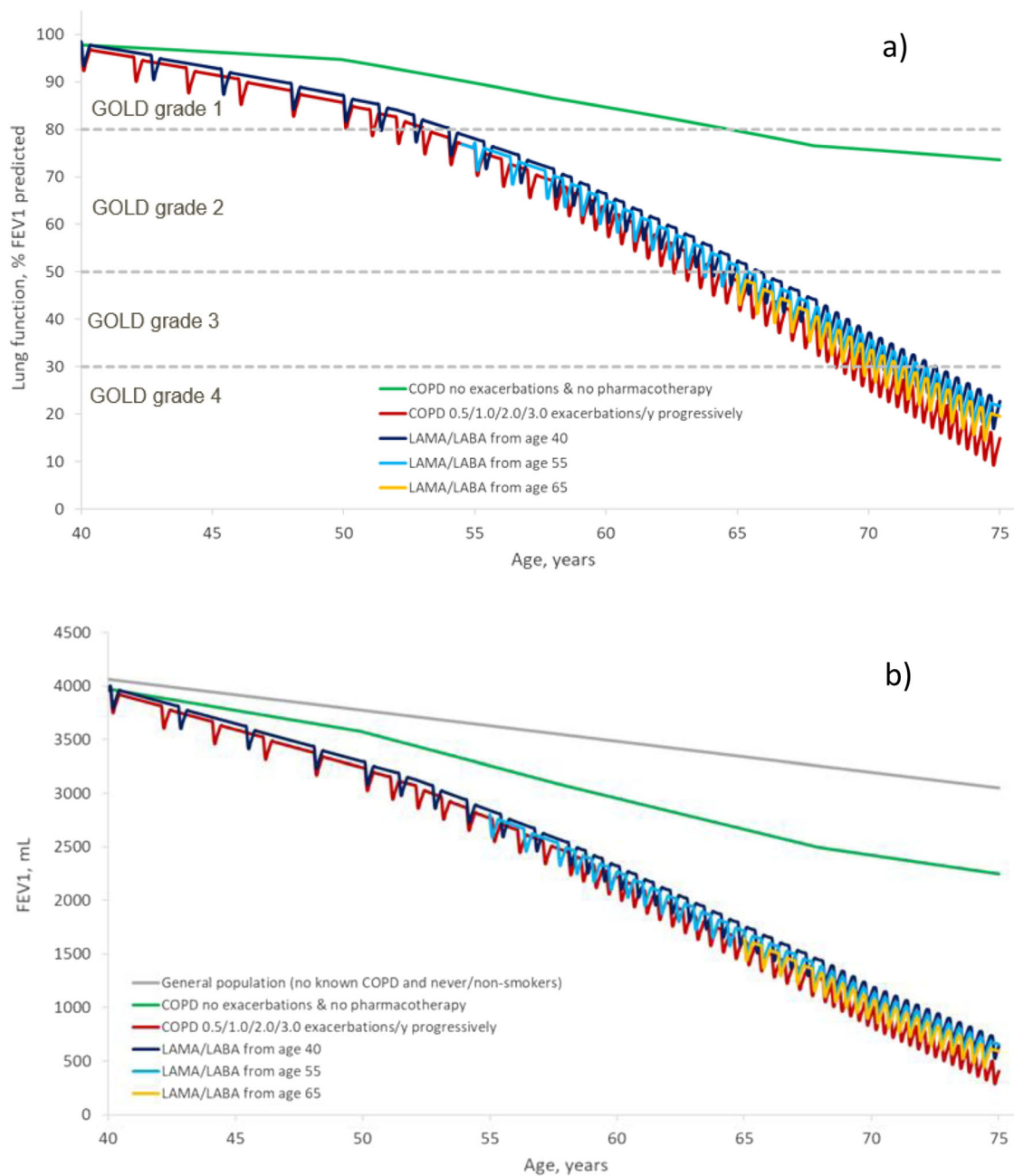
Fig. 3 COPD lung function decline and impact of commencing of LABA/LAMA therapy at age 40, 55 or 65 years, measured as **a** FEV$_1$ percent of predicted and **b** FEV$_1$ mL. *COPD* chronic obstructive pulmonary disease, *FEV$_1$* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *LAMA* long-acting anti-muscarinic antagonist

progressing from 0.5 to 1 per year provide reassurance about the model robustness, showing the potential for triple therapy benefits on disease progression even in patients with only 1 exacerbation per year. The model also assumed that treatment with triple and LABA/LAMA therapy modifies the decline in FEV$_1$, based on data from large, 1-year RCTs as shown in Fig. 1

[9, 33, 38–40, 42], and that this treatment effect would be similar over a long-term period. The model outputs in this analysis provide average values and do not consider separately the contribution of other factors which may impact lung function decline such as smoking history [59], or variation in ICS response which is associated with eosinophil counts [60]. These may be seen as limitations of the model; nevertheless, this analysis provides information on potential long-term treatment-related benefits that are difficult to study in the real world. Further analysis that accounts for different clinical characteristics may be informative.

In clinical practice, a variety of pathways to triple therapy are observed within and between countries [61]. However, the impact of pharmacological interventions at an earlier stage in disease progression has been unclear [13]. The benefits of early versus late initiation of triple therapy after an exacerbation have been shown in retrospective studies in terms of significantly reduced exacerbation rates in the following year [62, 63]. Our analysis adds to these findings by showing that reductions in exacerbations can lead to long-term benefits in slowing lung function decline and disease progression.

Although starting triple therapy in all patients at an early stage of COPD may not be practical, use of a treatable traits approach to determine patients at high risk of exacerbation and rapid FEV_1 decline could be one way of identifying patients who would benefit from early triple therapy [60]. In these subgroups, optimization to triple therapy at an early stage of COPD could preserve valuable lung function and delay disease progression. In the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), Woodruff et al. reported that current/former smokers with respiratory symptoms but preserved airway function had a higher risk of exacerbations than asymptomatic smokers [64]. In an analysis of 30 months treatment with ICS in 50 steroid-naïve patients with moderate to severe COPD, long-term predictors of better ICS effects on FEV_1 decline were a lower smoking burden, less hyperinflation and more preserved diffusion capacity, i.e. in patients with less advanced disease [65]. Previous modelling prediction

studies have identified factors associated with the risk of future exacerbations in COPD [24–26]. For example, prior exacerbations, FEV_1 percent predicted, eosinophil count, sex, region, COPD Assessment Test score, prior treatment and reliever medication use were highly significant factors associated with future exacerbation risk, and showed a greater benefit of ICS-containing treatments in patients with higher eosinophil counts, greater number of prior exacerbations and those who had received more prior maintenance therapies [24].

A limitation of this analysis is that exacerbations were modelled as occurring at regular intervals with the assumption that there would be recovery from each exacerbation before the next occurred, whereas in real-life, patterns of exacerbations are likely to be more random [58]. However, this approach was not thought to have influenced the overall outcome since we modelled the average outcomes over a long period of time. In addition, the sensitivity analysis, which assumed a different exacerbation rate pattern, also demonstrated the benefit of triple over LAMA/LABA treatment. Another limitation is that the inputs for increase in FEV_1 with triple or dual therapy represent average values across COPD age groups as data split by age groups were not available. In addition, the scenarios we focused on were therapy (LAMA/LABA or triple) or 'no therapy' from age 40, 55 or 65, whereas in clinical practice patients follow several different treatment pathways to triple therapy, and patients may change treatments between classes [61]. This has not been factored into the current model. Nonetheless, we can still infer from our findings the likely outcomes for these alternative scenarios. A further limitation is that we did not consider patient mortality in this model and the model outputs show lung function declining beyond a point where many patients may not survive. However, if the model had omitted data once lung function fell below a "survivability threshold", it would not have changed the observed conclusions. There may be many other causes of death in this population making such events difficult to predict and model. It should also be noted that we did not consider the risk/benefit aspect or the cost implications of

starting triple therapy earlier versus later. Finally, in this analysis, reduction in exacerbations by pharmacotherapy was the model input for simulation of lung function decline. This may have introduced an unintentional bias in favour of ICS-containing treatments including triple therapy and, as previously highlighted, starting triple therapy early may require a treatable traits approach to identify patients most eligible for early treatment. On the other hand, as pharmacotherapy can improve lung function through other mechanisms, this model may underestimate the benefits of early pharmacotherapy on long-term disease progression. In this study we developed a simple, hypothesis-generating model and future, more refined models could consider other factors that were not included in our model.

CONCLUSION

This simulation modelling analysis has demonstrated the potential benefits of starting pharmacotherapy earlier in the course of COPD in terms of slowing disease progression. Greater benefits were demonstrated with early initiation of triple versus LAMA/LABA therapy.

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Compliance with Ethics Guidelines. This article is not based on any new studies with

human participants or animals performed by any of the authors.

Data Availability. Information on GSK's data sharing commitments and requesting access can be found at: https://www.gsk-studyregister.com/en/

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