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ORIGINAL RESEARCH

Prompt versus Delayed Triple Therapy in COPD: Solutions to Time-Related Biases in Observational Studies

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Background: Recent observational studies have reported that prompt initiation of single-inhaler triple therapy after a COPD exacerbation is more effective than delayed initiation. We show that their study design, by "peeking into the future" to define the timing of treatment initiation, introduces time-related biases, particularly protopathic bias. These biases can be avoided using the "cloning" approach to emulate a randomized trial approach.

Methods: We formed a cohort of patients with COPD who had an exacerbation (index) after September 2017, using the United Kingdom's Clinical Practice Research Datalink (CPRD). Using the "cloning" trial emulation technique, each subject was assigned to both the prompt and the delayed initiator arms as of the index date and censored according to their treatment over time. The Cox model was used to compare the incidence of the first exacerbation after the index exacerbation, over one year, after weighing by inverse probability of censoring. We also replicated the biased approach of the recent studies, based on peeking into the future.

Results: The cohort included 91,958 eligible subjects who had an exacerbation, generating 91,958 prompt initiator clones and 91,958 delayed initiator clones. The hazard ratio (HR) of a moderate or severe exacerbation, comparing prompt versus delayed initiators, was 0.98 (95% CI: 0.80–1.19), while it was 1.26 (95% CI: 0.81–1.96) for severe exacerbation. The replication of the time-related biased approach comparing prompt with delayed initiation resulted, correspondingly, in HRs of 0.73 (95% CI: 0.65–0.81) and 0.58 (95% CI: 0.46–0.74).

Conclusion: Using a trial emulation approach, prompt treatment with single-inhaler triple therapy after a COPD exacerbation was not more effective than delayed treatment at reducing the incidence of subsequent exacerbations. The method used by previous studies, suggesting significant effectiveness with prompt treatment initiation, was affected by time-related biases induced by peeking into the future. A randomized controlled trial can confirm these findings.

Keywords: cohort studies, COPD exacerbations, protopathic bias, real-world evidence, treatment timing

Introduction

Maintenance therapy is recommended for patients diagnosed with chronic obstructive pulmonary disease (COPD). These treatments include long-acting muscarinic antagonists (LAMAs) and long-acting beta$_2$-agonists (LABAs), with an inhaled corticosteroid (ICS) added according to the frequency of exacerbations.[1] Currently, several single-inhaler triple combinations of these treatment classes are available.

Besides the general recommendations for which inhaler combination to use, the question of when to initiate maintenance therapy with these inhalers has been put forward. Recent observational studies have investigated the comparative effectiveness of prompt versus delayed timing of initiating single-inhaler triple inhaler therapy after a COPD exacerbation.[2–6] These studies found that prompt initiation of single-inhaler triple therapy was associated with significant reductions in the rates of moderate and severe exacerbations, compared with delayed initiation. Such observational studies present major methodological challenges related to the definition of timing of initiation in relation to the timing of the outcome events, that can result in time-related biases.

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We review these studies and discuss methodological aspects of their study design that can introduce bias in the results. We illustrate the biases using a general practice clinical database and present results of the analysis using an approach that avoids these biases.

The Published Studies

As the published observational studies used a similar design, we describe the first one in detail to explain the approach.[2] The Mannino study evaluated the impact of prompt versus delayed initiation of single-inhaler triple therapy (SITT) with fluticasone furoate, umeclidinium, and vilanterol, following a COPD exacerbation, using a US claims database. Patients with a COPD exacerbation between September 2017 and September 2019 were identified, with the first exacerbation occurring in that period taken as the index exacerbation. The index date was taken as the date of discharge for exacerbations requiring hospitalisation and the date of the physician visit for moderate exacerbations. The study cohort was formed exclusively from those who initiated a SITT within 6 months after the index date, with SITT timing classified as prompt (initiation within 30 days after the index date; N = 529) or delayed (initiation 31–180 days after the index date; N = 1,375). Patients were aged 40 years or more at the index date, had at least 12 months of continuous health insurance coverage before index (baseline), no exacerbation and no SITT prescription during this baseline period. The subjects needed at least 6 months of coverage after the index. Subjects were followed from the index date until the end of the observation period for the occurrence of COPD exacerbations and other outcomes. The technique of inverse probability of treatment weighting was used to adjust the rate ratio of these outcomes for differences in baseline characteristics between the prompt and delayed groups. Patients in the prompt initiation group had a 21% lower rate of COPD exacerbation (rate ratio 0.79; 95% CI: 0.65–0.94) and a 28% lower incidence of a first exacerbation (hazard ratio 0.72; 95% CI: 0.62–0.83) compared with delayed initiators.

Methodological Issues

A randomized trial of this question would enroll patients at the index exacerbation and randomly allocate them to either the prompt or delayed treatment strategy. The allocation of the two groups is thus known at the time of randomization (index date) with outcome events counted as of this time, and which can thus occur prior to treatment initiation. The published observational studies, on the other hand, had to peek into "future" to define the two treatment groups, such as treatment initiation within 30 days after the index (prompt) or at 31–180 days after the index (delayed). This use of "future" time creates several methodological challenges and can lead to potential biases in observational studies. We use the Mannino study described in detail above as an example to explain the methodological issues.[2]

The first methodological issue with the observational studies involves the outcome (exacerbations) allowed to occur prior to the initiation of triple therapy, which can introduce protopathic bias.[7] Indeed, some physicians may wait for a second exacerbation, namely the first during follow-up, as an indication to initiate triple therapy, as per guidelines.[1] Thus, it may not be the treatment that led to the exacerbation, but the reverse. In particular, patients with early exacerbations will likely receive their triple inhaler after day 30, when the exacerbation ended, and thus more likely to be classified in the "delayed" treatment group, a bias compounded by the longer duration of this delayed period. This could explain the observational study's reported median times to the first COPD exacerbation of 367 versus 200 days for the prompt and delayed initiation groups, respectively.[2] Moreover, the corresponding Kaplan–Meier curve shows that around 10% of the delayed group had their first exacerbation in the first 30 days, the period defining "prompt" treatment, and that 48% of that group had their first exacerbation before 6 months, the end of the "delayed" treatment period.

The second methodological issue relates to the cohort selection that imposes a period of continuous health insurance coverage after the index date, resulting in potential selection bias from immortal time.[8,9] Indeed, the cohort included only patients with at least 6 months of coverage after the index date, thus excluding patients who die in this 6-month period, even if they had initiated triple therapy and had exacerbations before death. By this criterion, patients must survive to initiate treatment, whether prompt or delayed, even if they had exacerbations before death. This imposition of 6 months of coverage after an index that inherently excludes deaths can result in selection bias that could favor one group over the other. The Mannino study reports that 25% of the original 668,011 subjects were excluded because they had less than 6 months of eligibility, with no information on mortality.[2]

Study Design to Avoid Bias

The study design that avoids these biases must attempt to emulate the randomized trial when using these observational data, while not looking into the future. The key with the randomized trial is that the timing of inhaler initiation, namely allocation to a prompt or delayed treatment regimen, is known at the time of randomisation, so that the two groups can be properly compared on the rate of exacerbation during a prespecified follow-up period after the index exacerbation. In this case, exacerbation events can precede the inhaler initiation but will follow the random treatment group assignment time. The difference in the rates between the two groups will provide the effect of prompt versus delayed treatment.

The observational study must thus also seek to allocate "exposure" (prompt or delayed inhaler initiation) at the index date to avoid the methodological biases raised above when this exposure allocation is based on looking in the future. To accomplish this, it is important to recognize that a subject who has not yet received the inhaler at the index date could, in fact, belong to both the prompt and delayed group at that time point and up until inhaler therapy is initiated. To resolve this dilemma, the concept of "cloning" is used in observational research to assign each patient to the two possible treatment strategies (prompt and delayed inhaler initiation) that the patient could belong to at the index date.[10–12] Thus, the patient is "cloned" so that their data are included twice in the analysis, though the follow-up will be censored according to the timing of the inhaler initiation and the outcome events, which could be counted in one, two, or none of the groups depending on where the clones are censored.

As an illustration for the outcome of time to first exacerbation, consider, for example, a patient who initiates triple therapy on day 15, thus within 30 days (Figure 1, subject 1). This patient will generate two clones, a "prompt" clone that will be considered as exposed to the prompt treatment strategy for the entire follow-up, whose follow-up will end at the time of the event, and a "delayed" clone that will be considered as exposed to the delayed treatment strategy and censored at 14 days, the day at which we still did not know the membership of its parent. The second example (subject 2) is a patient who initiates triple therapy on day 60 (during the 31–180-day period). This patient will generate two clones, the first is a "prompt" clone that will be censored at 30 days, the time they can no longer be prompt, and a "delayed" clone that will be classified as "delayed" exposure for the entire follow-up, whose follow-up will end at the time of the event (Figure 1, subject 2). The third example (subject 3) does not initiate triple therapy at all during follow-up. The "prompt" clone will be censored at 30 days and the delayed clone follow-up will end at the time of the event within the 31–180 period (Figure 1, subject 3). The fourth example (subject 4) is a patient who initiates triple therapy on day 35 (during the 31–180-day period), who has their first exacerbation on day 20. The two generated clones, one prompt and one delayed, will both have an outcome event at day 20, at which point their follow-up stops (Figure 1, subject 4). Figure 2 displays the corresponding cloning patterns illustrating the situation where the outcome involves the frequency of exacerbations over time.

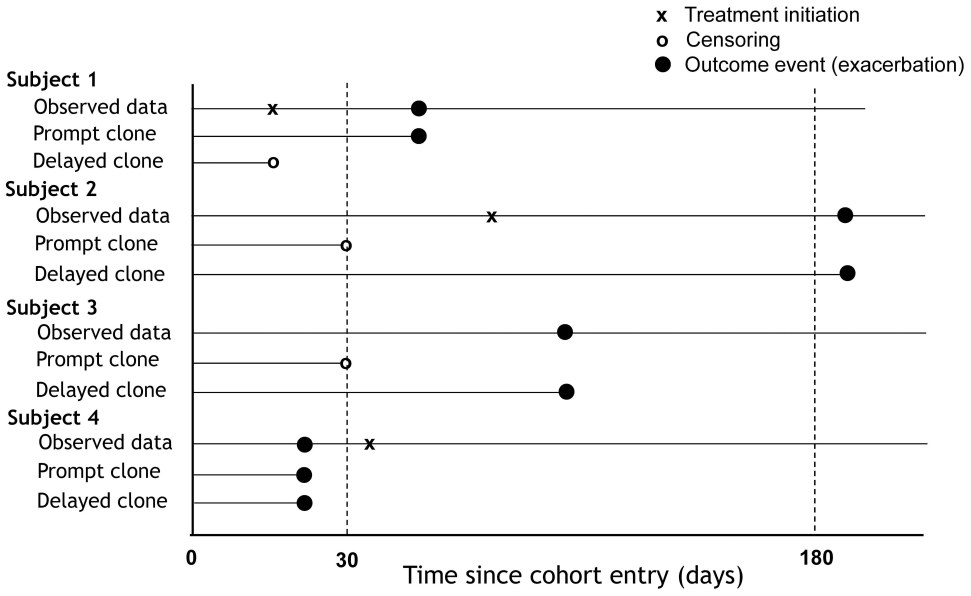

Figure 1 Illustration of cloning approach for the analysis of time to first exacerbation.

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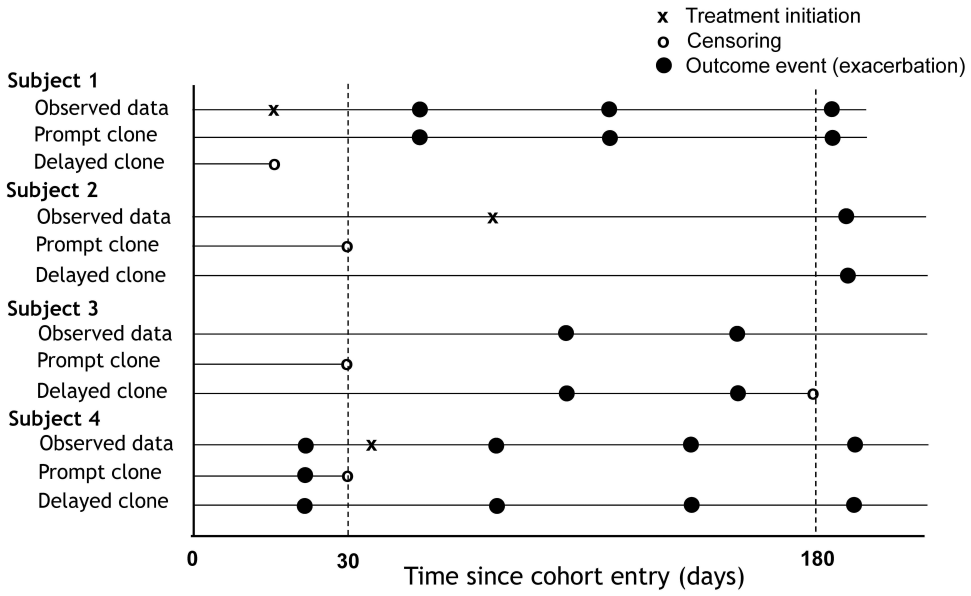

Figure 2 Illustration of cloning approach for the analysis of the frequency of exacerbations.

This cloning approach addresses the bias resulting from peeking into the future to define exposure. Nonetheless, simply computing the corresponding cumulative incidences or rates of exacerbation for the two cloned treatment strategies will still produce bias from giving equal weights to the clones. This is addressed by accounting for the artificial censoring of the clones at specific times, which can be done using inverse probability of censoring weights (ICPW).[11]

Illustration

We formed a cohort of patients with COPD from the Clinical Practice Research Datalink (CPRD), a primary care database from the United Kingdom (UK) that contains primary care medical records for over 50 million people enrolled in more than 1800 general practices. These data have shown to be of high quality, including for studies of COPD.[13–17]

The study cohort included all patients with a diagnosis of COPD, treated with maintenance therapy, at or after age 40 who had a moderate or severe exacerbation of COPD after 15 September 2017, the year single-inhaler triple therapy became available in the UK. A moderate exacerbation was defined by a new prescription for prednisolone, while a severe exacerbation was defined as a hospitalization for COPD (ICD-10: J41, J42, J43, J44). The first such exacerbation defined the index date. All subjects had to have at least one year of medical history prior to the index date (baseline period). Patients receiving triple therapy, either in a single inhaler or multiple inhalers, in the year before the exacerbation defining cohort entry, were excluded. All subjects were followed for up to one year after the index date, with follow-up ending at death, 31 March 2021, or the end of the patient's registration in the practice, whichever occurred first.

The covariates measured at baseline included age, sex, body mass index (BMI), smoking status and alcohol abuse. The severity of COPD was measured using the type of index exacerbation (moderate, severe), the number of COPD hospitalisations and the use of other respiratory drugs (SABA, SAMA, theophylline), during the one-year baseline period, as well as by the percent predicted FEV_1. A prescription for prednisolone, LABA, LAMA, ICS, and respiratory antibiotics in the month prior to the index date were also considered. Baseline co-morbidity in the one-year baseline period was measured using clinical diagnoses, hospitalizations, and prescriptions (Table 1).

Each cohort subject was cloned and assigned to both the prompt initiators arm (initiation within 30 days of the index date) and to the delayed initiators arm (initiation 31–180 days after the index date). Within each treatment group, clones were artificially censored at the time that the treatment they received was no longer compatible with their group membership. To account for the bias introduced by this artificial censoring mechanism, IPCW was estimated by pooled logistic regression, separately for prompt initiators at day 30, for delayed initiators at index date, between day 1 and day

Table 1 Baseline Characteristics of the Overall Study Cohort of 91,958 Subjects with an Index Exacerbation, Generating 91,958 Clones of Prompt and 91,958 Clones of Delayed Initiation of Single-Inhaler Triple Therapy, After Weighing by Inverse Probability of Censoring

	Prompt Initiator Clones*	Delayed initiator clones*
Number of subjects	91,958	91,958
Sum of weights	91,635	91,632
Age at cohort entry, mean (SD)	70.2 (11.3)	70.2 (11.3)
Female sex, n (%)	48,604 (53.0)	48,603 (53.0)
Smoking status, n (%)		
Smoker	41,584 (45.4)	41,583 (45.4)
Ex-smoker	37,354 (40.8)	37,353 (40.8)
Non-smoker	12,170 (13.3)	12,170 (13.3)
Missing	526 (0.6)	526 (0.6)
Obesity Status, n (%)		
Obese	30,024 (32.8)	30,023 (32.8)
Non-Obese	58,203 (63.5)	58,201 (63.5)
Missing	3,408 (3.7)	3,408 (3.7)
Alcohol Abuse, n (%)	2,117 (2.3)	2,117 (2.3)
FEV_1 (%predicted), mean (SD)	63.8 (19.0)	63.9 (19.0)
Blood eosinophil count, 106/L, mean (SD)**	254.0 (211.0)	254.0 (211.2)
Severity of dyspnea, n (%)		
None-Mild	38,646 (42.2)	38,646 (42.2)
Moderate-Severe	39,264 (42.8)	39,262 (42.8)
Missing	13,724 (15.0)	13,724 (15.0)
Respiratory events and medications in year prior to cohort entry, n (%)		
Type of initial COPD exacerbation		
Severe	5,645 (6.2)	5,645 (6.2)
Moderate	85,989 (93.8)	85,987 (93.8)
Hospitalization for COPD (not including initial exacerbation)		
None	88,023 (96.1)	88,021 (96.1)
One or more	3,612 (3.9)	3,612 (3.9)
Prednisolone (prior month)	5,297 (5.8)	5,314 (5.8)
Asthma	28,120 (30.7)	28,119 (30.7)
Pneumonia hospitalisation	4,722 (5.2)	4,722 (5.2)
LABA (prior month)	39,939 (43.6)	39,938 (43.6)
LAMA (prior month)	27,756 (30.3)	27,755 (30.3)
Inhaled corticosteroids (prior month)	28,040 (30.6)	28,039 (30.6)
Short-acting beta-agonist	80,329 (87.7)	80,326 (87.7)
Short-acting anti-muscarinic	5,029 (5.5)	5,029 (5.5)
Methylxanthines	2,154 (2.4)	2,154 (2.4)
Respiratory antibiotics (prior month)	15,204 (16.6)	15,204 (16.6)
Comorbidity in year prior to cohort entry, n (%)		
Cancer	5,439 (5.9)	5,439 (5.9)
Diabetes	18,587 (20.3)	18,587 (20.3)
Heart failure	5,910 (6.4)	5,910 (6.4)
Myocardial Infarction	696 (0.8)	696 (0.8)
Stroke	2,142 (2.3)	2,142 (2.3)
Renal disease	6,575 (7.2)	6,575 (7.2)

(*Continued*)

Table 1 (Continued).

	Prompt Initiator Clones*	Delayed initiator clones*
Medications in year prior to cohort entry, n (%)		
ACE inhibitors	22,765 (24.8)	22,764 (24.8)
ARBs	11,660 (12.7)	11,660 (12.7)
Beta-Blockers	18,739 (20.4)	18,739 (20.4)
Calcium-Channel Blockers	24,948 (27.2)	24,947 (27.2)
Thiazides diuretics	8,995 (9.8)	8,995 (9.8)
Statins	43,804 (47.8)	43,803 (47.8)
PPIs	47,641 (52.0)	47,640 (52.0)
NSAIDs	10,607 (11.6)	10,606 (11.6)
Opioids	37,923 (41.4)	37,922 (41.4)

Notes: *Weighted by inverse probability of censoring. FEV_1 % predicted and blood eosinophil count data based on 75% and 80% of patients with available values, respectively

30 and at day 180, as a function of the baseline covariates. IPCW estimation for prompt initiators, delayed initiators at index date and at day 180, was based on time updated values of the baseline covariates and the type of initial exacerbation (moderate or severe). For the delayed initiators, estimation of IPCW between day 1 and day 30 also included the time since cohort entry (linear, quadratic and cubic terms). Only prompt initiators starting treatment between day 16 and 30 were upweighted to replace clones censored on day 30. Similarly, only delayed initiators between day 152 and 180 were upweighted to replace clones censored on day 180. In addition to the artificial censoring associated with the cloning process, patients were also censored when they initiated triple therapy in multiple inhalers (same day prescription for LABA, LAMA and ICS). To account for this type of censoring another IPCW was estimated in the full cohort and before cloning, using pooled logistic regression and with the same set of variables. Final time-varying weights for each section of person-time were obtained from the cumulative product of all IPCWs.

For data analysis, we used the Cox proportional hazards model to compare the incidence of an exacerbation during the one-year follow-up, weighted for the inverse of the probability of censoring. The corresponding 95% confidence intervals (CI) for the hazard ratios were obtained using the non-parametric bootstrap method based on 1000 random samples. Similarly, weighted cumulative incidence curves were estimated over the one-year follow-up, as well as differences and ratios of cumulative incidence at 3-month time points during follow-up.

We also replicated the approach used in the Mannino study, as described above.[2] Briefly, the study cohort included exclusively the subjects who had a prompt (within 30 days after the index date) or delayed (31–180 days after the index date classification) treatment initiation, restricted to those who had no exacerbation prior to the index date and at least 6 months of coverage after the index date. Inverse probability of treatment weighting, with stabilised weights, was used to adjust the hazard ratio of exacerbation, using the bootstrap method based on 1000 random samples outcomes to estimate the corresponding confidence interval. Since our study cohort on which the cloning analysis was based included subjects with exacerbations prior to the index date, we repeated the analysis, but not restricted to those who had no exacerbation prior to the index date and at least 6 months of coverage after the index date. The study protocol was approved by CPRD's Research Data Governance Committee (protocol # 23_002846) and the Research Ethics Board of the Jewish General Hospital (protocol # JGH-2024-3847), Montreal Canada.

Results

The overall study cohort included 91,958 eligible subjects who had an exacerbation after September 2017. There were 4,876 new-users of single-inhaler triple therapy within 180 days after the index COPD exacerbation. Of these, 1,394 were prompt initiators and 3,482 delayed initiators of single-inhaler triple therapy, with 87,082 who either received it after 180 days or not at all. The prompt initiators appear more severe, with lower FEV_1 percent predicted and more likely to have a hospitalised exacerbation as the index event (Table S1).

Table 2 Hazard Ratio of a Moderate or Severe Exacerbation for Prompt versus Delayed Initiation of Single-Inhaler Triple Therapy, Estimated Using Cloning to Define the Treatment Strategy Over Time, Weighed by Inverse Probability of Censoring

	Number of Subjects*	Before Weighing		After Weighing**		
		Number of First Events	Person-Months	Number of First Events	Person-Months	Hazard Ratio (95% CI)
Moderate or severe exacerbation event						
Prompt initiators	91,958	18,748	86,431	56,131	554,845	0.98 (0.80–1.19)
Delayed initiators	91,958	42,858	329,297	55,843	540,482	1.00 (reference)
Severe exacerbation event						
Prompt initiators	91,958	1,595	98,878	9,321	884,378	1.26 (0.81–1.96)
Delayed initiators	91,958	4,184	481,807	7,510	902,126	1.00 (reference)

Notes: *Includes number of subjects actually exposed and their clones. **Weighed by inverse probability of censoring.

The cloning of these subjects generated 91,958 prompt initiator clones and the same number of delayed initiator clones, including 426 clones who initiated triple therapy in multiple inhalers on the index date and 419 clones who initiated single-inhaler triple therapy on the index date (Table 1).

Of the 91,532 clones assigned to the prompt initiation strategy, 18,748 had a moderate or severe exacerbation after the index date, during 86,431 person-months of follow-up, resulting in an unadjusted incidence rate of a first exacerbation of 0.217 per patient per month (Table 2). The corresponding incidence rate for clones assigned to the delayed initiation strategy was 0.130 per patient per month. After weighing for censoring, the incidence rates are 0.101 and 0.103 per person per month, respectively, for the clones assigned to the prompt and delayed initiation regimens (HR 0.98; 95% CI: 0.80–1.19). The adjusted cumulative incidence curves of a moderate or severe exacerbation, weighted for censoring, are displayed in Figure 3. For severe exacerbations, the weighted incidence rates are 0.011 and 0.008 per person per month for the clones assigned to the prompt and delayed initiation regimens, respectively (HR 1.26; 95% CI: 0.81–1.96), with the corresponding adjusted cumulative incidence curves displayed in Figure 4. For the cumulative incidence curves given in Figures 3 and 4 the estimates of the differences and ratios of these cumulative incidences between the prompt and delayed initiators at different time points in follow-up are displayed in Table 3.

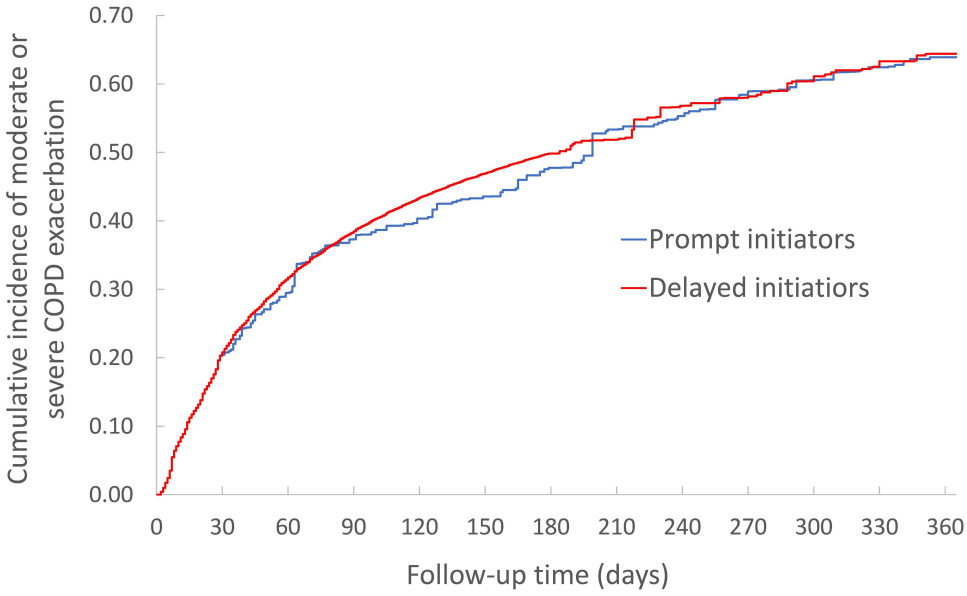

Figure 3 Cumulative incidence of the first moderate or severe exacerbation, for the prompt and delayed initiators, using the cloning approach, weighted by inverse probability of censoring.

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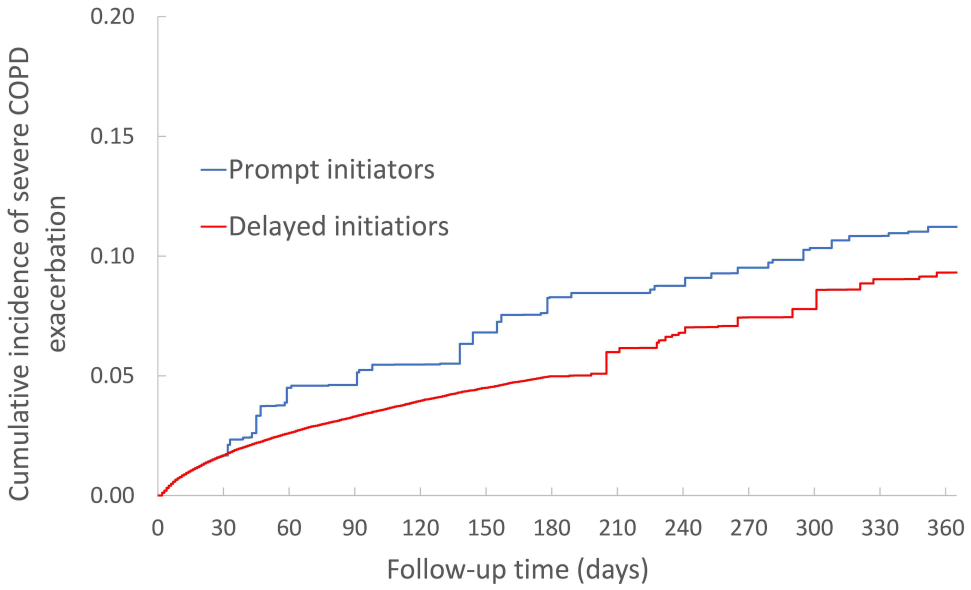

Figure 4 Cumulative incidence of the first severe exacerbation, for the prompt and delayed initiators, using the cloning approach, weighted by inverse probability of censoring.

For the replication of the Mannino study, the analysis was restricted to the 2,650 new-users of single-inhaler triple therapy within 6 months after the index COPD exacerbation, with no prior exacerbations and at least 6 months of follow-up. Of these, 809 were prompt initiators of single-inhaler triple therapy and 1,841 were delayed initiators, who were similar in terms of baseline clinical characteristics after weighing (Table 4). The hazard ratio of a first moderate or severe exacerbation was 0.73 (95% CI: 0.65–0.81), comparing prompt with delayed initiation, while it was 0.58 (95% CI: 0.46–0.74) for a severe exacerbation (Table 5). These results were similar after removing the restrictions of 6 months of coverage and no prior exacerbations (Table 5).

Table 3 Difference and Ratio of the Cumulative Incidence of Exacerbation Over Follow-up Time Comparing Prompt versus Delayed Initiation of Single-Inhaler Triple Therapy, Estimated Using Cloning to Define the Treatment Strategy Over Time, Weighted by Inverse Probability of Censoring

	Cumulative Incidence of Exacerbation per 100			
	Prompt Initiators	Delayed Initiators	Difference (95% CI)	Ratio (95% CI)
Moderate or severe exacerbation				
90 days	37.3	38.2	−1.0 (−7.0 to 5.1)	0.97 (0.83–1.15)
180 days	47.8	49.8	−2.1 (−8.9 to 4.7)	0.96 (0.83–1.11)
270 days	58.4	58.0	0.4 (−8.6 to 9.5)	1.01 (0.86–1.18)
360 days	63.9	64.4	−0.5 (−10.3 to 9.3)	0.99 (0.85–1.16)
Severe exacerbation				
90 days	4.6	3.3	1.3 (−0.5 to 3.2)	1.40 (0.93–2.11)
180 days	8.3	5.0	3.3 (0.1 to 6.5)	1.66 (1.11–2.50)
270 days	9.5	7.4	2.1 (−2.0 to 6.1)	1.28 (0.81–2.03)
360 days	11.2	9.3	1.9 (−2.6 to 6.4)	1.20 (0.77–1.87)

Table 4 Baseline Characteristics of the 809 Prompt and 1,841 Delayed Initiators of Single-Inhaler Triple Therapy, Identified from the Cohort of 91,958 Subjects with an Index Exacerbation, Crude and Weighted by Inverse Probability of Treatment, Used to Replicate the Approach of Mannino

	Unweighted		Weighted*	
	Prompt Initiators	**Delayed Initiators**	**Prompt Initiators**	**Delayed Initiators**
Number of subjects	809	1,841	809	1,841
Sum of weights			808	1,841
Age at cohort entry, mean (SD)	70.2 (10.6)	70.6 (10.7)	70.2 (10.5)	70.5 (10.8)
Female sex, n (%)	364 (45.0)	885 (48.1)	381 (47.2)	868 (47.2)
Smoking status, n (%)				
Smoker	427 (52.8)	952 (51.7)	421 (52.1)	959 (52.1)
Ex-smoker	330 (40.8)	747 (40.6)	330 (40.9)	748 (40.6)
Non-smoker	51 (6.3)	134 (7.3)	55 (6.8)	127 (6.9)
Missing	<5(0.1)	8 (0.4)	<50.2)	6 (0.3)
Obesity Status, n (%)				
Obese	254 (31.4)	580 (31.5)	255 (31.5)	580 (31.5)
Non-Obese	530 (65.5)	1202 (65.3)	528 (65.3)	1202 (65.3)
Missing	25 (3.1)	59 (3.2)	26 (3.2)	59 (3.2)
Alcohol Abuse, n (%)	20 (2.5)	52 (2.8)	22 (2.8)	50 (2.7)
FEV1 (%predicted), mean (SD)	57.4 (19.4)	59.7 (19.1)	59.2 (19.2)	58.9 (19.2)
Blood eosinophil count, 106/L, mean (SD)**	252.2 (187.0)	260.7 (197.6)	259.4 (188.7)	256.6 (195.7)
Severity of dyspnea, n (%)				
None-Mild	286 (35.4)	724 (39.3)	310 (38.4)	702 (38.1)
Moderate-Severe	471 (58.2)	979 (53.2)	440 (54.5)	1007 (54.7)
Missing	52 (6.4)	138 (7.5)	58 (7.2)	132 (7.2)
Respiratory events and medications in year prior to cohort entry, n (%)				
Type of initial COPD exacerbation				
Severe	150 (18.5)	239 (13.0)	121 (14.9)	271 (14.7)
Moderate	659 (81.5)	1602 (87.0)	688 (85.1)	1570 (85.3)
Asthma	145 (17.9)	342 (18.6)	146 (18.0)	337 (18.3)
Pneumonia hospitalisation	49 (6.1)	105 (5.7)	49 (6.1)	108 (5.9)
LABA (prior month)	391 (48.3)	923 (50.1)	397 (49.1)	912 (49.5)
LAMA (prior month)	311 (38.4)	747 (40.6)	322 (39.9)	735 (39.9)
Inhaled corticosteroids (prior month)	201 (24.8)	440 (23.9)	192 (23.7)	443 (24.1)
Short-acting beta-agonist	726 (89.7)	1659 (90.1)	725 (89.7)	1656 (89.9)
Short-acting anti-muscarinic	38 (4.7)	74 (4.0)	34 (4.3)	77 (4.2)
Methylxanthines	9 (1.1)	33 (1.8)	12 (1.5)	29 (1.6)
Respiratory antibiotics (prior month)	111 (13.7)	272 (14.8)	119 (14.8)	267 (14.5)
Comorbidity in year prior to cohort entry, n(%)				
Cancer	43 (5.3)	108 (5.9)	48 (6.0)	105 (5.7)
Diabetes	140 (17.3)	352 (19.1)	153 (18.9)	343 (18.6)
Heart failure	69 (8.5)	125 (6.8)	59 (7.3)	135 (7.3)
Myocardial Infarction	8 (1.0)	17 (0.9)	8 (1.0)	18 (1.0)
Stroke	21 (2.6)	43 (2.3)	22 (2.7)	46 (2.5)
Renal disease	71 (8.8)	126 (6.8)	61 (7.5)	137 (7.5)

(*Continued*)

Table 4 (Continued).

	Unweighted		Weighted*	
	Prompt Initiators	Delayed Initiators	Prompt Initiators	Delayed Initiators
Medications in year prior to cohort entry, n(%)				
ACE	223 (27.6)	487 (26.5)	215 (26.6)	493 (26.8)
ARB	102 (12.6)	220 (12.0)	98 (12.2)	223 (12.1)
Beta-Blockers	190 (23.5)	422 (22.9)	185 (22.8)	425 (23.1)
Calcium-Channel Blockers	206 (25.5)	498 (27.1)	212 (26.3)	487 (26.5)
Thiazides diuretics	81 (10.0)	166 (9.0)	74 (9.2)	171 (9.3)
Statins	396 (48.9)	929 (50.5)	408 (50.4)	922 (50.1)
PPIs	377 (46.6)	906 (49.2)	394 (48.8)	893 (48.5)
NSAIDs	79 (9.8)	204 (11.1)	86 (10.6)	197 (10.7)
Opioids	291 (36.0)	751 (40.8)	317 (9.3)	724 (9.3)

Notes: * Weighted by inverse probability of treatment. FEV_1 % predicted and blood eosinophil count data based on 85% and 79% of patients with available values, respectively

Table 5 Hazard Ratio of Moderate or Severe Exacerbation for Prompt versus Delayed Initiation of Single-Inhaler Triple Therapy, Used to Replicate the Approach of Mannino, Estimated Using the Cox Proportional Hazards Model, Adjusted by Inverse Probability of Treatment Weighing

	Number of Subjects	Number with a First Exacerbation	Person-Months	Incidence Rate*	Hazard Ratio** (95% CI)
Subjects without prior exacerbation and at least 6 months of follow-up					
Moderate or severe exacerbation event					
Prompt initiators	809	479	5,159	9.3	0.73 (0.65–0.81)
Delayed initiators	1,841	1,311	9,317	14.1	1.00 (reference)
Severe exacerbation event					
Prompt initiators	809	90	8,552	1.0	0.58 (0.46–0.74)
Delayed initiators	1,841	338	18,388	1.8	1.00 (reference)
Subjects having at least 6 months of follow-up					
Moderate or severe exacerbation event					
Prompt initiators	1,089	694	6,487	10.7	0.71 (0.65–0.78)
Delayed initiators	2,780	2,127	12,739	16.7	1.00 (reference)
Severe exacerbation event					
Prompt initiators	1,089	130	11,501	1.1	0.60 (0.50–0.73)
Delayed initiators	2,780	530	27,696	1.9	1.00 (reference)
Full cohort					
Moderate or severe exacerbation event					
Prompt initiators	1,394	825	7,056	11.7	0.72 (0.67–0.79)
Delayed initiators	3,482	2,496	13,860	18.0	1.00 (reference)
Severe exacerbation event					
Prompt initiators	1,394	172	12,288	1.4	0.68 (0.58–0.81)
Delayed initiators	3,482	614	29,430	2.1	1.00 (reference)

Notes: *Per 100 per month. **Using stabilized weights by inverse probability of treatment.

Discussion

In this large-scale real-world study, we found that prompt treatment with single-inhaler triple therapy after a COPD exacerbation was not more effective than delayed treatment on reducing the incidence of a subsequent exacerbation. We showed that the methods used by previous studies that suggested significant effectiveness with prompt therapy, were

affected by major time-related biases that favored the prompt treatment group.[2,3,6] For example, our illustration showed that, using the corrected approach, the hazard ratio of a COPD exacerbation was 0.98 (95% CI: 0.80–1.19) with prompt versus delayed treatment, while the corresponding HR with the time-related biased method employed by the previous studies was a significant 0.73 (95% CI: 0.65–0.81).

The time-related biases affecting the previous studies first involved "peeking into the future" to define prompt and delayed treatment, with a return to time zero to start follow-up for outcome exacerbation events. This approach thus allowed treatment initiation occurring after outcome events, which introduces protopathic bias.[7] Indeed, multiple exacerbations, the study outcome, are an indication to initiate triple therapy, as recommended by the GOLD guidelines.[1] The other source of bias, namely selection bias from immortal time, resulting from imposing 6 months of coverage after the index date, was present in two of the studies to date.[2,6] This criterion excludes subjects who died during this period, when they could have initiated triple therapy and had exacerbations, which could be differential in the two treatment groups. While other studies did not impose this 6-month condition, they did introduce protopathic bias.[3–5] Our bias analysis showed that this 6-month imposition did not affect the findings, implying that the major time-related bias in these studies is protopathic bias, a bias present in all studies.

This approach has also been used in several other observational studies have investigated the comparative effectiveness of prompt versus delayed initiation of triple therapy, though including triple therapy in multiple inhalers after a COPD exacerbation.[18–22] These studies also found that prompt initiation of triple therapy was associated with significant reductions in the rates of exacerbations, and related costs, compared with delayed initiation. These findings are thus also affected by the same protopathic bias.

The "cloning" approach that we used is specifically designed to avoid the protopathic bias resulting from peeking into the future to define the treatment strategy. This cloning approach emulates a randomized trial by allocating the treatment strategy, prompt or delayed initiation of triple therapy, as of the index date, thus not looking in the future. Cloning involves creating data replicates of each patient, one for each of the study treatment strategies (in this case, prompt and delayed initiation) that the patient could belong to at the index date.[10–12] The patient's data are thus included twice in the analysis, censored by the timing of exposure and outcome events. While the same outcome events can be counted in multiple regimens in this approach, a censor-weighted data analysis and the bootstrap can account for the replicated data.

Our study has some limitations typical to observational studies. The inhaler information is based on written prescriptions and can thus introduce some exposure misclassification, including on the timing of the actual treatment initiation, which can lag behind the prescription date. Thus, the 30- and 180-day thresholds used to define prompt and delayed treatment will necessarily be affected by this misclassification, which should differentially affect the shorter prompt treatment period. Indeed, we can assume that some subjects with a prescription date just prior to 30 days will be misclassified as prompt initiators if they in fact initiate their inhaler after 30 days. The use of censoring weights, however, because they are calculated using the observed exposure timing, does not account for this misclassification. To account for such exposure measurement error would require validating exposure in a subset of the study population and incorporating sensitivity analyses alongside censoring weights. Also, the outcome of a moderate exacerbation is defined only based on a prescription for prednisolone which, while a common practice in the UK, could introduce some misclassification. Our study also has strengths, besides the cloning approach that avoids the time-related biases of previous studies. Indeed, this approach is not affected by confounding as the cloning results in the same patients being replicated, making the two comparison groups identical on all subject characteristics.

In conclusion, this large-scale real-world study found that prompt treatment with single-inhaler triple therapy after a COPD exacerbation was not more effective than delayed treatment on reducing the incidence of a subsequent exacerbation. We showed that the methods used by previous studies that suggested significant effectiveness with prompt therapy, were affected by time-related biases that favored the prompt treatment group. For example, using the corrected approach, we found no reduction in the risk of a COPD exacerbation with prompt versus delayed treatment, while the time-related biased method used in previous studies suggested a significant 27% reduction in the outcome event.

Data Sharing Statement

This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. Because electronic health records are classified as "sensitive data" by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

SS attended, in the last three years, scientific advisory committee meetings or received speaking fees from AstraZeneca, Boehringer-Ingelheim, Novartis, and Panalgo. The authors report no other conflicts of interest in this work.

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