Comparative Real-World Effectiveness of Triple Therapy Versus Dual Bronchodilation on Lung Function Decline in Frequently Exacerbating Patients with COPD

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BACKGROUND

- The mainstay of therapeutic management in COPD is long-acting inhaled bronchodilators (LAMA and/or LABA)[1]
- Addition of Inhaled Corticosteroids (ICS) to LAMA+LABA is recommended in patients at risk for further exacerbations[1]
- Randomized controlled clinical trials (RCTs) have shown that patients on triple therapy (ICS+LAMA+LABA or TT) have a higher expiratory volume in 1 second (FEV_1) after one year, compared to those using dual bronchodilation (LAMA+LABA or DB) [2,3]
- Part of the patients in the RCTs stepped down from ICS
- Confirmation of this superiority of triple therapy in a representative population with a longer follow-up and no prior ICS exposure is needed from real world effectiveness studies

AIM

To compare the real world effectiveness of triple therapy with ICS+LAMA+LABA vs LAMA+LABA on lung-function decline among frequently-exacerbating COPD patients

DESIGN & METHODOLOGY

Design: Matched historical cohort study.

Data sources: The Clinical Practice Research Datalink (CPRD, www.cprd.com) and Optimum Patient Care Research Database (OPCRD, opcrd.co.uk)

*Index date: step-up **from no maintenance therapy or LAMA***

- COPD diagnosis
- ≥ 2 exacerbations
- Age ≥ 40 years
- Smoking history
- No other chronic resp. conditions

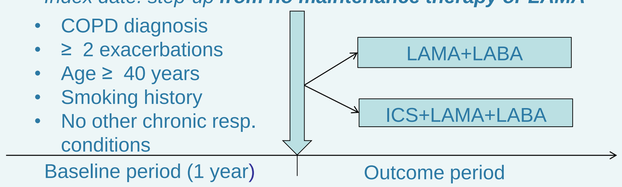

Figure 1 – Study design

References
1. GOLD report 2018
2. Papi A *et al.* Lancet 2018; 391: 1076–84
3. Lipson D *et al.* NEJM 2018;378:1671-80

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Primary outcome:

- Mean decline in FEV_1 (mL/year) over the follow-up period (index date until the last available FEV_1 measurement)

Secondary objective: Effect modification by:

- Age at index date
- Gender
- Smoking status at baseline
- Blood eosinophil count, most recent within 5 years
- Exacerbation burden in baseline year

Statistical analysis:

Multilevel model for change, where the intercept and slope (rate of FEV_1 decline over time) were modelled as random effects (allowing these to vary across individual). The level-1 component was the growth model within patients. A quadratic term for change in FEV_1 over time was explored. The level-2 component was the mean population difference in lung function decline with therapy. A time-varying predictor of treatment was used, representing the last therapy kind the patient was on in the 120 days preceding each FEV_1 measurement. Therefore, estimates for other therapies than TT or DB are also available.

Nearest neighbour propensity score calliper matching with a ratio of 1:3 was used, and models were adjusted on time-varying cumulative exposure measures for ICS, LAMA and LABA, age, gender, and identified residual confounders. Effect modification was explored by using an interaction term with time.

PATIENT SELECTION

Table 1 – Patient records selection flow

	LAMA+LABA	Triple therapy
COPD diagnosis (Read code)	299,103	
Stepped up to LAMA+LABA or Triple therapy	7,194	69,480
≥ 1 year baseline data	6,840	62,579
Age ≥40 at diagnosis	6,830	62,408
Smoking history	6,605	59,926
No other chronic respiratory diseases	5,406	40,948
Prior therapy: No maintenance or LAMA	3,784	13,718
≥2 exacerbations in baseline	493	2,619
≥2 FEV_1 measurements during follow-up	204	1,251
Matched patients	**198**	**552**

RESULTS

Table 2 – Characteristics of matched patients

Variable		LAMA+LABA (N=198)	Triple therapy (N=552)	SMD
Baseline				
Age (years)	Mean (SD)	67.3 (9.5)	67.8 (8.9)	5.8
Male gender	n (%)	105 (53.0)	307 (55.6)	5.2
Current smoker	n (%)	87 (43.9)	231 (41.8)	4.2
LAMA use	n (%)	327 (70.2)	838 (71.0)	2.4
Exacerbations	2, n (%)	114 (57.6)	299 (54.2)	3.6
	3, n (%)	55 (27.8)	191 (34.6)	
	4, n (%)	14 (7.1)	37 (6.7)	
	≥5, n (%)	15 (7.6)	25 (4.5)	
GOLD Grade	N (% non-missing)	163 (82.3)	442 (80.1)	1.8
	C, n (%)	100 (61.3)	275 (62.2)	
	D, n (%)	63 (38.7)	167 (37.8)	
Follow-up				
FEV1 observations in follow-up	Median (IQR)	3 (2-5)	3 (2-5)	
Follow-up (years)	Median (IQR)	2.3 (1.5-4.2)	3.1 (1.9-4.6)	

SD: Standard deviation; SMD: Standardised mean difference

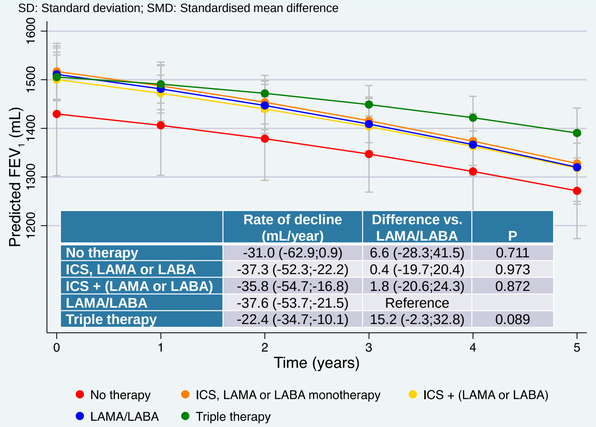

Figure 2 – Predicted FEV_1 trajectories and average rates of decline, by therapy, with 95% confidence intervals

Effect modification

Age at index date, gender and blood eosinophil count did not modify the effect of treatment on lung function decline significantly. Smoking status at baseline did modify the comparative effectiveness significantly (P=0.044); the difference between TT and DB was 20 mL/year larger in current smokers compared to former smokers.

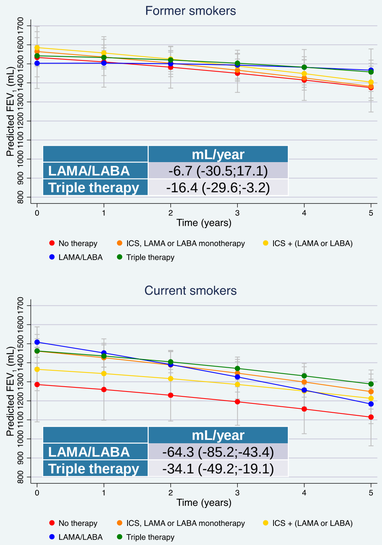

Figure 3 – Predicted FEV_1 trajectories, by smoking status and therapy, with 95% confidence intervals

CONCLUSION

- We observed a reduction of lung function decline with TT compared to DB of 15.2 mL (-2.3,32.8) consistent with the results supporting the efficacy of TT from RCTs. This difference was more prominent in current smokers.

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