Predictors of Comparative Real-World Effectiveness of Triple Therapy Versus Dual Bronchodilation in Frequently Exacerbating Patients with COPD

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BACKGROUND

- Randomised controlled clinical trials found benefit from triple therapy (ICS+LAMA+LABA) as compared with dual bronchodilation (LAMA+LABA) in patients with COPD who remained symptomatic despite treatment with one or two bronchodilators, in terms of reducing exacerbation risk[1,2]
- Blood eosinophil counts are currently recommended to be used as a biomarker to predict the likelihood of a beneficial response to additional ICS[3]
- There is a need for evidence on characteristics predicting real-world effectiveness of initiating triple therapy in ICS-naïve patients who experienced frequent COPD exacerbations

AIM

To study patient and therapy characteristics influencing the comparative effectiveness of triple therapy (TT) vs. dual bronchodilation (DB) among frequently exacerbating COPD patients

DESIGN & METHODOLOGY

Design: Matched historical cohort study

Data sources: Electronic medical data from 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

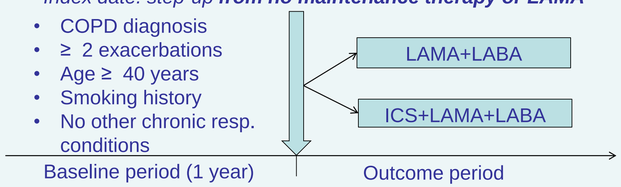

Figure 1 – Study design

References
1. Papi A *et al.* Lancet 2018; 391: 1076–84
2. Lipson D *et al.* NEJM 2018;378:1671-80
3. GOLD report 2019

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Primary outcome:

- Time until 1st exacerbation: acute oral corticosteroids or respiratory-related: hospitalisation, emergency attendance or antibiotics

Secondary outcomes:

- Time until 1st event:
  - Acute respiratory event: unplanned respiratory consultation
  - Treatment failure: an exacerbation or additional therapy
  - Acute oral corticosteroids
  - Respiratory-related antibiotics course
- Rate (number of events in 1st outcome year):
  - Exacerbations
  - Acute OCS courses
  - Respiratory-related antibiotics courses
  - Acute respiratory events
- Recording of mMRC score ≥ 2 within 18 months (yes vs. no)

Method of analysis: Stratified cox regression (Hazard Ratio), negative binomial (Rate Ratio) or logistic regression (Odds Ratio)

Effect modifiers: studied by interaction term in regression model for:

- Number of exacerbations in prior year
- Blood eosinophil count, most recent within 5 years
- FEV_1 % predicted
- GOLD group C or D

Predictor of ICS response in unmatched TT patients:

- ICS substance / particle size combinations

Confounding handling approach: Nearest neighbour propensity score calliper matching with a ratio of 1:3. Models were adjusted on residual confounders

PATIENT SELECTION

Table 1 – Patient records selection flow

	LAMA+LABA	Triple therapy
COPD diagnosis	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	492	2,603
Matched patients	**466**	**1,181**

RESULTS

Table 2 – Characteristics of patients and ICS substance use

Variable		LAMA+LABA (N=466)	Triple therapy (N=1,181)	SMD
Age (years)	Mean (SD)	69.2 (10.7)	69.4 (10.2)	2.0
Male gender	n (%)	233 (50.0)	603 (51.1)	2.1
Current smoker	n (%)	210 (45.1)	528 (44.7)	0.7
Exacerbations	2, n (%)	287 (61.6)	698 (59.1)	3.4
	3, n (%)	105 (22.5)	284 (24.0)	
	4, n (%)	34 (7.3)	101 (8.6)	
	≥5, n (%)	40 (8.6)	98 (8.3)	
Blood eosinophil count (10^9 /L)	N (% non-missing)	391 (83.9)	983 (83.2)	2.2
	<0.15, n (%)	118 (30.2)	298 (30.3)	
	0.15-0.34, n (%)	190 (48.6)	468 (47.6)	
	≥0.35, n (%)	83 (21.2)	217 (22.1)	
FEV_1 % predicted	N (% non-missing)	373 (80.0)	957 (81.0)	8.0
	Mean (SD)	55.8 (23.1)	53.7 (23.7)	9.2
GOLD Grade	N (% non-missing)	389 (83.5)	976 (82.6)	7.9
	C, n (%)	236 (60.7)	554 (56.8)	
	D, n (%)	153 (39.3)	422 (43.2)	
ICS substance / particle size	**Unmatched triple therapy patients**		2,603	
	Beclometasone / extrafine, n (%)		211 (8.1)	
	Beclometasone / fine, n (%)		13 (0.5)	
	Fluticasone / fine, n (%)		1,650 (63.4)	
	Budesonide / fine, n (%)		729 (28.0)	

SD: Standard deviation; SMD: Standardised mean difference

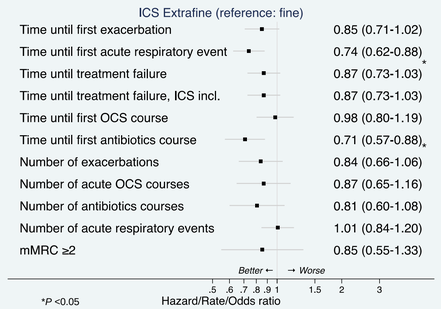
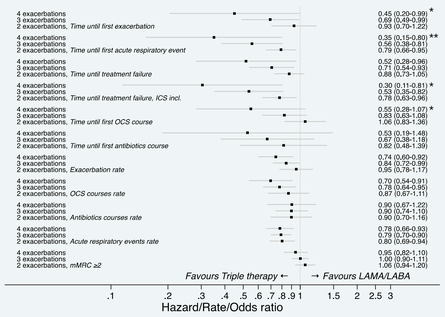
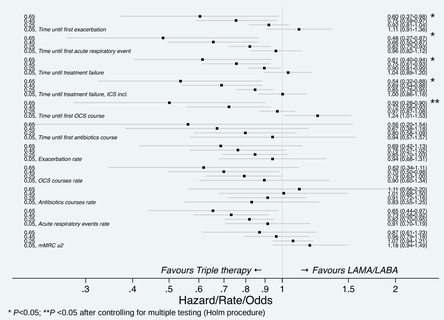


Figure 1– Adjusted effect sizes (95% confidence intervals) extrafine vs. fine particle size ICS



* P<0.05; **P <0.05 after controlling for multiple testing (Holm procedure)

Figure 2 – Adjusted effect sizes by the number of exacerbations



* P<0.05; **P <0.05 after controlling for multiple testing (Holm procedure)

Figure 3 – Adjusted effect sizes by the blood eosinophil count (10^9/L)

CONCLUSION

- Effectiveness of triple therapy compared with dual bronchodilation in patients with frequent COPD exacerbations increased with:
  - The number of exacerbations in prior year
  - Increasing blood eosinophil count
- Extrafine beclometasone was associated with a longer time to the first acute respiratory event and antibiotics course as compared to fine ICS

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