

Research in Real Life

Evaluation of patients with COPD and CKD who would benefit from aclidinium bromide treatment.

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Draft protocol

## **Characterising patient groups with chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) who may benefit from initiation of long-acting muscarinic antagonist (LAMA) therapy or a switch from tiotropium for safety reasons**

To characterise populations of patients with COPD and CKD who could benefit from treatment with aclidinium bromide (Eklira®) as an alternative to tiotropium



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## OBJECTIVES

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The aim of this study is to characterise populations of patients with chronic obstructive pulmonary disease (COPD<sup>1</sup>) and chronic kidney disease (CKD<sup>2</sup>) who could benefit from treatment with acclidinium bromide (Eklira®).

This will be carried out by characterising the acclidinium bromide eligible population and evaluate the proportion of patients who:

1. Are being incorrectly treated with tiotropium and could be treated with acclidinium bromide instead.
2. Are not receiving any long-acting muscarinic antagonist (LAMA) therapy but would be justified in having LAMA treatment; and could therefore be started on acclidinium bromide.

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## BACKGROUND

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COPD is one of the leading causes of morbidity and mortality worldwide [1]. Patients with COPD often suffer from other co-morbidities, one of which is chronic kidney disease (CKD), frequently found even in mild COPD [2].

CKD is a growing public health problem. For example a study by the New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project estimated age-standardised prevalence of stages 3b-5 CKD in the UK adult population at 8.5% (10.6% females and 5.8% in males) [3] (See appendix B for CKD staging).

Patients with COPD are often treated with the LAMA tiotropium [4]. However for patients with moderate-to-severe CKD (where creatinine clearance is  $\leq 50$  ml/min) renal impairment can result in reduced drug clearance of tiotropium [5]. Therefore, in these individuals tiotropium is only licenced for use when the expected benefit outweighs the risk [5].

Sometimes GPs are wary of prescribing a LAMA because of the associated problems with tiotropium clearance in patients with renal failure. Therefore LAMA therapy is frequently not prescribed due to GPs' cautiousness in prescribing tiotropium, even though LAMA therapy would be justified.

Acclidinium bromide has no such licencing indications as no significant pharmacokinetic differences (e.g. in how the drug is absorbed, distributed, metabolised and eliminated by the body) were seen between subjects with normal renal function and subjects with renal impairment [6, 7]. Therefore patients with renal failure could be started on acclidinium bromide due to the improved safety profile compared to tiotropium.

This study aims to characterise the acclidinium bromide eligible population and evaluate the proportion of patients who could be treated with acclidinium bromide instead of tiotropium.

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<sup>1</sup> COPD is defined as a common, preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases

<sup>2</sup> CKD is defined as a progressive decrease in renal function, identified by a blood test for creatinine clearance, higher levels of creatinine indicate reduced glomerular function.

This study will focus on the following patient groups:

**Study group 1:**

- Patients with COPD and CKD
- Current tiotropium prescription

**Study group 2:**

- Patients with COPD and CKD
- Patients with COPD symptoms (mMRC  $\geq 2$ ; CAT  $\geq 10$ ) OR are in GOLD group C and experience frequent exacerbations (see appendix A for GOLD group guidelines), justifying LAMA therapy
- LAMA therapy not delivered due to GPs' cautiousness in prescribing tiotropium, even though LAMA therapy would be justified

Patient populations may be characterised in terms of those that would benefit from acclidinium bromide treatment as an alternative to tiotropium, potentially allowing patients to be stratified into treatment groups.

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#### DATASOURCE

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This study will use the Optimum Patient Care Research Database (OPCRD) which comprises anonymous data extracted from primary care practices in order to perform reviews of their chronic respiratory services. Two types of anonymised patient data are typically collected:

1. Routine clinical data
  - OPC software interfaces with primary care practice management systems and extracts disease coding and prescribing information.
2. Questionnaires
  - Patients identified as recipients of the respiratory service under review are invited to complete validated disease assessment questionnaires to better understand their current health status (and/or possible reasons for sub-optimal status).
  - Anonymised questionnaires are assigned a unique code to aid matching routine data to questionnaire results.

The OPCRd has been approved by Trent Multi Centre Research Ethics Committee for clinical research use. The anonymous, longitudinal patient data offers a high-quality data source for use in clinical, epidemiological and pharmaceutical research. It enables research to be carried out across a broad range of respiratory areas.

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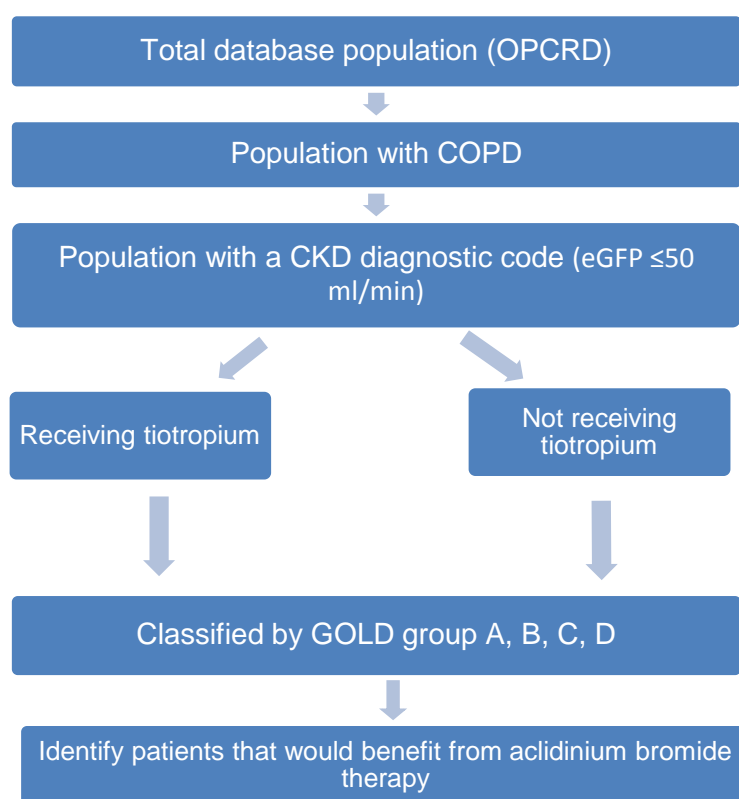
#### STUDY DESIGN

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The study will be a retrospective database analysis. Patients with both a COPD and a CKD diagnostic code (creatinine clearance  $\leq 50$  ml/min) will be separated into two groups:

1. Those currently receiving tiotropium (have had a prescription at some point over the last year since the last extraction) (study group 1).
2. Those with COPD symptoms [(mMRC  $\geq 2$ ; CAT  $\geq 10$ ) OR are in GOLD group C and experience frequent exacerbations], which justify LAMA therapy but are not receiving tiotropium (study group 2).

For both of the above groups this will be a one year cross sectional study of patients.



*Figure 1: Study design*

## Inclusion Criteria

In order to be included in the study, patients must fit the following criteria:

- (1) COPD diagnosis (diagnostic code AND/OR confirmed by spirometry reading)
- (2) CKD diagnosis (diagnostic code constituting an estimated glomerular filtration rate (eGFR; see appendix B) reading  $\leq 50$  ml/min)
- (3) Age  $\geq 40$

## Exclusion Criteria

None.

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## MEASURED OUTCOMES

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### Primary outcome

To characterise the acclidinium bromide eligible population<sup>3</sup> and evaluate the proportion of patients who could be treated with acclidinium bromide instead of tiotropium.

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<sup>3</sup> Acclidinium bromide eligible population is defined as patients with CKD (creatinine clearance  $\leq 50$  ml/min) who are being inappropriately treated with tiotropium (study group 1) and patients in

Focus of the study will be given to evaluating the proportion of patients who are:

- being incorrectly treated with tiotropium
- not receiving any LAMA therapy but that would be justified in having LAMA treatment; and could therefore be started on aclidinium bromide

### Patient characterisation

The following patient characteristics will be recorded:

- age
- sex
- BMI, measure of obesity (if available)
- smoking status (i.e. current smoker, previous smoker, non-smoker)
- evidence of prior disease or illness (e.g. asthma)
- presence of additional diseases (e.g. type-2 diabetes, osteoporosis), assessed individually and/or in combination using Charlson comorbidity index<sup>4</sup>
- drug history and long-term medication
- number of severe COPD-related events (exacerbations)<sup>5</sup>
- lung function categorised by GOLD stage (1, 2, 3, 4)
- COPD severity (risk and symptoms) categorised by GOLD group (A, B, C, D)
- health status<sup>6</sup>
- current management by GOLD therapy guidelines
- CKD diagnostic code (split by stage 1-5 and with eGFR information)

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### STATISTICAL ANALYSIS

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Summary statistics will be calculated for the following variables by LAMA therapy and compared:

- Demographics (including age, sex, BMI, smoking status)
- Co-morbidities
- Number of exacerbations in the year before the index date (ATS and clinical definition)
- GOLD group status
- CKD diagnostic code

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GOLD groups B and D, or patients in GOLD group C who experience frequent exacerbations, who would be justified in using a LAMA but have not yet been prescribed one (study group 2). These two populations represent groups of patients that could be switched over to aclidinium bromide, due to lack of contraindication in renal failure, or those who could be started on aclidinium bromide, respectively.

<sup>4</sup> **Charlson comorbidity index:** 10-year likelihood of patient mortality based on number and type of additional diseases (e.g. arthritis, cancer, COPD, type-2 diabetes) he or she has.

<sup>5</sup> **COPD severe exacerbations:** Where an exacerbation is defined as an occurrence of:

1. Unscheduled hospital admission / A&E attendance for COPD (definite code) or lower respiratory related events (i.e. with a lower respiratory read code); OR
2. Lower respiratory tract infections (LRTI) treated with antibiotics (**definite** code); OR
3. Acute use of oral steroids (definite plus possible courses); OR
4. Antibiotics use with a lower respiratory read code within a  $\pm 5$ -day window.

<sup>6</sup> **COPD assessment test (CAT) and/or modified Medical Research Council (mMRC) score:**

CAT on scale from 0-40, higher scores denote greater severity mMRC on scale from 0-4, higher scores denote greater severity

For variables measured on the interval or ratio scale, summary statistics produced will be:

- Sample size (n)
- Percentage non missing
- Mean
- Variance/standard deviation
- Range (minimum- maximum)
- Median
- Inter-quantile range (25th and 75th percentile)

For categorical variable the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and percentage by category (distribution)

Outcomes will be compared using a Mann Whitney U test/Chi squared Test (for variables measured on the interval or ratio scale/ categorical variables respectively.)

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### TIMELINE, DELIVERY AND COSTINGS

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Proposed timelines summary:

	Number of weeks of work required
Database analysis and data extraction	8
Statistical analysis	8
Report delivery	2
First draft of manuscript	4-6 weeks from final report

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### RESEARCH TEAM

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**Chief Investigator:** Professor David Price, Professor of Primary Care Respiratory Medicine, Centre of Academic Primary Care, University of Aberdeen and Director of Research in Real Life.

**Steering Committee:** To be arranged with the study sponsor if required.

**Research Team:** Research in Real Life

**Project Director:** Catherine Hutton

**Senior Statistician:** Annie Burden

**Senior Data Analyst:** Julie von Ziegenweidt

**Researcher:** Emily Davis

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### REFERENCES

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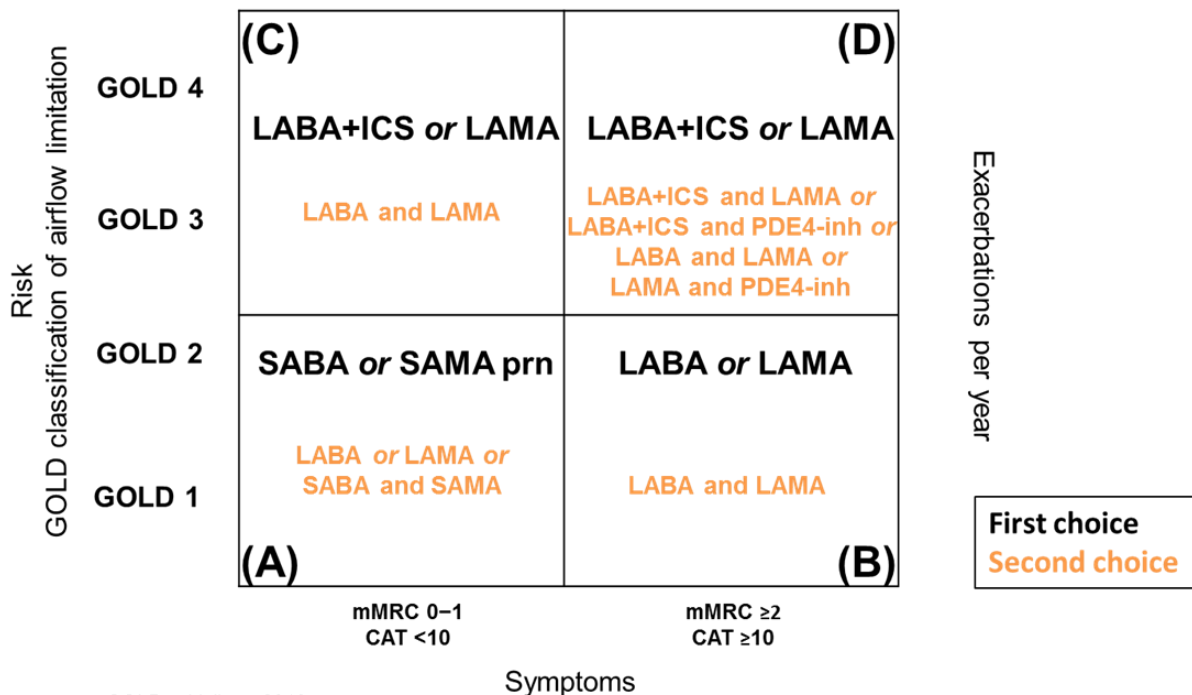
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## APPENDIX A: GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD) GUIDELINES

Categories to improve management of COPD, according to GOLD guidelines.



- The GOLD staging system classifies airflow limitation severity in COPD.  
In patients with  $FEV_1/FVC < 0.70$ :  
GOLD 1 - mild COPD;  $\geq 80$   $FEV_1$  % predicted  
GOLD 2 - moderate COPD; 50–79  $FEV_1$  % predicted  
GOLD 3 - severe COPD; 30–49  $FEV_1$  % predicted  
GOLD 4 - very severe;  $< 30$   $FEV_1$  % predicted or chronic respiratory failure
- The mMRC score is a 5-point (1–5) scale based on the severity of dyspnea deduced from the mMRC measure of breathlessness questionnaire. Degree of breathlessness related to activities:
  1. Not troubled by breathlessness except on strenuous exercise
  2. Short of breath when hurrying or walking up a slight hill
  3. Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
  4. Stops for breath after walking about 100m or after a few minutes on level ground
  5. Too breathless to leave the house, or breathless when dressing or undressing
- COPD Assessment Test (CAT) is an 8-item questionnaire measuring health status impairment in COPD. CAT scores range from 0–40 with a high score representing poor health status. CAT comprises items relating to the severity of cough, sputum, dyspnea, chest tightness, capacity for exercise and activities, confidence, sleep quality and energy levels.

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## APPENDIX B: CHRONIC KIDNEY DISEASE STAGING

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Stages of chronic kidney disease		
stage	eGFR <sup>7</sup> (ml/min/1.73m <sup>2</sup> )	Description
1	≥90	Normal or increased eGFR, with other evidence of kidney damage
2	60-89	Slight decrease in eGFR, with other evidence of kidney damage
3a	45-59	Moderate decrease in eGFR, with or without other evidence of kidney damage
3b	30-44	
4	15-29	Severe decrease in eGFR, with or without other evidence of kidney damage
5	<15	Established renal failure

### Suffixes:

- **p**: the addition of **p** to a stage (e.g. 3Ap, 4p) means that there is significant proteinuria
- **T**: the addition of **T** to a stage (e.g. 3AT) indicates that the patient has a renal transplant.
- **D**: the addition of **D** to stage 5 CKD (e.g. 5D) indicates that the patient is on dialysis

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<sup>7</sup> An effective way of assessing how well your kidneys are working is to calculate your glomerular filtration rate (GFR). GFR is a measurement of how many millilitres (ml) of waste fluid your kidneys can filter from the blood in a minute (measured in ml/min).

It is difficult to measure the GFR directly, so it is estimated using a formula. The result is called the estimated GFR or eGFR. Calculating your eGFR involves taking a blood sample and measuring the levels of a waste product called creatinine and taking into account your age, gender and ethnic group. The result is similar to the percentage of normal kidney function.

<http://www.nhs.uk/Conditions/Kidney-disease-chronic/Pages/Diagnosis.aspx>