Title page

TITLE:

A comparison of medication adherence/persistence for asthma and chronic

obstructive pulmonary disease in the United Kingdom

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Abstract

AIM: To describe and compare adherence and persistence with inhaled therapies in patients with asthma or COPD in the United Kingdom (UK).

METHODS: A retrospective prescribing database cohort was obtained from 44 general practitioner surgeries in NHS Forth Valley Scotland. Patients with physician-diagnosed asthma or COPD who received inhaled therapy between January 2008 and December 2009 were included. Four classes of inhaled therapy were assessed: inhaled corticosteroids; long-acting beta-agonists; combination therapy inhalers and; long-acting muscarinic antagonists. Adherence was calculated using the medication possession ratio (MPR) and persistence was determined using Kaplan-Meier survival analysis for the time to discontinuation (TTD) over one year. Two step-wise logistic regressions were performed to assess the contribution of diagnosis to adherence/persistence.

RESULTS: 12,923 patients were included in the analysis: 10,177 patients with asthma and 2,746 patients with COPD. 24.8% of medication episodes for asthma and 45.0% of medication episodes for COPD were classified as having an adequate medication supply (MPR of 80-120%). The overall median TTD was 90 days (IQR: 50-184 days) for patients with asthma and 115 days (58-258 days, comparison p<0.001) for patients with COPD. Patients with COPD were found to be more likely to achieve an MPR of at least 80% (OR: 1.32, 95% CI: 1.20-1.46), but had a similar likelihood of persistence at one year to patients with asthma.

CONCLUSION: Adherence and persistence with respiratory therapies in the UK is relatively low. There is suggestion that patients with COPD may display more adherent behaviours than patients with asthma.

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What is already known about this topic:

- Patients with respiratory disease are particularly likely to have poor adherence to medicines due to complex medication regimens and difficulty using inhaler devices.

- It is unknown whether patients with asthma and COPD have different medication use behaviours.

What this article adds:

- Adherence for maintenance inhaler therapies in respiratory disease is low, but higher among patients with COPD compared to patients with asthma.

- Less than 20% of patients in this UK cohort with respiratory disease remained persistent with inhaled therapy at one year.

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Main text

INTRODUCTION:

Medication adherence refers to the degree to which a patient's medication-taking behaviour coincides with agreed medical advice, and largely has supplanted the term 'compliance,' which infers a clinician-directed therapy decision without patient input.[1] Medication persistence examines whether a patient follows the recommendation of continuing treatment for a prescribed length of time.[2] According to the World Health Organization (WHO), approximately half of patients across the world are non-adherent with treatment prescribed for chronic disease, leading to decreased treatment effectiveness, decreased patient quality of life, and increased healthcare costs.[1] As clinical research develops new therapies for patients with chronic disease it is important to identify and optimise medication taking behaviours.[3-4]

Treatment non-adherence in respiratory disease is particularly common. For patients with asthma, reported non-adherence rates range from 30-70%[5] and are thought to contribute significantly to the prevalence of severe refractory disease.[6] Most studies quantifying adherence in asthma have focused on children although adults are of equal concern as non-adherence occurs across all demographic categories.[7] In patients with chronic obstructive pulmonary disease (COPD), complex medication regimens and multiple comorbidities result in adherence rates of approximately 50%.[8] A lack of perceived benefit led to 30% of patients with COPD intentionally discontinuing their therapy in one analysis.[9] For both conditions, rates of non-

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adherence reported in clinical trials are likely to be underestimated due to the type of patients selected for trials and the influence of the trial environment itself.

Respiratory disease presents a unique challenge for patient adherence/persistence. In addition to the common barriers that all patients with chronic disease face, a number of device-related factors complicate the situation, including dislike of inhaled formulations, improper inhaler technique, and need for additional equipment such as spacers.[10] Of additional importance is how patients perceive their disease in terms of severity and awareness,[11] which for respiratory disease – with a variable symptom time course in asthma, and misunderstanding of disease symptoms as 'normal' in COPD – is an important contributor.

Almost all available respiratory medications are utilised in the treatment of both asthma and COPD. Accordingly, some studies have analysed adherence jointly without regard to diagnosis,[12-13] despite the different pathology, symptoms and management of each condition. To our knowledge, no single analysis has compared the differences in respiratory medication utilisation between patients with asthma or COPD, and accordingly, the aim of this study was to describe and compare adherence and persistence with inhaled therapies for patients with physician-diagnosed asthma and COPD in the United Kingdom (UK).

METHODS:

Patients

The present study is a retrospective database cohort analysis of prescribing data from National Health Services (NHS) Forth Valley in Scotland. Data were provided

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by the NHS Forth Valley Airways Managed Clinical Network in coordination with the

E-PRS clinical recording tool program (Campbell Software Solutions©, Irvine, UK). E-

PRS was designed as a computer-integrated clinical audit program to improve

clinical care at practice level (described elsewhere[14]) but in short, collectively

formed a database of patients with physician-diagnosed asthma and/or COPD

treated in 44 general practitioner (GP) surgeries from 2007 to 2009. The reference

health board covers a geographic population of nearly 300,000 patients, while the

database contains information on approximately 22,000 distinct patients with

physician-diagnosed asthma/COPD. The departmental ethics group at the University

of Strathclyde determined no formal ethics review was needed for use of the dataset.

Patients (children and adults) included in the analysis had (1) a GP-recorded

diagnosis of asthma or COPD, and (2) at least one prescription issued for a

qualifying inhaled maintenance medication between January 1, 2008, and December

31, 2009 (the study period), including inhaled corticosteroids (ICS), long-acting beta

agonists (LABA), ICS/LABA combination therapy inhalers, or long-acting muscarinic

antagonists (LAMA). Patients were assessed separately by diagnosis, and patients

with a recorded dual-diagnosis of asthma and COPD were excluded from the

analysis. Demographic characteristics for each group were assessed, including age,

sex, maintenance medications received, and the proportion of patients who were

prescribed reliever medications (short-acting beta agonists [SABA] and oral

corticosteroids [OCS]) during the study period.

Adherence

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Medication adherence was assessed by calculating the medication possession ratio

(MPR) for each class of maintenance therapy received. Similar to other

analyses,[12,15-16] MPR was calculated by summing the days of medication supply

provided and dividing by the total time treated:

$$\text{MPR} = \frac{\text{total days of medication supply}}{\text{days between first and last fills}} \times 100\%$$

Medication supply was calculated according to the posology and inhaler size (e.g.

60-dose inhaler with prescriptive instructions of 1 inhalation twice daily = 30 days

supply) for each prescription. A sequence of at least two prescriptions during the

two-year study period was required to calculate an MPR. The calculation was

specific to therapeutic class, but not to dose or individual pharmacological agent.

Thus, a patient receiving sequential treatment with two different ICS inhalers (e.g.

fluticasone switched to beclometasone) or having a change in the dose mid-therapy

would have a single MPR calculation. However, a single patient may have multiple

MPRs if they received medications from more than one therapeutic class, such as

treatment with an ICS changed to treatment with a combination therapy inhaler. After

individual MPRs were calculated for each patient and medication, they were

aggregated by therapeutic class: ICS, combination therapy inhalers, LABA (for

patients with asthma or COPD), and LAMA (only for patients with COPD). The use of

LAMA was not quantified for patients with asthma due to a lack of treatment

recommendation in prevailing clinical guidelines. The proportion of patients having

achieved an adequate medication supply, defined as an MPR between 80 and

120%,[17] was also determined; MPRs less than 80% or over 120% were defined as

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undersupply or oversupply, respectively. The amount of SABA (in doses/day)

prescribed during each MPR was also quantified. This was achieved by summing the

number and size of SABA inhalers to determine the number of total SABA doses

prescribed, and then dividing by the number of days over which the maintenance

inhaler was prescribed (the denominator of the MPR calculation).

Persistence

Medication persistence was evaluated using a refill-sequence model and defined as

the difference in time between the first prescribing of a medication during the study

period and either the last prescribing, or an non-permissible gap in therapy

(whichever occurred first).[18-19] A patient was considered to have an unacceptable

gap if they failed to receive a prescription within 30 days after their previous

medication supply was due to run out. Patients were also classified by whether they

were on new or established therapy during the study period; patients were

considered to be on 'new' therapy if they had no history of being prescribed an agent

in the specified therapeutic class in the six months prior to the start of the study

period. At least one prescription for a maintenance medication during the first year of

the two-year study period was required to enable accurate calculation of a one-year

persistence rate. Median time to discontinuation (TTD) for each patient by

therapeutic class was calculated using a Kaplan-Meier survival analysis, with a time

censor utilised at one year post-medication initiation.

Statistical analysis

Two binary logistic regression models were utilised to separately assess predictors

of adherence and persistence. For adherence, the outcome of interest was

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achievement of an MPR of at least 80% (including both adequate supply and

oversupply); this binary measure was chosen over a continuous measure since

oversupply does not confer any demonstrable therapeutic benefit over adequate

supply. For persistence, a *post hoc* consideration of the Kaplan-Meier results

suggested a non-proportionality of hazards over time; therefore, logistic regression

(with an outcome of interest of persistence past 100 days of therapy) was utilised

over a Cox regression analysis. Patient- and treatment-related variables of interest

(age, sex, diagnosis, therapeutic class of medication) were assessed first in

univariate fashion; SABA and OCS utilisation (doses/day and receipt [yes/no],

respectively) during the study period were also entered in adherence model to

include a measure of disease control, and classification of treatment as

new/established therapy was utilised in the persistence model. Significant variables

from the univariate analysis were filtered into the final forward stepwise multivariate

models, with α set at 0.05 for entry and 0.10 for removal. Results were reported with

odds ratios (OR) and 95% confidence intervals (CI).

Minitab® 16 statistical software (Minitab Ltd., Coventry, UK) was used for analysis. A

Mann-Whitney test was used to compare differences between continuous measures

(median age, median doses/day of SABA), while chi-squared tests were used to

assess categorical differences (demographics, classification of medication supply). A

Wilcoxon test was used to test for differences in persistence as assessed by the

Kaplan-Meier analysis. A Bonferroni correction was applied to minimise error

resulting from multiple comparisons when appropriate.

RESULTS:

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Patient characteristics

A total of 12,923 patients were included in the analysis, 10,177 patients with asthma

and 2,746 patients with COPD (**Table 1**). Patients with asthma were more likely to

be female, and the median age of patients was predictably younger and more

variable than those with COPD. More patients with asthma (8873; 87.2%) than with

COPD (2746; 65.4%) were treated with a single therapeutic class of medication

during the study period (p<0.001). Patients with either disease were prescribed

SABA in similar proportions, although the use of OCS was greater among those with

COPD. A total of 17,354 episodes of maintenance medication use were assessed:

11,618 for asthma patients and 5,736 for COPD patients.

Medication adherence

Overall 24.8% (95% confidence interval [CI]: 24.0-25.6%) of medication episodes for

asthma and 45.0% (95% CI: 43.7-46.3%) of medication episodes for COPD were

classified as an adequate supply (p<0.001 for comparison). The proportion of

patients with an adequate MPR also varied according to therapeutic class (**Table 2**).

Adequate supply was highest for LAMA inhalers in patients with COPD at 52.2%;

patients with COPD had higher incidence of adequate supply and lower incidence of

undersupply for all three therapeutic classes available for comparison. Undersupply

accounted for approximately one-third to one-half of all episodes, with all therapies

for patients with asthma having an undersupply rate of greater than 50%. Oversupply

of medication was particularly common for prescribing of ICS in both diseases, at

27.0% for asthma and 34.8% for COPD.

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In the logistic regression for adherence, both male sex and increasing age were associated with higher odds of achieving an MPR of at least 80% (**Table 3**). Both a diagnosis of COPD and treatment with LAMA were associated with higher odds, although these effects were softened in the multivariate analysis with inclusion of other variables. The number of doses/day of SABA prescribed during the study period increased alongside MPR, with each additional dose/day correlating to an 11% increase in the odds of achieving an adequate MPR; receiving a prescription for OCS was also associated with an increased odds of an adequate MPR, although this effect failed to meet significance for inclusion in the multivariate model.

Medication persistence

For asthma, the overall median TTD was 90 days (IQR: 50-184 days) and for COPD, the overall median TTD was 115 days (IQR: 58-258, comparison p<0.001); the percentage of patients persisting at one year was 11% and 16% for asthma and COPD, respectively (**Figure 1**). Persistence by therapeutic class was greater for patients with COPD than asthma for both LABA (96 vs. 61 days, p=0.008) and combination inhalers (116 vs. 85 days, p<0.001), but similar for ICS (101 vs. 100 days). The highest persistence overall was seen for LAMA inhalers in COPD, with a median TTD of 123 days and 18% of patients persisting after one year.

In the logistic regression for persistence, male sex and age were associated with higher odds of persisting past 100 days of therapy (**Table 4**). Therapy with a LAMA or ICS produced the similarly highest odds among therapeutic classes, but diagnosis

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failed to meet significance for inclusion in the final model. Newly initiated therapy was associated with 19% lower odds of persisting past 100 days, compared to patients on already established therapy.

DISCUSSION:

The current analysis demonstrates a relatively low rate of adherence/persistence for inhaled therapies for the treatment of respiratory disease, and reveals that among use of the same medications, patients with asthma and COPD display different medication use behaviour.

Less than one-quarter of patients with asthma and less than one-half of patients with COPD were classified as having an adequate medication supply. Other studies using administrative dispensing databases have demonstrated similar rates to those found in this prescribing analysis.[12-13,15-16,20-21] However, to the best of our knowledge, no single analysis has demonstrated enhanced adherence among patients with COPD for the same inhaled therapies within an adjusted analysis. There is evidence that patients with COPD display more adherent behaviours as they age,[22] and similarly our analysis found that age over 40 years is an independent contributor to having an adequate medication supply. However, older patients also face unique barriers that complicate medication adherence and may not be captured with prescribing data, including cognitive decline, lack of dexterity and polypharmacy.[23] Patients with COPD may also experience more consistent and severe disease symptomology, and may be inclined to be more adherent than patients with asthma. Although the inclusion of patients prescribed more than

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reliever therapy would presume that the population studied had a chronic form of asthma, the natural episodic time course of patient symptoms in asthma may have resulted in sporadic treatment periods interlaced with drug-free intervals, rendering a lower level of overall adherence.

Adherence to prescribed therapy has been shown to have an association with disease outcomes in respiratory disease, resulting in lower rates of emergency room visits and hospitalisations.[24-26] Other measures of disease control, such as exacerbation rates, may be less sensitive and require high levels of adherence to provide noticeable improvement.[27] Our multivariate analysis found that patients with higher level prescribing of SABA reliever therapy were more likely to have higher level prescribing of their maintenance therapy, a relationship that has been detected previously.[15,28] It may be expected that a high use of reliever therapy should correspond with poor adherence to maintenance therapy; accordingly, it has been suggested previously that symptomatic patients may have a weaker sense of control and ownership of their illness, resulting in lower motivation and overall medication adherence.[29] However, the direction of causation in the relationship between reliever and maintenance therapy is unclear, as patients who are symptomatic as defined by increased use of reliever therapy may be inclined to develop better adherence to their maintenance therapy.[1] The perceived necessity of a medication by the patient has also been shown to correlate with adherence[29] and the relative severity of the disease consequences[11,30] may further complicate the situation.

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More than 80% of patients failed to remain on prescribed therapy at 12 months post-initiation, not unlike an analysis of Canadian claims data that found a range of 47 – 93% for non-persistence at one year among inhaled therapies.[31] Medication persistence calculations are sensitive to how stringent the definition is for an allowable medication gap. The current analysis set this threshold at 30 days; a *post hoc* sensitivity analysis extending this gap to 60 days increased the overall median TTD to 114 days (20% persisting at one year) for asthma and 152 days (22% persisting at one year) for COPD, respectively (data not shown). Despite these results, the enhanced effect of COPD diagnosis seen in the regression for adherence failed to replicate in the regression for persistence. Medication persistence is not only a measure of long-term adherence, but also of treatment stability, as the TTD may be influenced by patients with therapy changes, such as for patients with asthma 'stepping up' from ICS therapy alone to ICS/LABA combination inhaler therapy. The percentage of patients treated with more than one class of maintenance therapy was significantly higher among patients with COPD than with asthma and likely softened the effect of both COPD diagnosis and treatment with LAMA in the multivariate regression for persistence – both variables that were significant on a univariate basis, and significant within the adherence regression. The shape of persistence curves and the further lessened persistence among patients with newly initiated therapy suggests that the overall low persistence is primarily influenced by the large drop-off of patients early in therapy, often after the first couple of prescriptions. Accordingly, initiation of therapy appears to be an appropriate target for promoting good medicine use in patients with respiratory disease. Although no single set of interventions has been successful in consistently

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improving adherence, [3] our results would suggest that research should focus

efforts during the first three months of therapy.

Among the inhaled therapies assessed, LAMAs were associated with the best

adherence/persistence, which may be a function of the increased convenience of

once-daily dosing.[32] Medication adherence is known to decrease as dosing

frequency increases,[33] and all other therapies in the present analysis have a

standard twice-daily dosing regimen. Therapy with an ICS had the lowest percentage

of patients (with either disease) identified as having an adequate level of medication

supply (MPR 80-120%), but was also found to have a comparatively high rate of

adherence/persistence in the regression analyses. For adherence, this was likely

influenced by the inclusion of oversupply in the binary outcome, but for persistence,

the reasons are less clear. There may have been some influence of inhaler size on

the results, as most available combination therapy inhalers and LABAs are packaged

in 60-dose or 120-dose units, largely corresponding to a 30-day supply per inhaler.

However, the most commonly utilised ICSs in this analysis are supplied in 200-dose

units, which may correspond to as much as a 100-day supply for a single inhaler.

This may have led to higher odds of persistence for ICS within our calculations, as a

single prescribing event provides a longer medication supply. An additional point to

consider is the effect that ICS dose titration may have on adherence and

persistence. It is possible that clinicians may initially prescribe a higher dose of ICS

(or a higher number of puffs from an inhaler) which is then scaled back based on the

patient's symptoms; this may explain some variation in the results.

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There are several limitations with the current study. All database studies estimate

adherence/persistence as it is not always feasible to obtain serum drug

concentrations or individually assess patients in large numbers. Access to

medication is used as a proxy for adherence in this study and thus we are unable to

discern whether the patient actually takes the medication or if he/she uses an inhaler

device correctly; therefore, by definition the results are ceiling estimates.

Furthermore, the current study used prescribing data obtained from the GP.

Prescriptions are generally written for an initial supply, and a patient only continues

therapy by obtaining a new prescription, either by visiting the GP themselves, or

more commonly through a 'managed repeat' service where the pharmacist

communicates with the GP for further supply. While the first prescription is initiated

by the GP, there is a great degree of patient-initiated action required for follow-up

supply, which may influence the large-drop off seen early in therapy. Similarly,

hospitalisations, particularly for patients with COPD may lead to changes or

disruptions in therapy that effect the calculations. Lastly, the regression models

provide an indication of the variables when considered together, but indicate (via the

c-statistic) that other variables that were unable to be accounted for within this

analysis likely have an effect on the outcome; however, this modest fit is a common

finding among adherence studies.[34] In particular, in a prescribing database, we

were unable to correlate the results of the regression with clinical outcomes, such as

hospitalisations and overall disease control. However, we attempted to include a

proxy for symptoms by quantifying SABA and OCS utilisation among patients.

In conclusion, adherence and persistence with respiratory therapies in this UK cohort

was relatively low. There is indication that patients with COPD may display more

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adherent behaviours than their counterparts with asthma. Efforts to increase

medication persistence should likely be targeted to focus follow-up efforts during the

first months of therapy.

AUTHOR CONTRIBUTIONS:

JRC and ABM came up with the concept and designed the study. JRC, BFJ, ABM

and DTS analysed the study data. ACB, FW and MR interpreted the results. JRC

drafted the manuscript, and all authors critically reviewed and approved the

manuscript. ACB is the guarantor.

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Table 1: Patient characteristics

n (%) unless otherwise stated	Asthma (n=10,177)	COPD (n=2746)
Male sex	4317 (42.4)	1367 (49.8) ‡
Median age, years (IQR)	41 (22 – 57)	70 (63 – 77) ‡
< 20 years	2204 (21.7)	0 (0)
20-39 years	2561 (25.2)	7 (0.3)
40-59 years	3235 (31.8)	418 (15.2)
60-80 years	1900 (18.7)	1853 (67.5)
≥ 80 years	277 (2.7)	468 (17.0)
Therapies received		
ICS	6520 (64.1)	682 (24.8) ‡
CMB	4087 (40.2)	1504 (54.8) ‡
LABA	874 (8.6)	274 (10.0) †
LAMA	N/A	1736 (63.2)
Received SABA	9456 (92.9)	2534 (92.3)
Received OCS	2426 (23.8)	1179 (42.9) ‡

CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; IQR: interquartile range; n: number; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids; SABA: short-acting beta agonists
† indicates p<0.05 for comparison with asthma group
‡ indicates p<0.001 for comparison with asthma group

Table 2: Medication supply as assessed by MPR, by therapeutic class and diagnosis

n (%)	ICS ‡		LABA ‡		CMB ‡		LAMA
	Asthma	COPD	Asthma	COPD	Asthma	COPD	COPD
Undersupply	3156 (50.4)	250 (34.2)	466 (57.6)	163 (44.9)	2385 (52.5)	833 (39.6)	768 (30.3)
Adequate	1414 (22.6)	227 (31.0)	220 (27.2)	122 (33.6)	1247 (27.4)	909 (43.2)	1324 (52.2)
Oversupply	1692 (27.0)	255 (34.8)	123 (15.2)	78 (21.5)	915 (20.1)	363 (17.2)	444 (17.5)

CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; n: number; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist
‡ indicates p<0.001 for comparison within therapeutic class

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Table 3: Results of logistic regression for adherence

Variable	Crude OR (95% CI) †	Adjusted OR (95% CI) ‡§	Adjusted OR p-value
Sex			
Female	1 (reference)	1 (reference)	0.013
Male	1.15 (1.08 – 1.23)	1.09 (1.02 – 1.16)	
Age			
0-19 years	1 (reference)	1 (reference)	<0.001
20-39 years	1.03 (0.93 – 1.15)	0.94 (0.84 – 1.06)	
40-59 years	1.27 (1.16 – 1.41)	1.17 (1.06 – 1.30)	
60-79 years	1.85 (1.68 – 2.03)	1.51 (1.35 – 1.69)	
80+ years	2.04 (1.75 – 2.37)	1.60 (1.35 – 1.89)	
Diagnosis			
Asthma	1 (reference)	1 (reference)	<0.001
COPD	1.99 (1.86 – 2.12)	1.32 (1.20 – 1.46)	
Therapeutic class			
ICS	1 (reference)	1 (reference)	<0.001
LABA	0.83 (0.73 – 0.94)	0.68 (0.59 – 0.77)	
CMB	1.02 (0.96 – 1.09)	0.87 (0.81 – 0.94)	
LAMA	2.19 (1.98 – 2.42)	1.33 (1.17 – 1.52)	
SABA (doses/day)	1.11 (1.10 – 1.12)	1.11 (1.10 – 1.12)	<0.001
OCS			
No	1 (reference)	N/A	0.824
Yes	1.24 (1.16 – 1.31)		

CI: confidence interval; CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; N/A: not applicable; OCS: oral corticosteroids; OR: odds ratio; SABA: short-acting beta agonist

† univariate analysis with MPR ≥ 80% utilised as outcome

‡ multivariate analysis adjusted by sex, age, diagnosis, therapeutic class and SABA utilisation, with MPR ≥ 80% utilised as outcome

§ model fit assessed by c-statistic: 0.68 (95% CI: 0.67-0.69)

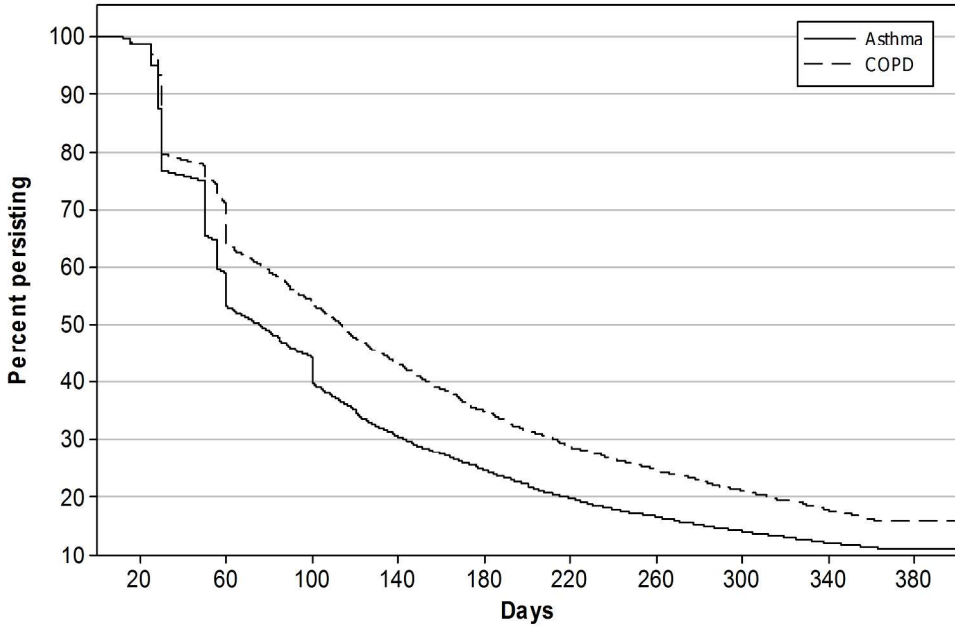**Table 4**: Results of logistic regression for persistence

Variable	Crude OR (95% CI) †	Adjusted OR (95% CI) ‡§	Adjusted OR p-value
Sex			
Female	1 (reference)	1 (reference)	<0.001
Male	1.14 (1.07 – 1.21)	1.14 (1.07 – 1.21)	
Age			
0-19 years	1 (reference)	1 (reference)	<0.001
20-39 years	0.91 (0.82 – 1.01)	0.97 (0.87 – 1.08)	
40-59 years	1.09 (0.99 – 1.21)	1.17 (1.06 – 1.29)	
60-79 years	1.48 (1.35 – 1.63)	1.58 (1.43 – 1.75)	
80+ years	1.53 (1.31 – 1.79)	1.61 (1.37 – 1.90)	
Diagnosis			
Asthma	1 (reference)	N/A	0.444
COPD	1.31 (1.22 – 1.41)		
Therapeutic class			
ICS	1 (reference)	1 (reference)	<0.001
LABA	0.66 (0.58 – 0.74)	0.60 (0.53 – 0.68)	
CMB	0.89 (0.83 – 0.95)	0.81 (0.76 – 0.88)	
LAMA	1.23 (1.11 – 1.37)	0.94 (0.84 – 1.06)	
Type of therapy			
Established	1 (reference)	1 (reference)	<0.001
New	0.78 (0.72 – 0.84)	0.81 (0.75 – 0.87)	

CI: confidence interval; CMB: combination therapy inhaler; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; N/A: not applicable; OR: odds ratio

† univariate analysis with persistence > 100 days utilised as outcome

‡ multivariate analysis adjusted by sex, age, therapeutic class and type of therapy, with persistence > 100 days utilised as outcome

§ model fit assessed by c-statistic: 0.57 (95% CI: 0.56-0.58)

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Kaplan-Meier survival curves for 1-year medication persistence for asthma and COPD patients overall