Original Article

Investigating the Association Between Biologic Initiation and Medication Adherence in Severe Asthma: An Analysis of Linked Data

Amy Shackleford, MSc[a], Liam G. Heaney, MD[a,b], P. Jane McDowell, PhD[a,b], Gwyneth A. Davies, MD[c], Claire Butler, PhD[b], Joan Sweeney, PhD[b], and John Busby, PhD[a] *Belfast and Swansea, United Kingdom*

What is already known about this topic? Poor adherence to inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) is common in patients with severe asthma and is associated with poorer clinical outcomes. However, the impact of biologic initiation on adherence and downstream clinical outcomes while on biologics remains unclear.

What does this article add to our knowledge? The introduction of biologics had little impact on population-level adherence; however, there were substantial changes in individual patients. Poorer adherence to ICS/LABA was associated with higher exacerbation rates and fractional exhaled nitric oxide for biologic-treated patients in the long term.

How does this study impact current management guidelines? Regular counseling on the importance of inhaled therapy adherence is required for patients receiving biologics. Poorer adherence is associated with worse clinical outcomes but is potentially modifiable through novel interventions.

BACKGROUND: Poor adherence to inhaled therapy is common among patients with asthma. Findings from previous studies exploring inhaled corticosteroid (ICS) adherence in biologic-treated populations are inconsistent and have not investigated the long-term outcomes.

OBJECTIVE: To assess the long-term impact of introducing biologics on ICS/long-acting β_2-agonist (LABA) adherence and to investigate the effect of poor ICS/LABA adherence on clinical outcomes among biologic-treated patients.

METHODS: A retrospective cohort study of adults who attended the Northern Ireland Regional Severe Asthma center between September 2015 and November 2021 was performed. Medication possession ratios (MPRs) for ICS/LABA medication were calculated using community dispensing records. Good adherence was defined as an MPR ≥75%. We compared adherence before and after biologic initiation, examined the correlates of adherence, and used multivariable longitudinal models to assess the impact of adherence on asthma outcomes.

RESULTS: Of 207 included patients, 58 (28.0%) had suboptimal adherence before biologic initiation. This was associated with higher deprivation (43.1% vs 25.2%; $P = .012$) and fractional exhaled nitric oxide (50 vs 32 parts per billion; $P = .043$). Population-level MPRs were stable during the study; however, adherence varied for individual patients. A total of 69 (33.3%) patients had poor adherence 1 year after biologic initiation. Although a substantial reduction in exacerbation rates was seen for both groups after biologic initiation, those with good adherence had an additional 17.4% (95% confidence interval: 2.2%, 30.2%) reduction in exacerbations compared with those with poor adherence. We found no difference in asthma symptoms or lung function.

CONCLUSIONS: The introduction of biologics had little impact on population-level adherence; however, there were substantial changes for individual patients. Good adherence to ICS/LABA was associated with lower exacerbation rates among biologic-treated patients with severe asthma. © 2025 The Authors. Published by Elsevier Inc. on behalf of the American

[a]School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, United Kingdom

[b]Belfast Health and Social Care Trust, Belfast, United Kingdom

[c]Population Data Science, Swansea University Medical School, Swansea, United Kingdom

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Corresponding author: John Busby, PhD, Centre for Public Health, Queen's University, Belfast BT12 6BA, United Kingdom. E-mail: john.busby@qub.ac.uk.

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Abbreviations used
ACQ-5- Asthma Control Questionnaire 5
ATS- American Thoracic Society
CI- Confidence interval
ED- Emergency department
ERS- European Respiratory Society
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
HCRU- Health care resource utilization
ICS- Inhaled corticosteroids
IQR- Interquartile range
LABA- Long-acting β_2-agonist
MPR- Medication possession ratio
OCS- Oral corticosteroids
SD- Standard deviation
T2- Type 2

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Asthma is a heterogeneous respiratory disease affecting approximately 300 million individuals globally.[1] Around 5% to 10% of patients have severe disease,[2] defined as asthma requiring maximally optimized inhaled treatment for control or asthma, which remains uncontrolled despite this treatment,[1] which disproportionately contributes to asthma morbidity and costs.[3] Known to be efficacious in suppressing airways inflammation, inhaled corticosteroids (ICS) are a standard treatment used across the spectrum of asthma severity and are often prescribed as ICS/long-acting β_2-agonist (LABA) combination inhalers for severe asthma. Poor adherence has been consistently demonstrated among a substantial proportion of patients with difficult and severe asthma,[4,5] with evidence that it contributes to poorer outcomes, including increased exacerbation rates and reduced lung function.[6,7]

Over the last few decades, the increasing knowledge of the underlying inflammatory pathways in asthma has led to the development of monoclonal antibodies. These target several effector molecules of the inflammatory cascade allowing greater disease control, minimizing oral corticosteroid (OCS) exposure, preventing accelerated lung function decline,[8,9] and enabling a minority of patients with severe asthma to achieve clinical remission.[10] Given that poorer inhaler adherence is associated with a belief that the inhaled therapies are unnecessary,[11] there is some concern that patients may reduce their adherence to background inhaled anti-inflammatory treatment on the initiation of highly effective biologics. Previous work has demonstrated that poor ICS adherence after commencement of biologic therapies was associated with an increase in exacerbations;[12] however, this study was limited by the cross-sectional assessment of adherence and outcomes, the short-term follow-up, and baseline imbalance between study groups.

This study aimed to assess the long-term impact of biologic initiation on ICS/LABA adherence and investigate the effect of ICS/LABA adherence on clinical outcomes among biologic-treated patients.

METHODS

Study design and patient population

This was a single-arm observational cohort study set within the Northern Ireland Regional Severe Asthma service. Eligible patients first attended the clinic between September 2015 and November 2021, met European Respiratory Society (ERS)/American Thoracic Society (ATS) severe asthma criteria, and received their first biologic within the clinic. Patients were excluded if their biologic start date was unknown, study entry was less than 1 year before biologic introduction, study exit date was less than 1 year after index date, and clinical data were not available at the time of biologic prescription (or within 60 days prior) or at annual review (between 6 and 18 months after biologic initiation). The index date was the date of first biologic treatment. Patients exited the cohort on December 2, 2022, the date data were last extracted from the clinic. Within the clinic, data are collected on patient demographics, medical history, lung function, asthma treatment, and symptom burden at baseline and annual review. Data from the clinic were linked to the Northern Ireland Honest Broker Service, which provided population-wide data on community dispensed medication, emergency department (ED) visits, hospital admissions, and sociodemographic data.

Exposures, outcomes, and covariates

ICS adherence was calculated for each year using the variable medication possession ratio (MPR). The annual MPR is a commonly used measure of medication adherence and was calculated by dividing the number of days of ICS/LABA supply in the year by 365.[13] Detailed dosing information was not available within the study dispensing records, and so this was imputed using the most common dosage for each inhaler type (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Where possible, annual MPRs were calculated from 3 years before biologic initiation to 4 years after biologic introduction. MPRs were truncated at 150% as larger measures were thought to be infeasible. An MPR $\geq$75% was defined as good adherence in line with previous work by d'Ancona et al.[12,14]

Biologic information, including medication start and stop dates, were extracted from the clinic and defined as a prescription of omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab. Socioeconomic status was measured using the quintile of the 2017 Northern Ireland Multiple Deprivation Measure. Exacerbations were asthma episodes requiring rescue systemic corticosteroids. Asthma hospitalization was any admission with a primary diagnosis of asthma (International Classification of Diseases, 10th Revision, code: J45), and asthma ED visits were those that included the word "asthma" within the diagnosis field. Spirometry measures were assessed following the ERS/ATS guidelines, and percentage predicted values were calculated using the GLI 2012 multiethnic reference values.[15] Patient-reported outcomes were measured using the Asthma Control Questionnaire (ACQ-5) for symptoms and the EQ-5D-5L for health-related quality of life. Follow-up data were collected in the clinic annually.

Statistical analysis

Descriptive statistics were calculated using means (standard deviation [SD]), medians (interquartile range [IQR]), and counts (percentage). We compared patient demographic and clinical characteristics by adherence in the year before biologic-therapy initiation (<75% vs $\geq$75%) and a year after biologic introduction (<75%

TABLE I. Baseline patient characteristics, stratified by the medication possession ratio (MPR) in the year before biologic introduction

Characteristics	All patients	MPR		*P* value
		Poor (<75%)	Good (≥75%)	
No. of patients	207	58	149	
MPR at baseline (%)	92 (32)	55 (18)	106 (25)	
Demographics				
Female	123 (59.4%)	37 (63.8%)	86 (57.7%)	.424
Age (y)	54.4 (12.9)	52.5 (12.3)	55.1 (13.1)	.201
Age of onset (y)	26.5 (12.0, 40.0)	26.0 (13.0, 40.0)	27.5 (12.0, 40.0)	.819
Asthma duration (y)	25.6 (13.3, 37.6)	23.6 (13.3, 36.1)	25.7 (13.4, 37.8)	.622
Deprivation tertile				
1 (most)	62 (30.2%)	25 (43.1%)	37 (25.2%)	**.015**
2	74 (36.1%)	21 (36.2%)	53 (36.1%)	
3 (least)	69 (33.7%)	12 (20.7%)	57 (38.8%)	
Deprived	62 (30.2%)	25 (43.1%)	37 (25.2%)	**.012**
BMI (kg/m^2)	31.2 (6.7)	32.4 (8.2)	30.8 (6.0)	.123
Obese	108 (52.7%)	33 (56.9%)	75 (51.0%)	.448
Ever smoker	82 (39.8%)	23 (39.7%)	59 (39.9%)	.978
Atopic disease	59 (45.7%)	17 (43.6%)	42 (46.7%)	.747
HCRU (last year)				
Exacerbations	4 (3, 6)	4 (3, 7)	4 (2, 6)	.152
Any ED attendance	71 (34.5%)	24 (41.4%)	47 (31.8%)	.191
Any hospital admissions	59 (28.6%)	19 (32.8%)	40 (27.0%)	.413
Lung function				
FEV_1 (L)	2.1 (0.8)	2.1 (0.9)	2.1 (0.7)	.636
FEV_1 (% predicted)	69.8 (20.5)	69.5 (22.2)	70.0 (19.9)	.873
FVC (L)	3.2 (1.0)	3.3 (1.1)	3.2 (1.0)	.873
FVC (% predicted)	86.2 (17.6)	85.5 (18.5)	86.4 (17.3)	.747
FEV_1-FVC	64.0 (12.5)	64.2 (12.6)	63.9 (12.5)	.914
Patient-reported outcomes				
ACQ-5 score	2.9 (1.4)	3.0 (1.5)	2.8 (1.4)	.456
Uncontrolled asthma (ACQ-5 >1.5)	152 (78.8%)	47 (82.5%)	105 (77.2%)	.416
EuroQoL Utility	0.72 (0.45, 0.92)	0.72 (0.53, 0.92)	0.72 (0.41, 0.92)	.812
T2 biomarkers				
FeNO (ppb)	34 (21, 58)	50 (18, 85)	32 (21, 50)	**.043**
Blood eosinophil count ($N/10^9$ L)	0.34 (0.14, 0.56)	0.24 (0.13, 0.49)	0.38 (0.15, 0.57)	.071
Highest blood eosinophil count ($N/10^9$ L)	0.75 (0.60, 1.06)	0.78 (0.63, 1.22)	0.73 (0.60, 1.03)	.366
IgE (IU/mL)	115 (45, 320)	108 (45, 403)	119 (48, 305)	.800
Asthma medication				
Maintenance OCS		41 (70.7%)	107 (72.3%)	.818
Maintenance OCS (mg)	10 (8, 10)	10 (8, 12)	10 (8, 10)	.837
ICS dose (BDP equivalent [μg])	2000 (2000, 2000)	2000 (2000, 2000)	2000 (2000, 2000)	.981
Theophylline	53 (38.1%)	19 (46.3%)	34 (34.7%)	.197
LAMA	51 (36.4%)	14 (34.1%)	37 (37.4%)	.718
Leukotriene receptor antagonists	70 (50.0%)	18 (43.9%)	52 (52.5%)	.353
Maintenance macrolides	Censored	<10 patients	13 (8.8%)	.784
Nebulizer	32 (23.0%)	11 (26.8%)	21 (21.4%)	.490
SABA inhalers	10 (4, 18)	8 (3, 17)	10 (4, 18)	.287

Data are presented as n, mean (standard deviation), median (interquartile range), or n (%). Counts censored to prevent disclosure.
p-values in bold are significant at the 5% level.
ACQ-5, Asthma Control Questionnaire-5; *BMI*, body mass index; *BDP*, beclometasone dipropionate; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HCRU*, health care resource utilization; *ICS*, inhaled corticosteroids; *LAMA*, long-acting muscarinic antagonists; *OCS*, oral corticosteroids; *SABA*, short-acting β_2-agonist.

vs ≥75). Formal hypothesis tests were conducted using *t* tests, Kruskal-Wallis tests, and χ^2 tests as appropriate. We calculated mean MPRs and compared them with the year before biologic initiation using paired *t* tests. The proportion of patients achieving good adherence was also calculated for each year, with 95% confidence intervals (CIs) being calculated using the binomial distribution.

Multivariable analyses were conducted using linear (ACQ-5, EuroQoL, lung function, fractional exhaled nitric oxide [FeNO],

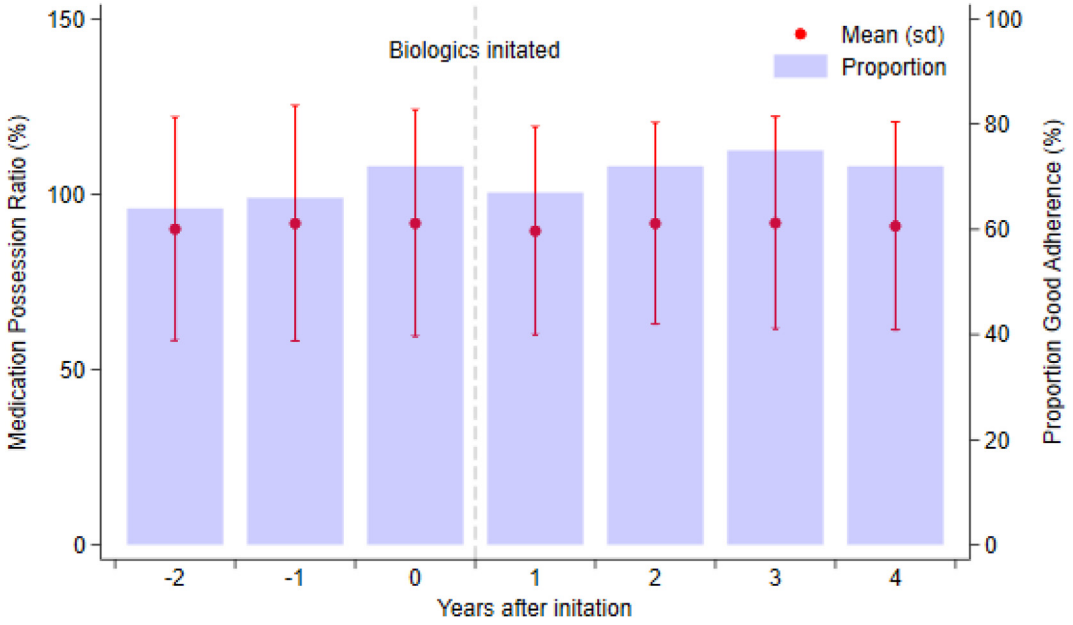

FIGURE 1. Medication possession ratio across 7 years of the study. Values are reported as mean (sd) and proportion (%) of good adherence (medication possession ratio ≥75%). *sd*, Standard deviation.

and blood eosinophil count), logistic (ED attendance and hospital admissions), and negative binomial (exacerbations) longitudinal models. These models implicitly adjusted for fixed patient-level factors; however, we additionally adjusted for study calendar year to account for temporal trends in study outcomes, including those that may have been driven by the COVID-19 pandemic. We chose this limited set of adjustment variables to prevent overadjustment bias, whereby variables that lie on the causal pathway between inhaler adherence and study outcomes are included in the model.[16] Each patient was included as a random intercept in the model, which allowed their responses to vary and appropriately accounted for the nonindependence of observations. Model coefficients, standard errors, and CIs were estimated comparing the difference between patients with poor and good adherence. The primary exposure of interest was annual MPR, which was included in the models as a binary covariate of good (MPR ≥75%) versus poor (MPR <75%) adherence. Previous methods have shown a significant correlation between change in FeNO and change in lung function in patients who reduce their ICS dose;[17] therefore, Spearman's rank correlation coefficient was used to assess whether this association was present in our study after 1 year on biologics. Stata 18 (TX) was used for all statistical analyses, and results adhered to Office for National Statistics disclosure guidelines.[18]

RESULTS

Cohort description and temporal trends in adherence

Of the 263 patients who met initial study criteria, 22 patients were excluded because of an unknown biologic start date and 34 patients were excluded because of an absence of clinical data at baseline or follow-up. The remaining 207 patients were eligible for this study (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org), with patient demographic and clinical data reported in Table I. Of note, these patients had a high burden of disease with high exacerbation rates (median: 4), impaired lung function (forced expiratory volume in 1 second [FEV_1]% mean: 69.8%), and high ACQ-5 score (mean: 2.9). Comorbidities were frequent, particularly gastroesophageal reflux disease (23.2%), nasal polyps (20.8%), hypertension (19.3%), and depression/anxiety (16.4%; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Over 80% of patients were initially prescribed mepolizumab, the first available anti−IL-5 during the follow-up period, and most remained on this medication throughout the study (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

At the population level, mean adherence and the proportion of patients with good adherence were stable across the 7 years of the study, with the mean MPRs ranging from 89.6% to 91.8%, and proportion of patients with good adherence ranging from 63.9% to 74.8% (Figure 1). Patients with good adherence before initiation of biologic therapy continued to be more adherent when on biologics (Figure E2 and Table E4, available in this article's Online Repository at www.jaci-inpractice.org); however, there was substantial variation in adherence at the individual patient level across the study. For example, of the 149 patients with good adherence in the year before biologic initiation, 32 (21.5%) had poor adherence by first annual review (Figure E2 and Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Prebiologic adherence

Fifty-eight (28.0%) patients had evidence of poor adherence (MPR <75%) in the year before biologic-therapy initiation. These patients were more likely to be from deprived areas (43.1% vs 25.2%; $P = .012$; Table I). They exhibited differences in type 2 (T2) biomarkers with significantly higher FeNO (50 vs 32 parts per billion; $P = .043$) and lower blood eosinophil counts (0.24 vs 0.38 $N/10^9$ L; $P = .071$) among those with poor adherence when compared with those with good adherence.

TABLE II. Patient characteristics at first-year follow-up, stratified by medication possession ratio (MPR) 1 year after biologic introduction

Characteristics	All patients	MPR		*P* value
		Poor (<75%)	Good (≥75%)	
No. of patients	207	69	138	
MPR at year 1 (%)	90 (30)	58 (15)	105 (22)	
$\Delta_{baseline}$	−2 (27)	−14 (24)	4 (26)	**<.001**
HCRU (last year)				
Exacerbations	1 (0, 3)	2 (0, 4)	1 (0, 2)	**.049**
$\Delta_{baseline}$	−3 (−5, −1)	−3 (−5, −1)	−3 (−5, −1)	.902
ED attendances	0 (0, 0)	0 (0, 0)	0 (0, 0)	.385
$\Delta_{baseline}$	0 (−1, 0)	0 (−1, 0)	0 (−1, 0)	.575
Hospital admissions	0 (0, 0)	0 (0, 0)	0 (0, 0)	.798
$\Delta_{baseline}$	0 (0, 0)	0 (0, 0)	0 (0, 0)	.853
Lung function				
FEV_1 (L)	2.2 (0.8)	2.1 (0.8)	2.2 (0.8)	.341
$\Delta_{baseline}$ (mL)	70.8 (431.3)	−44.8 (430.6)	130.8 (420.9)	**.006**
FEV_1 (% predicted)	73 (21.1)	71 (23.7)	74 (19.6)	.342
$\Delta_{baseline}$	3.2 (13.9)	0.3 (15.6)	4.7 (12.7)	**.031**
FVC (L)	3.3 (1.0)	3.2 (1.0)	3.4 (1.0)	.362
$\Delta_{baseline}$ (mL)	83.7 (451.2)	−18.7 (469.8)	136.1 (433.9)	**.021**
FVC (% predicted)	89.1 (17.7)	86.9 (19.2)	90.2 (16.8)	.215
$\Delta_{baseline}$	3 (12.2)	1.2 (13.2)	4 (11.5)	.123
Patient-reported outcomes				
ACQ-5 score	2.1 (1.4)	2.1 (1.5)	2.1 (1.4)	.904
$\Delta_{baseline}$	−0.8 (1.2)	−1.0 (1.2)	−0.7 (1.3)	.177
EuroQoL Utility	0.75 (0.49, 0.94)	0.75 (0.41, 0.90)	0.78 (0.53, 0.94)	.347
$\Delta_{baseline}$	0.00 (−0.07, 0.11)	0.02 (−0.08, 0.10)	0.00 (−0.07, 0.16)	.917
T2 biomarkers				
Blood eosinophil count ($N/10^9$ L)	0.06 (0.03, 0.10)	0.07 (0.03, 0.10)	0.06 (0.02, 0.10)	.44
$\Delta_{baseline}$	−0.24 (−0.49, −0.06)	−0.24 (−0.51, 0.00)	−0.24 (−0.49, −0.08)	.427
FeNO (ppb)	37 (21, 63)	44 (25, 73)	36 (21, 54)	**.047**
$\Delta_{baseline}$	0 (−15, 15)	6 (−18, 18)	−1 (−15, 15)	.307
Biologic response				
Reduced or discontinued OCS	Censored	>43 (>81.11%)	81 (86.2%)	.602
≥50% reduction in exacerbations	140 (77.3%)	47 (71.2%)	93 (80.9%)	.135
≥50% reduction in OCS use	112 (76.2%)	41 (77.4%)	71 (75.5%)	.803

Data are presented as mean (standard deviation), median (interquartile range), or n (%). Counts censored to prevent disclosure.
ACQ-5, Asthma Control Questionnaire-5; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HCRU*, health care resource utilization; *OCS*, oral corticosteroids.

There was no evidence of higher disease severity in the year before biologic initiation among patients with poor prebiologic ICS adherence, with similar exacerbation rates (4 vs 4; $P = .152$), asthma symptoms (ACQ-5: 3.0 vs 2.8; $P = .456$), and FEV_1% (69.5% vs 70.0%; $P = .873$).

Postbiologic adherence and clinical outcomes

Substantial improvements in clinical outcomes were present at first-year follow-up, with ACQ-5 scores reducing by a mean of 0.8 (SD: 1.2), exacerbations reducing by a median of 3 (IQR: 1, 5), FEV_1 increasing by a mean of 70.8 mL (SD: 431.3; Table II). Of the 147 patients on OCS at baseline with complete dosing information, 112 (76.2%) patients reduced their OCS dose by ≥50%. Overall, 69 (33.3%) patients had poor adherence 1 year after biologic initation. These patients had similar baseline characteristics when compared with those with good adherence, although they were less likely to be prescribed leukotriene receptor antagonists (38.5% vs 56.8%; $P = .036$; Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

In general, there was little evidence of differences in outcomes by postbiologic ICS/LABA adherence at first-year follow-up, with a similar reduction in symptoms (ACQ-5: 1.0 vs 0.7; $P = .177$), improvement in health-related quality of life (EuroQoL Utility: 0.02 vs 0.00; $P = .347$), and the proportion of patients achieving at least a 50% reduction in maintenance OCS use (77.4% vs 75.5%; $P = .803$) when comparing those with poor and those with good 1-year postbiologic adherence, respectively (Table II). Although the number of exacerbations at first-year follow-up was higher among those with poor postbiologic adherence (2 vs 1; $P = .049$), the median reduction from baseline was similar (3 vs 3; $P = .902$). At 1 year, there was some evidence of differences in lung function response, with substantial improvements in FEV_1 among those with good adherence, which were not replicated among those with poor adherence (130.8 vs −44.8 mL; $P = .006$). We found no

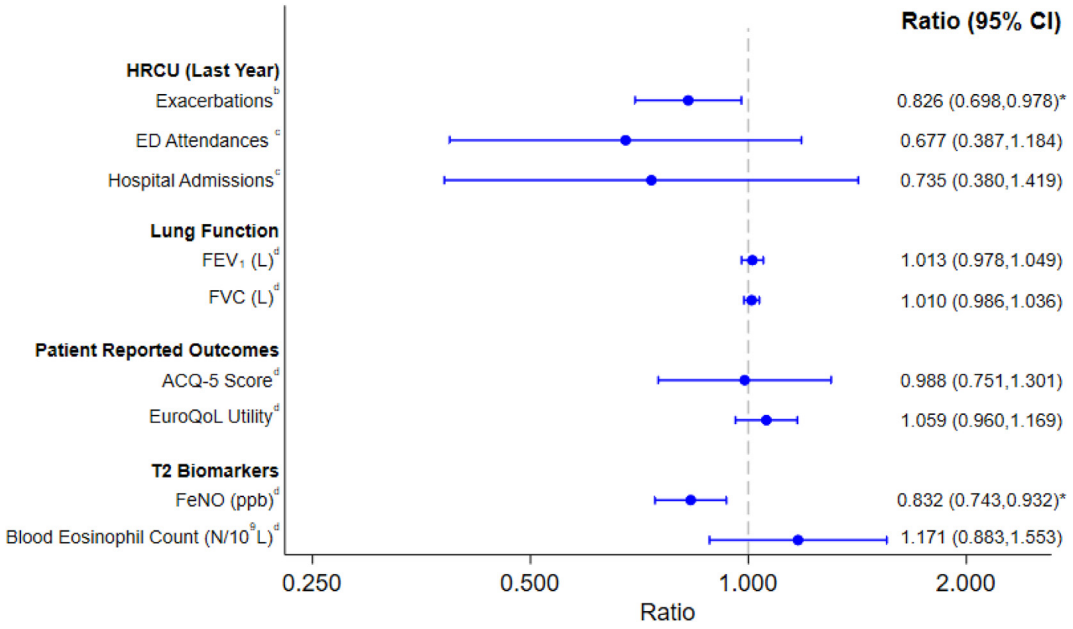

FIGURE 2. Multivariate regression comparing good (≥75%) versus poor (<75%) adherence and clinical outcomes. [a]Adjusted for biologic use and year. [b]Rate ratio. [c]Odds ratio. [d]Ratio. *Ratios significant at the 5% level. *ACQ-5*, Asthma Control Questionnaire-5; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity in 1 second; *HCRU*, health care resource utilization; *T2*, type 2.

correlation between change in FEV_1 and change in FeNO after 1 year on biologics (ρ: -0.055; $P = .446$).

In the multivariable analysis using all follow-up data (mean: 3.7 years), good adherence was associated with a decrease in FeNO (ratio: 0.832; 95% CI: 0.743, 0.932; $P = .002$) and a decrease in exacerbation rates (rate ratio: 0.826; 95% CI: 0.698, 0.978; $P = .026$; Figure 2, Table E6, available in this article's Online Repository at www.jaci-inpractice.org) when compared with those with poor adherence. There was evidence suggestive of a reduction in hospitalizations (odds ratio: 0.735; 95% CI: 0.380, 1.419; $P = .358$) and ED attendances (odds ratio: 0.677; 95% CI: 0.387, 1.184; $P = .171$); however, this was imprecisely estimated and not statistically significant. There was no evidence of a difference in other outcomes including FEV_1 (ratio: 1.013; 95% CI: 0.978, 1.049; $P = .468$) or ACQ-5 score (ratio: 0.988; 95% CI: 0.751, 1.301; $P = .933$).

DISCUSSION

We found that a substantial minority of patients had poor ICS/LABA adherence in the year before biologic initiation, who were more likely to live in deprived areas and have a higher FeNO than those with good adherence. The introduction of biologics had little impact on population-level adherence; however, there were substantial changes for individual patients. In the longer term, exacerbation rates were significantly lower among patients with good adherence although we did not find any association for asthma symptoms and lung function.

Poor ICS/LABA adherence in some patients with difficult-to-control and severe asthma has previously been reported in UK populations,[7] including among those receiving biologics.[12,14,19] For example, 22% of patients starting mepolizumab were found to have poor adherence (MPR <50%) before initiation of treatment.[12] Our findings of population-level adherence being unchanged after biologic initiation is in agreement with other UK-based studies.[12,14] These analyses have also suggested poorer biologic response among non-adherent patients taking mepolizumab[12] but not benralizumab;[14] however, comparison between these studies is difficult due to potential residual confounding. In particular, the baseline exacerbation rate in the mepolizumab study was much lower in the poorly adherent group than in those with good adherence (1.8 vs 3.2 per year), and so it is perhaps unsurprising that a differential response was observed. This potential bias was less apparent in the benralizumab study, while our longitudinal analysis offered a more robust design that used within-person changes over time and negated confounding by patient-level factors.

Within the United Kingdom, access criteria stipulate that patients should have their adherence confirmed before biologic initiation but does not state how this should be assessed.[20-22] Our results suggest that it is difficult to identify this poor adherence based on demographic factors and clinical presentation alone. Various methods are used to routinely assess adherence, which generally includes checking prescription or dispensing records, but can be supplemented with other novel methods. In particular, the FeNO suppression test leverages the relationship between ICS and FeNO to quickly differentiate poor adherence from ICS-resistant disease,[23,24] and has been shown to be a useful tool to guide biologic initiation.[25] Digital adherence monitoring, whereby patients are given a sensor-equipped ICS inhaler that records each medication use, has been implemented in several studies to assess medication adherence and has shown some promise for improving adherence[26,27] and streamlining biologic progression.[28,29]

Although population-level adherence remained high throughout the study, our results confirm that individual patient's adherence habits were variable over time. The drivers of changing adherence behaviors are likely to be complex and multifactorial; however, perceived value of treatment may play an important role.[11] In the context of biologics, the stark improvement in disease control offered by these treatments may result in some patients perceiving their inhalers as less necessary or valuable. This highlights the requirement for regular counseling on the importance of consistent inhaled therapy use and a possible need for future qualitative work to explore patients' perceptions of inhaled therapy after biologic initation. It should be noted that, even within the poorly adherent groups in our study, mean medicine possession ratios were more than 50%; therefore, our study does not address the clinical consequences of very low or nonexistent ICS adherence while receiving biologic therapy.

During the study, majority of our cohort were treated with mepolizumab, which does not fully suppress airway eosinophils and does not suppress IL-4/-13 pathways;[30] therefore, ongoing ICS may be required to prevent breakthrough inflammatory events that are still common in this population.[31] Furthermore, biologic therapies are targeted to specific parts of the T2 pathway, and although they are efficacious in reducing exacerbations and hospitalizations, asthma is a complex immune disease with multiple biological and physiological pathways activated simultaneously; this includes mast cell activation and airway smooth muscle dysfunction, which may be impacted by ICS and not be entirely dependent on T2-cytokines.[32,33] The importance of ongoing ICS adherence is likely to be heterogeneous, and for some patients, regular ICS can be safely tapered to as-needed treatment, whereas for others, reduction from regular ICS leads to lung function decline even when receiving anti−IL-5R therapy.[17] Risk prediction models, which may incorporate serial lung function or T2-biomarker measurements, are required to better guide this reduction and to identify patients where ongoing ICS adherence remains necessary to retain disease control. Furthermore, regular ICS therapy has been responsible for reduction in asthma-related deaths in recent decades, and we do not yet have data that assess mortality reduction with biologics alone without additional ICS therapy.

Our study relied on the MPR to measure adherence. Although this metric is commonly used clinically and within research studies, it is associated with several limitations including an inability to discern if the medication was taken adequately by the patient, either intentionally or nonintentionally, and a lack of consideration for the timing of medication refills. We calculated annual MPRs; however, systematic assessment for biologic eligibility is likely to have taken place over a shorter time period, particularly if other evidence supporting biologic suitability was available, such as a negative FeNO suppression test. Furthermore, inhalers that were dispensed within the clinic, for example, to facilitate digital monitoring, are not captured by community dispensing records.

The use of dispensing records for calculating MPR is a strength of our study; however, the clinical team only had access to prescribing records during biologic eligibility assessment, and this may explain why some patients managed to access biologics despite apparent suboptimal adherence. This is an example of primary nonadherence, whereby patients have their medication issued but not dispensed, and is a common occurrence with asthma prescriptions.[34] The lack of specific medication dosing information available was also a limitation in our study and required imputation of doses for calculating MPR. Despite these concerns, the consistent association we observed between adherence and FeNO, which is known to be ICS sensitive, does suggest that the MPR was a valid measure of adherence within our study.

The key strength of this study is the data upon which it is based. The inclusion of the high-quality specialist care data allowed identification of a well-characterized cohort of patients who were assessed by specialists as meeting ERS/ATS severe asthma criteria. It also enabled the inclusion of several variables that are not routinely available in routine health care datasets, such as type 2 biomarkers, spirometry, and patient-reported outcomes. To our knowledge, our study is the largest UK study to date, with substantially longer follow-up than previous analyses. However, there were still potential weaknesses with our study, including those common to observational studies such as loss to follow-up, missing data, and residual confounding. In addition, this study was completed within the United Kingdom, where access to biologics is tightly restricted and patients do not routinely pay out-of-pocket for asthma treatment. Therefore, it is unclear whether our results generalize to countries with less stringent biologic access criteria or health care systems where financial barriers are often a major barrier to treatment adherence. Most patients received mepolizumab, and our study contains no data on patients treated with tezepelumab, as this was not available during the study period. As tezepelumab is a broader-acting therapy targeting multiple inflammatory pathways, it is possible that it will enable a higher proportion of patients to reduce their ICS/LABA medications, while offering some protection against poor adherence. The concept of ICS reductions with tezepelumab is currently being tested in the ARRIVAL study (NCT06473779).

CONCLUSIONS

A substantial minority of patients receiving biologics had poor ICS/LABA adherence in the year before biologic initiation; these patients were more likely to live in deprived areas and have a higher FeNO at baseline assessment. Although the introduction of biologics had little impact on population-level adherence, there were substantial changes in individual patients. Our results suggest that poor adherence to ICS/LABA after biologic introduction was associated with higher exacerbation rates and FeNO. Future quantitative and qualitative work investigating the reasons for poor adherence among biologic-treated populations is required to design effective interventions aiming to improve patient outcomes.

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ONLINE REPOSITORY

TABLE E1. Imputed doses of inhaled corticosteroids

Medication	Daily dose
Fluticasone	
Relvar Ellipta 184 μg/dose/22 μg/dose dry powder inhaler (GlaxoSmithKline UK Ltd) 30 dose	1
Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd) 60 dose	2
Seretide 250 Evohaler	4
Seretide 500 Accuhaler	2
Fluticasone 250 μg/dose/salmeterol 25 μg/dose inhaler CFC free	4
Seretide 250 Evohaler (GlaxoSmithKline UK Ltd) 120 dose	4
Fluticasone furoate 184 μg/dose/vilanterol 22 μg/dose dry powder inhaler 30 dose	1
Flutiform 250 μg/dose/10 μg/dose inhaler (Napp Pharmaceuticals Ltd) 120 dose	4
Fluticasone propionate 500 μg/dose/salmeterol 50 μg/dose dry powder inhaler 60 dose	2
Fluticasone propionate 500 μg/dose/salmeterol 50 μg/dose dry powder inhaler	2
Seretide 250 Accuhaler	2
Relvar Ellipta 184 μg/dose/22 μg/dose dry powder inhaler	1
Relvar Ellipta 92 μg/dose/22 μg/dose dry powder inhaler (GlaxoSmithKline UK Ltd) 30 dose	1
Seretide 125 Evohaler	4
Sirdupla 25 μg/dose/250 μg/dose inhaler (Mylan) 120 dose	4
Fluticasone 250 μg/dose/salmeterol 25 μg/dose inhaler CFC free 120 dose	4
Trelegy Ellipta 92 μg/dose/55 μg/dose/22 μg/dose dry powder inhaler (GlaxoSmithKline UK Ltd) 30 dose	1
Fluticasone 125 μg/dose/salmeterol 25 μg/dose inhaler CFC free	4
Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd) 60 dose	2
Flutiform 250 μg/dose/10 μg/dose inhaler	4
Fluticasone 250 μg/dose/formoterol 10 μg/dose inhaler CFC free 120 dose	4
Fluticasone furoate 92 μg/dose/vilanterol 22 μg/dose dry powder inhaler 30 dose	1
Sirdupla 25 μg/dose/125 μg/dose inhaler (Mylan) 120 dose	4
Fluticasone propionate 250 μg/dose/salmeterol 50 μg/dose dry powder inhaler	2
Seretide 50 Evohaler	4
Seretide 125 Evohaler (GlaxoSmithKline UK Ltd) 120 dose	4
Fluticasone 250 μg/dose/formoterol 10 μg/dose inhaler CFC free	4
Seretide 100 Accuhaler	2
Flutiform 125 μg/dose/5 μg/dose inhaler (Napp Pharmaceuticals Ltd) 120 dose	4
Relvar Ellipta 92 μg/dose/22 μg/dose dry powder inhaler	1
Flixotide 500 μg/dose Accuhaler	2
Flixotide 500 μg/dose Accuhaler (GlaxoSmithKline UK Ltd) 60 dose	2
Fluticasone 125 μg/dose/salmeterol 25 μg/dose inhaler CFC free 120 dose	4
Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd) 60 dose	2
Flutiform 125 μg/dose/5 μg/dose inhaler	4
Fluticasone furoate 184 μg/dose/vilanterol 22 μg/dose dry powder inhaler	1
AirFluSal Forspiro 50 μg/dose/500 μg/dose dry powder inhaler (Sandoz Ltd) 60 dose	2
Flixotide 50 μg/dose Accuhaler	2
Fluticasone 125 μg/dose/formoterol 5 μg/dose inhaler CFC free 120 dose	4
Fluticasone 250 μg/dose inhaler CFC free	4
Fluticasone 50 μg/dose/salmeterol 25 μg/dose inhaler CFC free	4
Sirdupla 25 μg/dose/125 μg/dose inhaler (Mylan Ltd) 120 dose	4
Fluticasone 250 μg/dose/salmeterol 50 μg/dose dry powder inhaler 60 dose	2
Fluticasone 125 μg/dose/formoterol 5 μg/dose inhaler CFC free	4
Fluticasone 125 μg/dose inhaler CFC free	4
Flixotide 125 μg/dose Evohaler	4
Fluticasone furoate 92 μg/dose/vilanterol 22 μg/dose dry powder inhaler	1
Budesonide	
Symbicort 200/6 Turbohaler	4
Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd) 60 dose	2

(continued)

TABLE E1. *(Continued)*

Medication	Daily dose
Symbicort 400/12 Turbohaler	2
Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd) 120 dose	4
Budesonide 200 μg/dose/formoterol 6 μg/dose dry powder inhaler	4
Budesonide 400 μg/dose/formoterol 12 μg/dose dry powder inhaler	2
Budesonide 500 μg/2ml nebulizer liquid unit dose vials 20 unit dose	1
Budesonide 400 μg/dose/formoterol 12 μg/dose dry powder inhaler 60 dose	2
Symbicort 100/6 Turbohaler	4
Budesonide 1 mg/2 mL nebulizer liquid unit dose vials	1
DuoResp Spiromax 320 μg/dose/9 μg/dose dry powder inhaler (Teva UK Ltd) 60 dose	2
Budesonide 1 mg/2 mL nebulizer liquid unit dose vials 20 unit dose	1
Symbicort 200 μg/dose/6 μg/dose pressurized inhaler (AstraZeneca UK Ltd) 120 dose	4
Budesonide 200 μg/dose/formoterol 6 μg/dose inhaler CFC free 120 dose	4
DuoResp Spiromax 320 μg/dose/9 μg/dose dry powder inhaler	2
Budesonide 100 μg/dose/formoterol 6 μg/dose dry powder inhaler	4
Pulmicort 0.5 mg Respules	1
Pulmicort 200 Turbohaler (AstraZeneca UK Ltd) 100 dose	2
Pulmicort 1 mg Respules	1
Pulmicort 200 Turbohaler	2
Pulmicort 400 Turbohaler	2
DuoResp Spiromax 160 μg/dose/4.5 μg/dose dry powder inhaler (Teva UK Ltd) 120 dose	4
Budesonide 400 μg/dose dry powder inhaler	2
Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd) 120 dose	4
Budesonide 500 μg/2 mL nebulizer liquid unit dose vials	1
Budesonide 200 μg/dose/formoterol 6 μg/dose dry powder inhaler 120 dose	4
Budesonide 200 μg/dose dry powder inhaler	2
Pulmicort 100 Turbohaler	2
DuoResp Spiromax 160 μg/dose/4.5 μg/dose dry powder inhaler	4
Pulmicort 0.5 mg Respules (AstraZeneca UK Ltd) 20 unit dose 4 × 5 respules	1
Budesonide 500 μg/2 mL nebulizer liquid unit dose vials	1
Budesonide 1 mg/2 mL nebulizer liquid unit dose vials	1
Trixeo Aerosphere 5 μg/dose/7.2 μg/dose/160 μg/dose pressurized inhaler (AstraZeneca UK Ltd) 120 dose	1
Pulmicort 200 μg/dose inhaler CFC free	4
Pulmicort 100 μg/dose inhaler CFC free	4
Pulmicort 400 Turbohaler (AstraZeneca UK Ltd) 50 dose	2
Beclometasone	
Fostair 200 μg/dose/6 μg/dose inhaler (Chiesi Ltd) 120 dose	4
Clenil Modulite 100 μg/dose inhaler	4
Fostair 100 μg/dose/6 μg/dose inhaler	2
Clenil Modulite 200 μg/dose inhaler	4
Fostair 100 μg/dose/6 μg/dose inhaler (Chiesi Ltd) 120 dose	2
Trimbow 87 μg/dose/5 μg/dose/9 μg/dose inhaler (Chiesi Ltd) 120 dose	4
Clenil Modulite 100 μg/dose inhaler (Chiesi Ltd) 200 dose	4
Fostair NEXThaler 200 μg/dose/6 μg/dose dry powder inhaler (Chiesi Ltd) 120 dose	4
Clenil Modulite 50 μg/dose inhaler	4
Beclometasone 100 μg/dose/formoterol 6 μg/dose inhaler CFC free	2
Qvar 100 inhaler	4
Clenil Modulite 200 μg/dose inhaler (Chiesi Ltd) 200 dose	4
Fostair NEXThaler 100 μg/dose/6 μg/dose dry powder inhaler (Chiesi Ltd) 120 dose	2
Easyhaler Beclometasone 200 μg/dose dry powder inhaler	2
Qvar 100 Autohaler	4
Clenil Modulite 250 μg/dose inhaler	8
Fostair NEXThaler 100 μg/dose/6 μg/dose dry powder inhaler	2
Beclometasone 100 μg/dose/formoterol 6 μg/dose inhaler CFC free 120 dose	2
Pulvinal beclometasone dipropionate 400 μg/dose dry powder inhaler	2
Qvar 100 inhaler (Teva UK Ltd) 200 dose	4

(continued)

TABLE E1. *(Continued)*

Medication	Daily dose
Ciclesonide	
Alvesco 80 inhaler	2
Ciclesonide 160 μg/dose inhaler CFC free	2
Ciclesonide 80 μg/dose inhaler CFC free 120 dose	2
Ciclesonide 80 μg/dose inhaler CFC free	2
Alvesco 160 inhaler	2

CFC, chlorofluorocarbons.

TABLE E2. Comorbidity prevalence

Comorbidity	No. of patients (n) or n (%)
Allergic rhinitis	<10 patients
Anemia	<10 patients
Atopic dermatitis	<10 patients
Bronchiolitis	38 (18.4)
Cataract	<10 patients
Chronic rhinitis	<10 patients
COPD	10 (4.8)
Depression or anxiety	34 (16.4)
Diabetes	19 (9.2)
Eczema	<10 patients
EGPA	<10 patients
Gastroesophageal reflux	48 (23.2)
Hematological disease	<10 patients
Hypertension	40 (19.3)
Hypothyroidism	<10 patients
Inflammatory bowel disease	<10 patients
Immunodeficiency	<10 patients
Malignancy	<10 patients
Nasal polyps	43 (20.8)
Osteoporosis	18 (8.7)
Rheumatic disease	<10 patients
Rhinitis	<10 patients
Sleep apnea	<10 patients
Stroke/TIA	<10 patients
Substance abuse	<10 patients

Counts censored to prevent disclosure.
COPD, Chronic obstructive pulmonary disease; *EGPA*, eosinophil granulomatosis with polyangiitis; *TIA*, transient ischemic attack.

TABLE E3. Biologic status during the study

Years after biologic introduction	Biologic use	Count (n) or n (%)
0	Mepolizumab	>178 (>86.0%)
	Benralizumab	19 (9.2%)
	Other	<10 patients
1	Mepolizumab	171 (85.1%)
	Benralizumab	30 (14.9%)
	Other	<10 patients
	None	<10 patients
2	Mepolizumab	133 (73.5%)
	Benralizumab	48 (26.5%)
	Other	<10 patients
	None	<10 patients
3	Mepolizumab	95 (68.8%)
	Benralizumab	43 (31.2%)
	Other	<10 patients
	None	<10 patients
4	Mepolizumab	64 (70.3%)
	Benralizumab	27 (29.7%)
	Other	<10 patients
	None	<10 patients

Years after biologic introduction	Biologic status	Count (n) or n (%)
1	Continue	>180 (>87.0%)
	Switch	17 (8.2%)
	Stop	<10 patients
2	Continue	>145 (>74.4%)
	Switch	40 (20.5%)
	Stop	<10 patients
3	Continue	>95 (>62.9%)
	Switch	46 (30.5%)
	Stop	<10 patients
4	Continue	>56 (>57.7%)
	Switch	31 (32.0%)
	Stop	<10 patients

Counts censored to prevent disclosure.

TABLE E4. Medication possession ratio (MPR) across 7 years of the study, stratified by adherence in the year before biologic introduction

(A) MPR for all patients

Year	Mean MPR (SD) (%)	*P* value	Proportion of good adherence, N (%) (95% CI)
−2	90.1 (31.8)	.414	131 (63.9) (56.9%-70.5%)
−1	91.7 (33.5)	.881	136 (66.0) (59.1%-72.5%)
0	91.8 (32.3)	—	149 (72.0) (65.3%-78.0%)
1	89.6 (29.7)	.243	138 (66.7) (59.8%-73.0%)
2	91.7 (28.7)	.77	141 (72.3) (65.5%-78.5%)
3	91.8 (30.3)	.591	113 (74.8) (67.1%-81.5%)
4	91.0 (29.6)	.513	70 (72.2) (62.1%-80.8%)

(B) MPR for patients stratified according to adherence in the year before biologic introduction

Year	Adherence year biologics introduced	Mean MPR (SD) (%)	Proportion of good adherence, N (%)
−2	Good adherence	95.2 (32.2)	104 (70.3)
−1		99.0 (32.1)	111 (74.5)
0		105.9 (24.7)	149 (100.0)
1		98.0 (27.3)	117 (78.5)
2		97.6 (27.8)	114 (81.4)
3		96.3 (30.8)	85 (80.2)
4		96.6 (30.8)	55 (80.9)
−2	Poor adherence	76.7 (26.6)	27 (47.4)
−1		72.5 (29.6)	25 (43.9)
0		55.4 (17.8)	0 (0.0)
1		67.7 (23.9)	21 (36.2)
2		76.6 (25.3)	27 (49.1)
3		81.2 (26.5)	28 (62.2)
4		77.9 (22.0)	15 (51.7)

P values calculated using the paired *t*-test comparing mean for each year with mean at year 0. Good adherence as defined as MPR ≥75%.
CI, Confidence interval; *SD*, standard deviation.

TABLE E5. Baseline characteristics stratified by medication possession ratio 1 year after biologic introduction

	Medication possession ratio		
Characteristic	**Poor (<75%)**	**Good (≥75%)**	***P* values**
No. of patients	69	138	
MPR at baseline (%)	72 (26)	102 (31)	**<.001**
Demographics			
Female	39 (56.5%)	84 (60.9%)	.548
Age (y)	54.4 (12.6)	54.3 (13.1)	.960
Age of onset (y)	27.5 (14.0, 39.0)	26.0 (10.0, 40.0)	.853
Asthma duration (y)	27.4 (15.8, 35.3)	24.1 (12.2, 38.5)	.684
Deprivation tertile			
1 (most)	23 (33.8%)	39 (28.5%)	.461
2	26 (38.2%)	48 (35.0%)	
3 (least)	19 (27.9%)	50 (36.5%)	
Deprived	23 (33.8%)	39 (28.5%)	.432
BMI (kg/m^2)	31.3 (6.2)	31.2 (6.9)	.858
Obese	40 (58.0%)	68 (50.0%)	.280
Ever smoker	24 (34.8%)	58 (42.3%)	.296
Atopic disease	22 (44.0%)	37 (46.8%)	.753
HCRU (last year)			
Exacerbations	4 (3, 6)	4 (2, 6)	.166
Any ED attendance	27 (39.1%)	44 (32.1%)	.317
Any hospital admissions	21 (30.4%)	38 (27.7%)	.686
Lung function			
FEV_1 (L)	2.1 (0.9)	2.1 (0.7)	.612
FEV_1 (% predicted)	70.7 (23.4)	69.3 (18.9)	.648
FVC (L)	3.3 (1.1)	3.2 (1.0)	.881
FVC (% predicted)	85.9 (20.5)	86.3 (16.0)	.868
FEV_1-FVC	64.4 (11.4)	63.8 (13.1)	.745
Patient-reported outcomes			
ACQ-5 score	3.0 (1.4)	2.8 (1.5)	.202
Uncontrolled asthma (ACQ5 >1.5)	55 (83.3%)	97 (76.4%)	.262
EuroQoL Utility	0.70 (0.46, 0.87)	0.75 (0.41, 0.94)	.398
T2 biomarkers			
FeNO (ppb)	33 (18, 70)	34 (21, 53)	.708
Blood eosinophil count ($N/10^9$ L)	0.26 (0.10, 0.57)	0.35 (0.15, 0.56)	.296
Highest blood eosinophil count ($N/10^9$ L)	0.78 (0.59, 1.19)	0.73 (0.61, 1.03)	.735
IgE (IU/mL)	110 (48, 368)	116 (42, 293)	.901
Asthma medications			
Maintenance OCS	53 (76.8%)	95 (69.3%)	.261
Maintenance OCS (mg)	10 (8, 12)	10 (8, 10)	.685
ICS dose (BDP equivalent [μg])	2000 (2000, 2000)	2000 (1600, 2000)	.188
Theophylline	20 (38.5%)	33 (37.9%)	.950
LAMA	16 (30.8%)	35 (39.8%)	.285
Leukotriene receptor antagonists	20 (38.5%)	50 (56.8%)	**.036**
Maintenance macrolides	<10 patients	13 (9.6%)	.433
Nebulizer	13 (25.0%)	19 (21.8%)	.668
SABA inhalers	10 (4, 18)	10 (4, 18)	.861

Data are presented as mean (standard deviation), median (interquartile range), or n (%).

p-values in bold are significant at the 5% level.

ACQ-5, Asthma Control Questionnaire-5; *BDP*, beclometasone dipropionate; *BMI*, body mass index; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HCRU*, health care resource utilization; *ICS*, inhaled corticosteroids; *LAMA*, long-acting muscarinic antagonists; *MPR*, medication possession ratio; *OCS*, oral corticosteroids; *SABA*, short-acting β_2-agonist.

TABLE E6. Multivariable regression comparing good (≥75%) versus poor (<75%) adherence and clinical outcomes*

Outcome	Observations (N)	Patients (N)	Ratio (95% CI)	*P* values
HCRU (last year)				
Exacerbations†	736	206	0.826 (0.698, 0.978)	**.026**
Any ED attendance‡	743	206	0.677 (0.387, 1.184)	.171
Any hospital admissions‡	743	206	0.735 (0.380, 1.419)	.358
Lung function				
FEV_1 (L)§	718	206	1.013 (0.978, 1.049)	.468
FVC (L)§	714	206	1.010 (0.986, 1.036)	.410
Patient-reported outcomes				
ACQ-5 score§	686	205	0.988 (0.751, 1.301)	.933
EuroQoL Utility§	639	198	1.059 (0.960, 1.169)	.255
T2 biomarkers				
FeNO (ppb)§	715	205	0.832 (0.743, 0.932)	**.002**
Blood eosinophil count ($N/10^9$ L)§	730	206	1.171 (0.883, 1.553)	.272

p-values in bold are significant at the 5% level.
ACQ-5, Asthma Control Questionnaire-5; *CI*, confidence interval; *ED*, emergency department; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *HCRU*, health care resource utilization.
*Adjusted for biologic use and year.
†Rate ratio.
‡Odds ratio.
§Ratio.

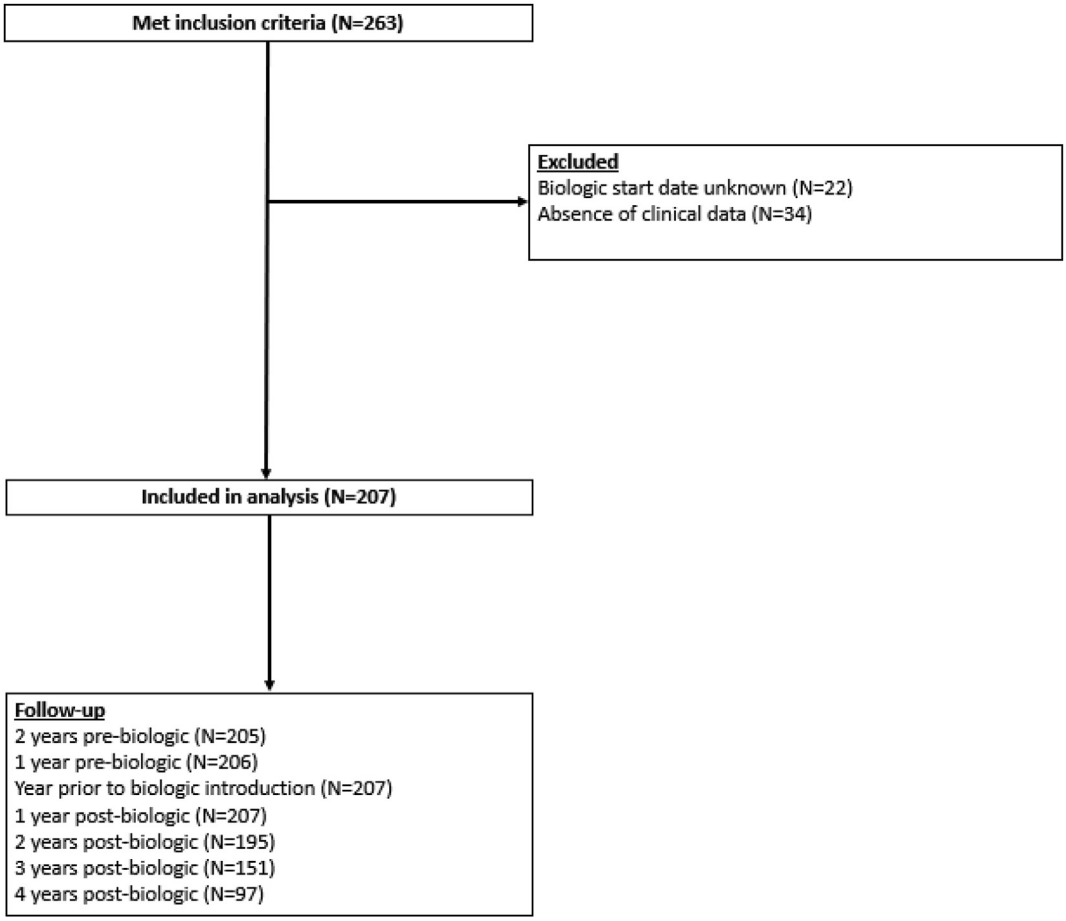

FIGURE E1. Patient flow diagram.

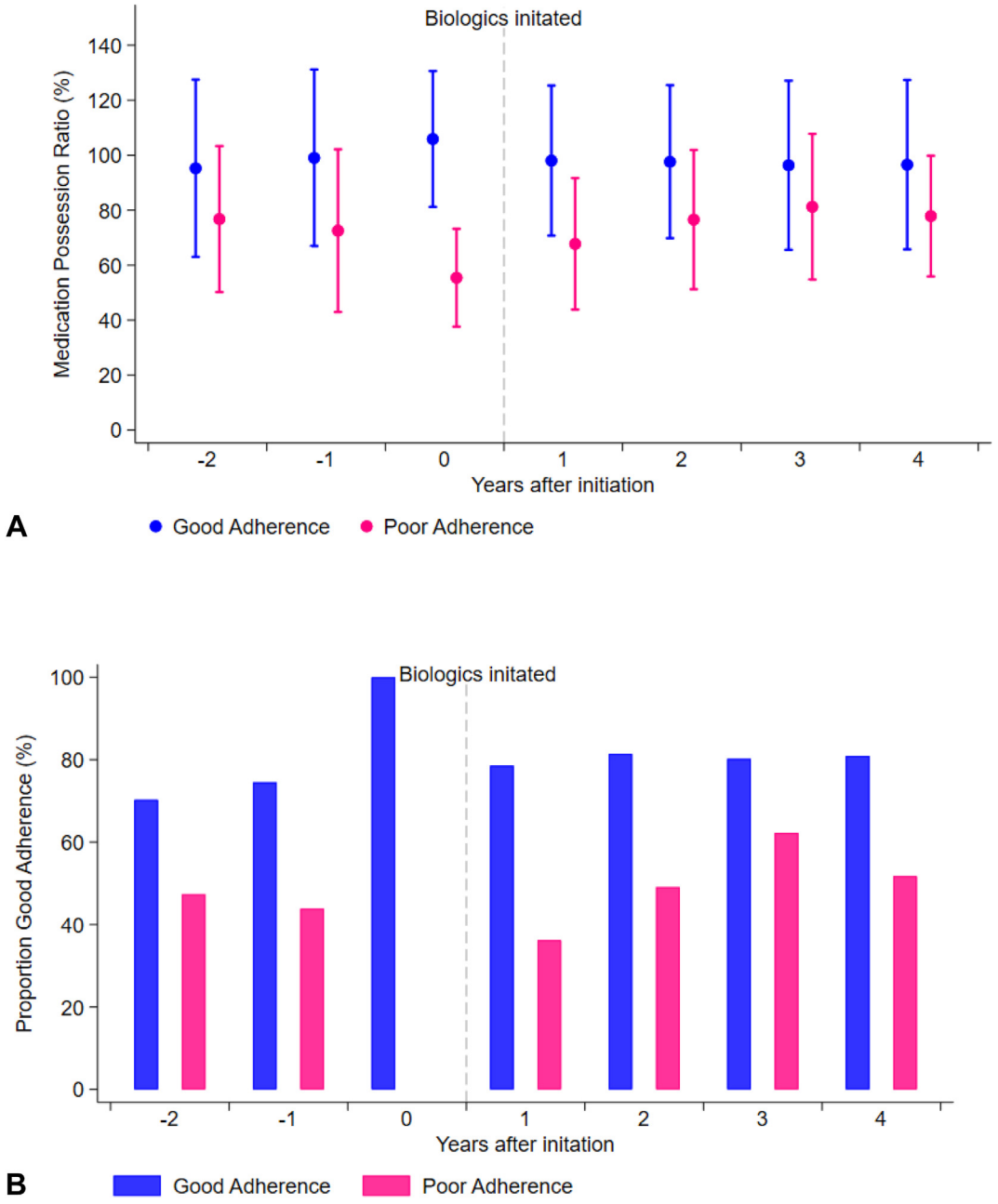

FIGURE E2. Medication possession ratio (MPR) across 7 years of the study, stratified by adherence in the year before biologic introduction. Patients were stratified into 2 groups according to their baseline adherence, MPR $\geq$75% (good) versus MPR $<$75% (poor). Both groups were assessed for mean MPR and proportion of good adherence for each of the 7 years of the study. (**A**) Mean MPR. (**B**) Proportion with good adherence (MPR $\geq$75%).