Original Article

Inhaled Corticosteroid Adherence Patterns in a Longitudinal Asthma Cohort

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What is already known about this topic? Inhaled corticosteroid (ICS) adherence in asthma is often low, and detrimental to health. Persistence with and implementation of treatment are distinct adherence components with different causes and consequences. Electronic records–based adherence calculations rarely consider this distinction.

What does this article add to our knowledge? During long-term ICS-based asthma treatment, nonpersistence periods alternated with periods of regular, albeit variable, ICS use (implementation). When accounting for (non-)persistence, implementation rates were relatively high, suggesting that nonpersistence contributes substantially to suboptimal ICS adherence.

How does this study impact current management guidelines? In clinical practice, assessing both (non-)persistence and implementation provides a more nuanced diagnosis of ICS adherence. These 2 adherence components should be separately investigated in relation to possible health consequences and tailored interventions.

BACKGROUND: Electronic prescribing records can enable exploration of medication adherence, but analysis decisions may influence estimates and require alignment to new consensus-based definitions.

OBJECTIVE: To compare different computations of inhaled corticosteroid (ICS) implementation in a primary care asthma population initiating ICS therapy when assessed within episodes of persistent use, and examine longitudinal variation in implementation.

METHODS: A historical cohort study was conducted on UK's Optimum Patient Care Research Database. Eligible patients had physician-diagnosed asthma, initiated ICS therapy, and had 3 or

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Abbreviations used
ICS- Inhaled corticosteroid
CMA- Continuous medication availability
OPCRD- Optimum Patient Care Research Database
ID- Index prescription date

more years of continuous registration. ICS treatment episodes were constructed on the basis of 3 definitions, permitting 30-, 90-, and 182-day gaps between prescriptions. Implementation was estimated using 2 continuous medication availability (CMA I and II) definitions to explore effects of carryover of previous prescriptions in 4 observation windows: 6, 8, 12, and 24 months. Impact of methodology was assessed by descriptive statistics, linear mixed models, and measures of agreement.

RESULTS: A total of 13,922 eligible patients (mean age, 39.9 years; 48.7% men) were identified. For CMA I, permitting a 90-day gap, mean ICS implementation for the 2-year period was 89.3% (±16.0%; range, 14.4%-100%). Sensitivity analyses with 30- and 182-day gaps resulted in increased (97.0% ± 7.2%) and decreased (81.1% ± 21.6%) estimates. CMA II produced estimates with varying concordance (0.69-0.87). Substantial variance was found between and within patients (intraclass coefficient, 0.30-0.36).

CONCLUSIONS: Different analysis choices resulted in substantial variation in implementation estimates, highlighting the need for transparent and clinically relevant methododology. Distinguishing between (non)persistence and implementation is important in clinical practice, and may require different interventions in routine consultations. **(J Allergy Clin Immunol Pract 2017;5:448-56)**

Key words: *Adherence; Asthma; CMA; Inhaled corticosteroids; OPCRD; Pharmacoepidemiology; Cohort study*

Medication adherence in people with chronic illnesses is generally low. In asthma, adherence to inhaled corticosteroids (ICSs), used as long-term controller medication, is often estimated to be below 50%.[1] Low adherence rates have been associated with increased mortality and morbidity, and escalating treatment costs.[2-4] Outside the strict control of randomized controlled trials, patients may decide, in agreement with their health care provider or independently, to adopt a symptom-driven approach to self-titrate therapy, for example, reducing daily ICS dose during periods with milder symptoms and increasing their daily ICS dose during periods with less controlled asthma.[5,6] Thus, ICS adherence requires careful consideration in routine asthma care.

To date, many studies have focused on identifying factors influencing medication adherence to develop adherence-enhancing interventions.[7,8] However, there is still a need to improve methods of assessing adherence given the substantial heterogeneity in terminology and measurements.[9,10] In a recent consensus-based taxonomy, Vrijens et al[10] described medication adherence as a process of taking medication as prescribed, with 3 components: initiation, implementation, and discontinuation (or nonpersistence). Initiation is the event of taking the first dose of a medication. Discontinuation is the event of omitting a next planned dose followed by no medication intake for a substantial time period (nonpersistence). Between initiation and discontinuation is a period of medication persistence, wherein implementation represents the extent to which the drug was used as prescribed during a specific period of active treatment. Long-term treatment may include several treatment episodes, which can be individually characterized by these components.[11] Adherence patterns in ongoing long-term treatment need to distinguish between 2 main adherence components: persistence (a time-to-event variable) and implementation (a statistic comparing actual medication use to prescribed use). Clinically relevant methods to implement this taxonomy in different conditions based on various data sources are yet to be developed and tested.[10]

Electronic medical records (EMRs)[12] represent a relatively accessible data source that includes information on many patients with minimal interference in the care process. EMRs can provide more ecologically valid assessments of medication adherence in long-term care compared with randomized controlled trials, which require high adherence to the trial medication to test its efficacy and therefore may not reflect accurately the reality of daily clinical practice.[12] However, arriving at a clinically meaningful adherence assessment is a complex process. Although it is known that the choice of algorithms may influence estimates,[13,14] evidence is scarce regarding the impact on adherence assessments of distinguishing implementation from persistence, and of different analytical choices on appropriate observation window lengths and data handling methods. Also, the extent to which adherence varies between and within persons in long-term care has received little attention. For an optimal use of administrative data sets in assessing long-term ICS adherence in routine care, understanding the impact of these analytical decisions on estimates, and their clinical implications, is essential.

This study aimed to compare different EMR-based methods to compute ICS adherence in asthma, and focused on 2 questions: (1) what is the impact of distinguishing implementation from persistence on adherence assessment, considering several analytical choices? and (2) does EMR-based implementation vary within and between patients in long-term care? Answering these questions may lead to improved diagnosis of (non-)adherence from routine data available in primary care, and subsequently more effective adherence support.

METHODS

Study design and setting

We conducted a historical cohort study using EMRs from primary care practices in the United Kingdom within the Optimum Patient Care Research Database (OPCRD),[15] a quality-controlled respiratory-enriched database. At the time of data extraction, OPCRD contained anonymized data for approximately 350,000 patients with asthma collected from more than 350 practices across the United Kingdom that subscribed for respiratory review service. The database includes information on diagnosis codes, clinical evaluation, and prescriptions (eg, date, drug name, amount, and dosage prescribed). Prescribing records are a good approximation for dispensing records in the United Kingdom.[16,17] The OPRCD has been approved by Trent Multicentre Research Ethics Committee for clinical research use. Use of the database for this study was approved by the OPCRD Annonymised Data Ethics and Transparency Committee (approval 2.9) and the protocol was registered with the

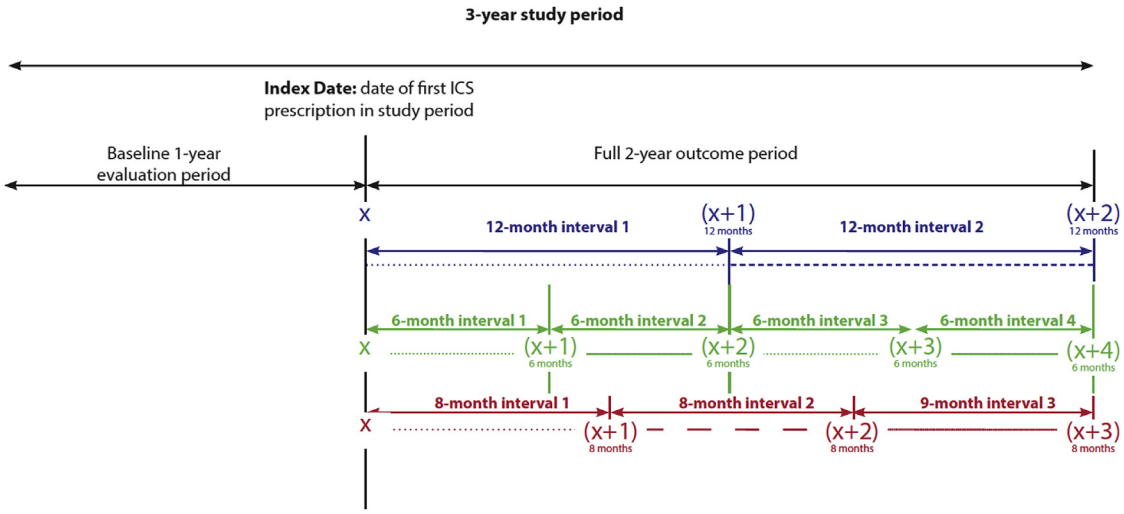

FIGURE 1. Observation windows for computing adherence and asthma control longitudinally.

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Study population

We identified all patients initiating ICS therapy between April 1987 and February 2012. The first ICS prescription date (ICS initiation) was considered as the index prescription date (ID), 1 year before the ID as the baseline period, and 2 years after the ID as the follow-up period (Figure 1). To be eligible for inclusion, patients had to have received 1 or more ICS prescription and 3 years of continuous medical history (1 year before and 2 years after the ID). From this source population, patients were included if they (1) had a recorded physician diagnosis of asthma 1 or more year before the ID, (2) were 6 years or older at the ID, (3) had received their first prescription for (any) ICS delivered via metered dose inhaler or dry powder inhaler at the ID, and (4) had active asthma therapy, that is, 2 or more prescriptions for ICS and/or short-acting beta agonists during each follow-up year. Patients were excluded if they received any prescriptions during the baseline year for (1) long-acting beta agonists, combination ICS/long-acting beta agonist therapy, and/or leukotriene receptor antagonists or (2) maintenance oral corticosteroids (defined as either a prescription for 1-mg tablets or $\geq$7 prescriptions for a daily prescribed dose of $\geq$10 mg). Patients were allowed to have asthma medication add-ons or switches in the follow-up period. By applying these selection criteria, we sought to identify new ICS users on long-term asthma treatment, and avoid including prevalent users because this would prevent the calculation of ICS adherence for a comparable 2-year period within the study sample.

Study outcome

The primary study end point was EMR-based ICS adherence estimated by continuous medication availability (CMA). To distinguish between persistence and implementation,[10] we applied methods previously described by Gardarsdottir et al[18] for computing treatment episodes, and adapted dispensing-based CMA methods described by Vollmer et al in the context of randomized controlled trials[19] to longitudinal observational data. Thus, we described adherence via 2 variables: treatment episode length (persistence) and CMA (implementation). Alternative calculations considered 4 observation window lengths: the full 2-year follow-up period, and the follow-up period split into two 1-year windows, three 8-month windows, and four 6-month windows (Figure 1).

Construction of treatment episodes. ICS treatment episodes were constructed per patient per observation window. A treatment episode was defined as a series of subsequent ICS prescriptions regardless of switching between different products and dose changes. Identification of treatment episodes took into account (1) a permissible gap of 90 days between the estimated end date of a prescription and the next prescription date (alternative gaps of 30 and 182 days were considered in sensitivity analyses only for the 2-year window), (2) changes in prescribed dosage (the current dosage prescribed was used in computing prescription duration from the date of prescription change), (3) switching ICS (if a different type of ICS was prescribed, no carryover of remaining days of the previous type was considered), and (4) carryover: if a patient had a new prescription for the same product before finishing their supply assuming 100% implementation, the number of days still left at the new prescription date was added to the treatment episode.

CMA computation. Two CMA measures were computed for various observation windows (Figure 2). The first method, CMA I (similar to CMA4 and CMA6 in Vollmer et al[19]) also referred to as the "proportion of days covered," does not take into account the period between the window start to first dispensing/prescription within the window. It also ignores carryover effects into the window from earlier prescriptions, and caps implementation values at 100%. Unlike CMA4, it considers carryover effects within the window, and subtracts the surplus of medication supply at the end of the window. The second method, CMA II (similar to CMA7[19]), is an improved marker that also considers carryover effects into the observation window, in addition to the carryover within the window and the surplus remaining at the end. Unlike CMA7, CMA II considers carryover of medication supply for more than 1 prescription before the window, as it examines all prescriptions before the window (in the recorded period) as part of determining treatment episodes, then computes implementation on the basis of the whole episode. Both markers assume 100% implementation until the prescribed supply ends. However, the different approach to integrating carryover

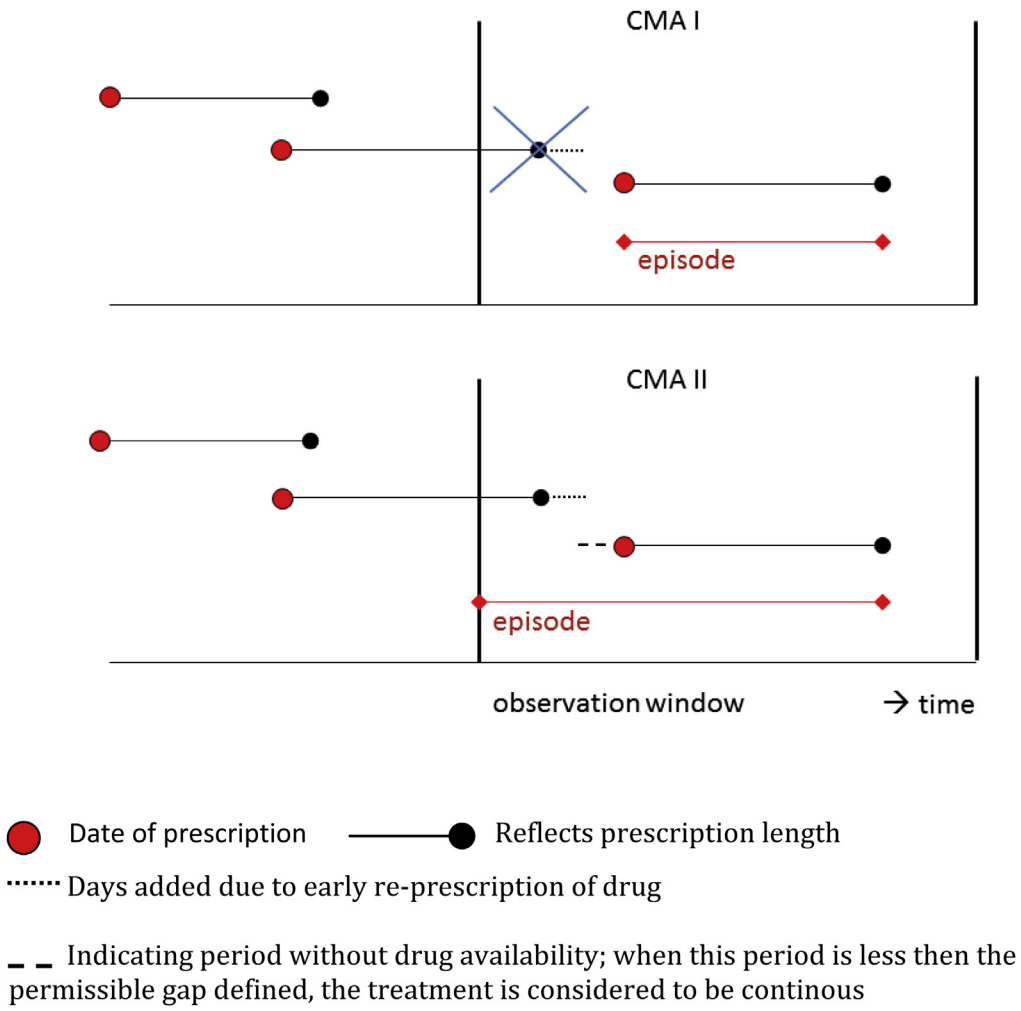

FIGURE 2. In the CMA I method, the carryover of a previous prescription into the observation window is not taken into account, yielding a treatment episode that uses info only from the prescription occurring within the window. In the CMA II method, the carryover into the observation window is taken into account, causing the treatment episode to start at the start of the observation window.

effects before the window reflects different assumptions on how leftover medication is used (no prior medication use once the first prescription is received vs use of prior medication until supply ends).

A global CMA computation for the 2-year period not accounting for treatment episodes (corresponding to CMA4[16]) was performed to obtain an estimate comparable with previous studies that did not distinguish between persistence and implementation. In essence, this computation is a CMA I method using a permissible gap of 730 days.

Other measures. The Charlson comorbidity index,[20] an index including 17 categories of comorbid disease weighted on the basis of their association with 1-year all-cause mortality, was calculated for all patients over the baseline year using clinical information available in the OPCRD. Body mass index and smoking status (current, past, and never) were calculated over 1 year before or after the ID (values closest to the ID). We assessed the use of other asthma medications, antibiotics, and oral corticosteroids during the baseline year (dichotomized as use vs nonuse). The socioeconomic score was derived per practice from the Index of Multiple Deprivation (2007), a composite index of relative deprivation at small area level, and used as quintiles (Q1 = most affluent and Q5 = most deprived).[21]

Data analysis

To ensure data quality, prescriptions were examined to address missing data and perform data management as follows: (1) code prescribed drugs into drug classes, (2) code dosage recommendations, (3) check consistency with inclusion criteria and accuracy of records, and (4) code the quantity prescribed.

Descriptive statistics were calculated for sample characteristics, treatment episode length, and CMA scores. These were also dichotomized into adherent and nonadherent at the commonly used cutoff point of 80% for comparison to previous literature. Chi-square testing was used to compare frequency data, and independent samples t testing or Mann Whitney U tests were used for comparison of means/medians between the final sample and the cases excluded after quality checks, as appropriate. CMA scores from different methods were compared using Wilcoxon rank-sum tests, Bland-Altman plots, and concordance correlation coefficients,[22,23] and assessed considering a minimal threshold of 0.90 for good agreement.

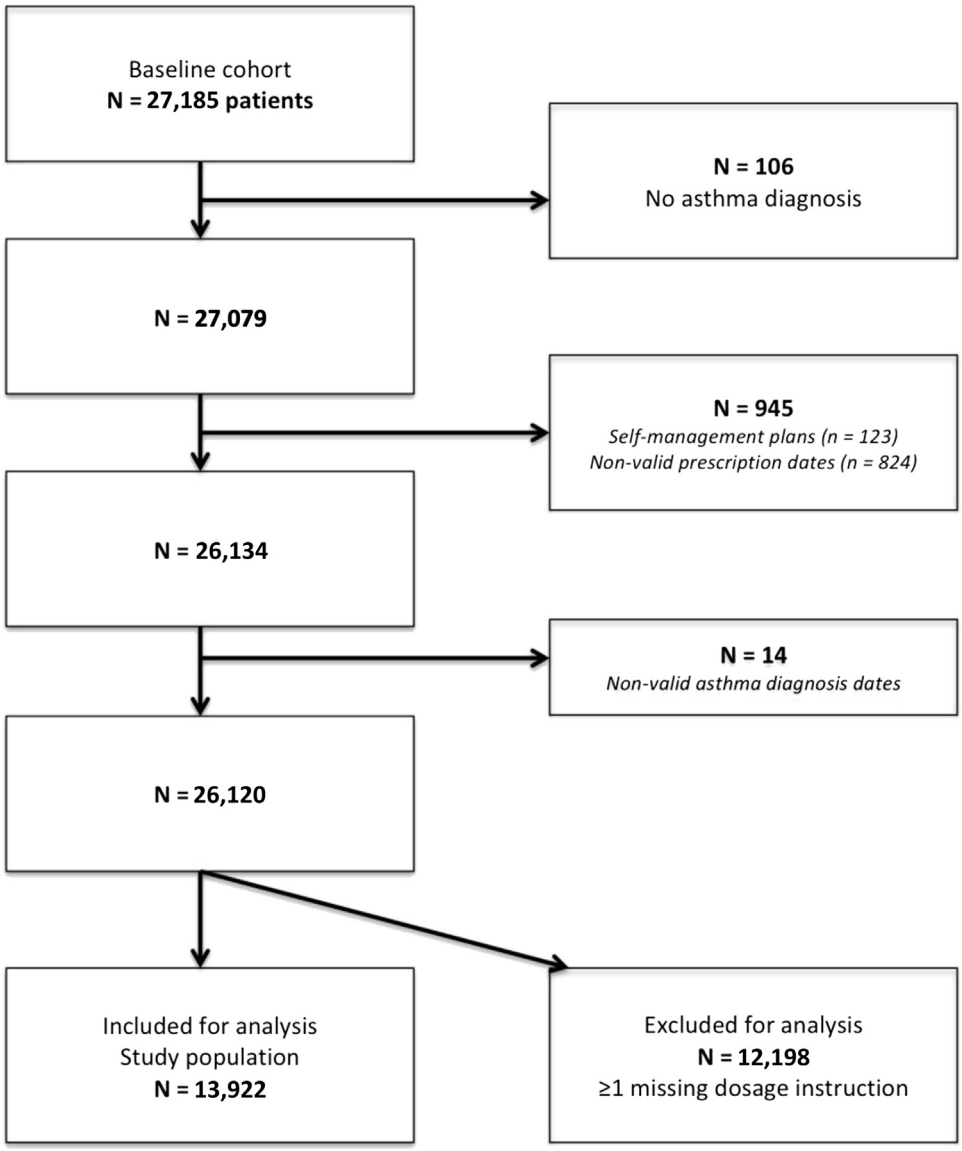

FIGURE 3. Flowchart study population: Data cleaning steps.

Longitudinal variance in CMA scores was examined via unconditional means and unconditional growth models for 6-month windows (90-day permissible gaps) to identify the proportion of variance at intraindividual and interindividual levels (intraclass coefficients) and the degree to which time (modeled as order of observation window, from 0 to 3) explains this variance. Six-month windows were selected for this analysis because they result in the highest number of observations per subject and therefore were most suited for longitudinal modeling. To reduce noise from patients using ICSs only sporadically, we excluded patients with at least 1 treatment episode of less than 14 days and patients with no treatment episodes in at least 1 window because they suggest a possible trial of therapy and prescription patterns unlikely to be characteristic of long-term ICS use and thus not applicable to longitudinal models. For patients with more than 1 episode per window, the mean CMA for all episodes was computed to obtain a single value per patient per episode. Data analyses were performed using SPSS for Windows version 20 (SPSS, Inc, Chicago, Ill) and R (R Core team, Vienna, Austria, 2012).

RESULTS

Sample characteristics

The baseline cohort consisted of 27,185 patients (see patient selection flowchart in Figure E1 in this article's Online Repository at www.jaci-inpractice.org). After conducting quality checks, patients without an asthma diagnosis (n = 106), patients with only self-management plans (n = 123), and patients with nonvalid prescription dates (n = 824) or nonvalid asthma diagnosis dates (n = 14) were excluded (Figure 3). In addition, patients with 1 or more missing dosage instructions at any point during the 2-year period were excluded (84% had instructions missing in all their prescriptions). This resulted in a final sample of 13,922 patients. Characteristics of individuals included for

TABLE I. Sample characteristics

Characteristic	Study population (N = 13,922)	Excluded for analysis (N = 12,198)	*P* value
General characteristics			
Male sex, % (n)	48.7 (6,779)	47.5 (5,793)	.05
Age (y), median (IQR)	39 (22-56)	40 (23-56)	.69
Socioeconomic status of GP practice postcode			
Q1 (most affluent)	18.1 (1,987/10, 949)	18.4 (2,015/10, 976)	<.001
Q2	23.0 (2,519/10, 949)	19.6 (2,149/10, 976)	
Q3	23.0 (2,521/10, 949)	25.5 (2,803/10, 976)	
Q4	20.3 (2,228/10, 949)	18.2 (1,995/10,976)	
Q5 (most deprived)	15.5 (1,694/10, 949)	18.4 (2,014/10,976)	
Smoking status			
Current	26.5 (2,176/8, 221)	26.7 (1,760/6,582)	.18
Former	19.5 (1,605/8, 221)	19.7 (1,297/6,582)	
Non	54.0 (4,440/8, 221)	53.6 (3,525/6,582)	
Clinical characteristics			
Body mass index, mean ± SD	26.5 ± 6.3	26.4 ± 6.7	.24
Charlson comorbidity index, mean ± SD	4.6 ± 2.9	4.6 ± 2.9	.96
Duration of asthma (y), median (IQR)	7.2 (3.2-15.1)	6.9 (3.2-14.6)	.051
Diagnosis rhinitis	2.7 (371)	2.6 (319)	.80
Diagnosis allergic rhinitis	9.1 (1,263)	7.0 (859)	<.001
Diagnosis hay fever	6.2 (857)	5.7 (690)	.09
Diagnosis COPD	3.1 (433)	3.4 (419)	.14
Diagnosis other respiratory diseases	0.3 (48)	0.2 (27)	.06
Diagnosis GERD	2.4 (331)	2.0 (244)	.04

COPD, Chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease; *GP*, general practitioner; *IQR*, interquartile range.

analysis were similar to those of patients excluded from analysis after quality checks (Table I).

More than half of the patients used short-acting beta agonists in the baseline year (54.8%) and one-third used antibiotics (31.9%). The prevalence of oral corticosteroid use was 8.9%. Use of other respiratory medicines, such as long-acting muscarinic antagonists (n = 1), short-acting muscarinic antagonists (1.6%, n = 225), or theophylline (n = 0), was very infrequent or absent. The median number of ICS-containing prescriptions per patient in the 2-year follow-up period was 7 (interquartile range, 7) and most prescriptions (94.0%) were for ICS in monotherapy.

Adherence estimates—Persistence and implementation

The number of treatment episodes over the follow-up period based on a 90-day gap ranged between 1 and 6, with 98.3% of patients having a maximum of 3 episodes. The median duration of the first treatment episodes was 255 days (interquartile range, 630), whereas subsequent episodes were considerably shorter (median 100 and 53 days for episodes 2 and 3, respectively). The median number of ICS prescriptions within the first treatment episode was 3 (interquartile range, 9).

Table II presents results for the different implementation calculations. For CMA I, permitting a 90-day gap, the mean ICS implementation for the 2-year study period was 89.3% (±16.0%; range, 14.4%-100%). Sensitivity analyses with 30-day and 182-day permissible gap showed that implementation estimates increased (97.0% ± 7.2%) and decreased (81.1% ± 21.6%), respectively. CMA II resulted in similar implementation percentages; however, concordance between the 2 measures was below acceptable thresholds, and was lower for shorter observation windows (Table III); differences were more substantial for higher implementation values as shown by Bland-Altman plots (Figure 4).

In contrast, a global 2-year adherence calculation not taking into account treatment episodes resulted in mean ± SD adherence of 60% ± 0.31%, and 35.26% of patients with adherence of 80% or more.

Examination of within-person and between-person variance in implementation

Variance in implementation estimates was assessed for 6-month windows for a subsample of 7258 cases for CMA I and 8805 cases for CMA II. For both CMAs, unconditional growth models with order of observation windows modeled as fixed and random effects showed a significantly improved fit over unconditional means models and models with window order only as fixed or as random effects (see Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org). Intraclass coefficients ranged between 0.30 and 0.36, indicating substantial variance between and within subjects.

DISCUSSION

The present study brings 2 main contributions to understanding ICS adherence in routine clinical care. First, it applied the newly developed adherence taxonomy to EMRs in a respiratory context, and showed that during long-term ICS-based asthma treatment, periods of likely drug holiday (nonpersistence) may alternate with periods of regular, albeit variable, ICS use (implementation). Second, it compared implementation

TABLE II. Differences in ICS implementation when using different definitions of the permissible gap in treatment episode calculation, follow-up time window, and method of calculation

	CMA I				CMA II			
Characteristic	No. of patients	No. of episodes	Implementation %, mean ± SD	Implementation ≥ 80%	No. of patients	No. of episodes	Implementation %, mean ± SD	Implementation ≥ 80%
Full 2-y follow-up period								
90-d gap*	13,922	24,924	89.3 ± 16.0	75.9%	13,922	24,924	89.3 ± 16.0	75.9%
Sensitivity analysis for permissible gap								
30-d gap	13,922	38,339	97.0 ± 7.2	95.4%	13,922	38,339	97.0 ± 7.2	95.4%
182-d gap	13,922	18,603	81.1 ± 21.6	59.7%	13,922	18,603	81.1 ± 21.6	59.7%
Follow-up period by observation window, using 90-d gap†								
0-12 mo	13,922	18,337	90.1 ± 15.6	77.8%	13,922	18,337	90.1 ± 15.6	77.8%
12-24 mo	12,419	14,309	89.7 ± 15.9	76.8%	12,648	14,447	88.8 ± 16.7	74.8%
0-6 mo	13,922	14,623	90.6 ± 15.3	78.9%	13,922	14,623	90.6 ± 15.3	78.9%
6-12 mo	10,828	10,942	92.1 ± 15.0	82.9%	11,859	11,969	90.1 ± 16.5	78.0%
12-18 mo	10,635	10,752	92.5 ± 14.4	83.7%	11,614	11,723	90.3 ± 16.3	78.3%
18-24 mo	10,444	10,566	92.1 ± 14.8	83.0%	11,500	11,608	90.6 ± 16.2	79.1%
0-8 mo	13,922	15,732	90.5 ± 15.3	78.6%	13,922	15,732	90.5 ± 15.3	78.6%
8-16 mo	11,479	12,041	90.3 ± 15.7	78.4%	12,097	12,618	89.2 ± 16.6	75.6%
16-24 mo	11,267	11,759	90.6 ± 15.6	79.1%	12,051	12,507	89.8 ± 16.6	77.0%

*Permissible gap between end date of prescription and start date of next prescription in calculation of treatment episodes.
†Full follow-up period divided into smaller observation windows, using the 90-d permissible gap in calculation of treatment episodes.

estimates under different analytical choices and found that differences in mean ICS implementation were generally small at population level, while agreement between methods was only moderate at individual level. These findings have important implications for routine asthma care, as well as for the study and clinical monitoring of ICS adherence using EMRs.

The mean ICS-implementation estimates in our study varied between 80% and 90%, substantially higher than in previous studies, which often report adherence rates around 50%[1,24-28] and are rather consistent with our global 2-year adherence mean score (60%). This difference may be explained by our stepwise approach to calculate ICS adherence, in line with the new taxonomy.[10] By constructing treatment episodes first, we distinguished between persistent and nonpersistent patients, which allowed a meaningful computation of CMA scores only for periods of active treatment (implementation of drug use). Evaluating implementation only during periods of persistence predictably led to higher estimates than those considering the entire outcome period as one continuous treatment episode. Including patients with at least 2 ICS or short-acting beta agonist prescriptions during the follow-up period might have increased estimates further by excluding more nonpersistent patients, as reflected in the slightly higher global 2-year adherence mean. Similar effects of distinguishing between nonpersistence and implementation have been reported in phase 4 clinical trial electronic monitoring data,[29] statin adherence,[30] and dispensing-based ICS adherence in children[28] and adults.[27] Our study is, to our knowledge, the first to outline thoroughly the methodological application of taxonomy-consistent adherence calculations separating implementation and persistence in respiratory research, and illustrate the effects of different analysis decisions. These results highlight the importance of accounting for periods of persistence when estimating accuracy of implementation, as results differ substantially from previously used global adherence estimates. In routine care, clinicians may need to consider the intervals between prescription/dispensing dates available in EMRs to ascertain whether they are likely due to nonpersistence or suboptimal implementation of dosage recommendations, and adjust their advice accordingly.

TABLE III. Agreement between CMA I and CMA II for the different observation windows (concordance and group differences)

Observation window	CCC (95% CI)	W (*P* value)
Second 1-y window	0.87 (0.86-0.87)	5,234,000 ($P < .001$)
Second 6-mo window	0.74 (0.73-0.74)	4,309,200 ($P < .001$)
Third 6-mo window	0.69 (0.68-0.70)	4,359,600 ($P < .001$)
6-mo window 4	0.74 (0.74-0.75)	3,547,400 ($P < .001$)
Second 8-mo window	0.82 (0.82-0.83)	4,282,800 ($P < .001$)
Third 8-mo window	0.83 (0.82-0.83)	4,115,000 ($P < .001$)

CCC, Concordance correlation coefficient; *W*, 1-sample Wilcoxon rank-sum test.

We used different analysis choices to calculate implementation. Sensitivity analyses with 30-day and 182-day permissible gaps led to higher and lower estimates, respectively. This finding was expected as a more liberal definition of continuous ICS treatment allows for longer periods of nonuse between prescriptions, and thus results in longer treatment episodes with lower implementation. In contrast, if 0-day gaps are stipulated, treatment episode length equals prescription duration, and implementation is 100%. These analyses illustrate that permissible gap length is an essential parameter for distinguishing persistence and implementation. Future research needs to investigate which clinical and EMR-related criteria need to inform this analytical choice. Second, stratification by observation window length did not show major differences in implementation at

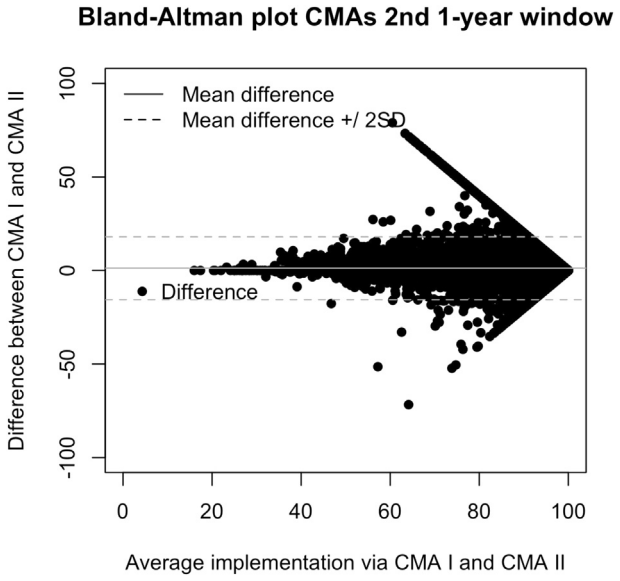

FIGURE 4. Bland-Altman plot for CMA estimates in second yearly observation window.

a population level, regarding mean values and proportions of patients showing 80% or more implementation. Therefore, considering shorter windows did not have an impact on estimates, while allowing the estimation of longitudinal between-person and within-person variation. CMA II resulted in marginally lower estimates than CMA I at a population level, due to considering carryover into the observation window and the interval between window start and first prescription. These findings are in line with previous studies on methods to calculate longitudinal implementation patterns.[18,19] From a clinical perspective, considering carryover is essential for optimal assessment of implementation in chronic conditions, as at any moment during long-term treatment patients might still have medication from a previous prescription. Therefore, if the start of the observation window does not coincide with the start of the treatment, a period of drug use will be unaccounted for in CMA I. Our analysis showed that carryover makes a difference at the individual level, even if the group-level estimates are very similar. This highlights the importance of analysis choices based on a clinically relevant rationale and communicated transparently to allow interpretation and comparison of results across studies. ICS implementation over 4 consecutive 6-month windows varied substantially between and within patients on long-term ICS medication, and agreement between CMA methods was below recommended levels of good concordance. This suggests that patients may adjust their use of ICS differently between consecutive treatment episodes despite recommendations for a fixed daily dose.[31] Therefore, estimating implementation at an individual level may need to focus on shorter (and clearly specified) observation windows to capture these fluctuations and estimate their possible impact on asthma-related outcomes. Moreover, these results may imply that the use of shorter windows and longitudinal models can also impact exposure classification into current/past use for risk estimation in pharmacoepidemiological studies, and need to be further explored in exposure analyses. When using EMRs in routine care, clinicians need to establish the appropriate gap between prescriptions/dispensations that would indicate treatment interruptions, the intervals for which an estimate of implementation is useful, and, if these 2 overlap, account for leftover medication to improve estimates.

Using EMRs offered a nonintrusive way to study ICS adherence, preventing biases associated with patient reports and limiting study inclusion biases and dropout. However, using EMRs also led to several limitations. First, to obtain a high-quality complete data set we only included those patients having sufficient prescription information. Because included and excluded patients had very similar clinical characteristics, it is unlikely that this selection has biased our results; therefore, results may generalize to the wider population of new ICS users in the OPCRD. Yet, results might not generalize to all patients with asthma in the OPCRD or more widely, and the study requires replication/adaptation to other patient populations and EMRs. Second, information on medication dispensing or actual medication use was lacking; therefore, persistence and implementation may have been overestimated. Although in the UK primary care, each dispensing event is preceded by a corresponding prescription, probably not all prescriptions are dispensed and then used as prescribed until finished. Electronic monitoring of medication intake is currently being implemented in smaller settings and improves adherence estimation[32]; however, it is less feasible for large-scale studies. Third, because primary care databases do not capture prescriptions issued by medical specialists, any concurrent prescribing or postreferral prescriptions are missing. This may underestimate the prescribed quantity, although to a limited extent because asthma is managed mostly in primary care.[33] Moreover, to allow comparison of implementation across observation windows, we calculated a single estimate per window, implicitly assuming that implementation is constant during that interval. However, it is likely that implementation varies within shorter intervals, and this variation may be linked with clinical outcomes. The future for EMR-based adherence might be in time-varying analyses that allow for more detailed longitudinal assessment of adherence and its causes and consequences.[34] Finally, this methodological study aimed to compare the impact of different analytical choices on adherence assessment. Causes (eg, asthma severity and seasonality) or consequences of adherence were therefore not considered and need further investigation.

CONCLUSIONS AND FUTURE PERSPECTIVES

This study found variation between and within implementation estimates, underlining the importance of conceptually sound assessments of adherence, careful and transparent analysis choices, and definitions to allow comparison of results across studies. For clinicians using EMRs to flag problems in adherence, these results mean that algorithms might need to be modified to distinguish between nonpersistence and suboptimal implementation by taking into account treatment gaps and computing implementation rates within active treatment episodes. Further comparative methodological studies are needed to identify appropriate analytical choices in specific EMR contexts (differences between countries, between prescription and dispensing, etc). The principle of distinguishing between persistence and implementation is an important addition to existing literature on EMR-based ICS adherence. We showed that implementation was not disconcertingly low as previously described in studies not making this distinction, thus highlighting the fact that nonpersistence has a substantial

contribution to long-term suboptimal adherence to ICS. Interruption of ICS treatment for longer time periods needs to be addressed differently by clinicians in routine asthma care because this might have different causes and consequences than suboptimal implementation. Similar recommendations have been made in the field of hypertension by Vrijens et al[29] and are important for any long-term treatment. Further exploring the longitudinal relation between adherence and clinical outcomes can provide more insight into the interrelation between nonpersistence, implementation, and both previous and subsequent outcomes.

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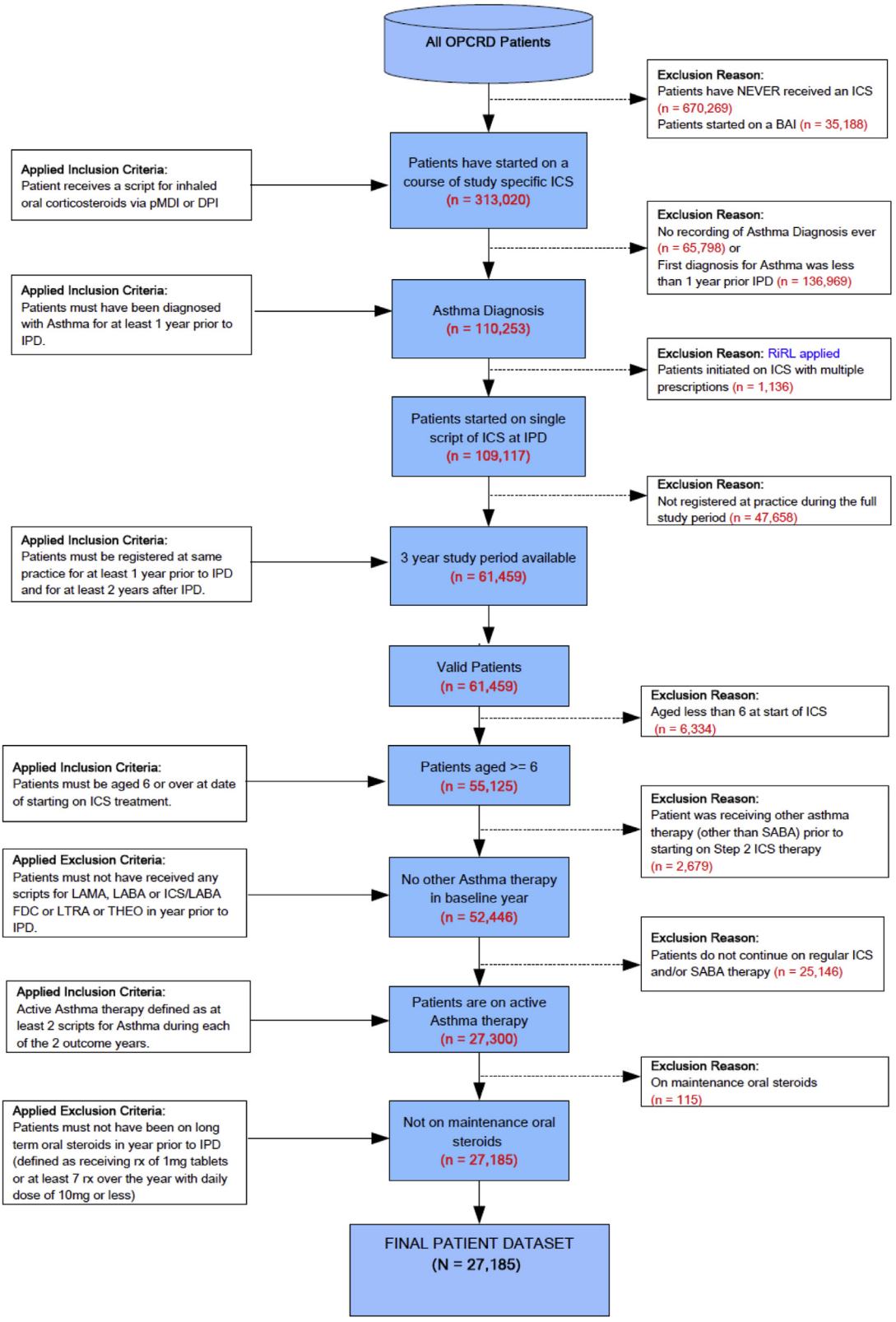

FIGURE E1. Flowchart of study to identify eligible patients. *BAI*, Breath-actuated pressurized metered dose inhaler; *DPI*, dry powder inhaler; *FDC*, fixed dosed combination; *IPD*, index prescription date; *LABA*, long-acting beta agonist; *LAMA*, long-acting muscarinic receptor antagonists; *LTRA*, leukotriene receptor antagonist; *pMDI*, pressurised metered-dose inhaler; *RiRL*, Research in Real Life; *SABA*, short-acting beta agonist; *THEO*, theophylline.

TABLE E1. Unconditional means and unconditional growth models for CMA I and CMA II at 6-mo windows

	CMA I		CMA II	
Parameter estimates	**Unconditional means**	**Unconditional growth**	**Unconditional means**	**Unconditional growth**
Fixed effects				
Mean CMA window 1 (intercept)	90.43* (0.13)	90.39*(0.17)	89.44* (0.12)	89.02* (0.15)
Rate of change (window order)	—	0.69* (0.07)	—	0.17* (0.07)
Variance random effects				
Within person (level 1)	169.00	158.13	180.41	167.06
Between person (level 2 intercept)	71.25	90.19	87.35	94.06
Rate of change (window order)	—	6.04	—	7.98
Correlation	—	−.66	—	−.61
AIC	238,498.3	238,324.7	292,417.3	292,240.7
ICC	.30	.36	.33	.36

AIC, Akaike information criterion; *ICC*, intraclass coefficient.
*$P < 0.001$.

TABLE E2. Model comparison for longitudinal models of CMA I and CMA II

Model	***df***	**AIC**	**BIC**	**logLik**	**Test**	**L. ratio**	***P* value**
CMA I							
Unconditional means (1)	3	238,498.3	238,523.2	−119,246.2	1 vs 2	179.64828	<.001
Unconditional growth (2)	6	238,324.7	238,374.3	−119,156.3	2 vs 3	76.62217	<.001
No random effect of time (3)	4	238,397.3	238,430.4	−119,194.7	3 vs 4	15.02439	<.001
No fixed effect of time (4)	5	238,414.3	238,455.7	−119,202.2	2 vs 4	91.64656	<.001
CMA II							
Unconditional means (1)	3	292,417.3	292,442.7	−146,205.7	1 vs 2	182.6558	<.001
Unconditional growth (2)	6	292,240.7	292,291.5	−146,114.3	2 vs 3	175.8662	<.001
No random effect of time (3)	4	292,412.5	292,446.4	−146,202.3	3 vs 4	169.9510	<.001
No fixed effect of time (4)	5	292,244.6	292,286.9	−146,117.3	2 vs 4	5.915223	.015

AIC, Akaike information criterion; *BIC*, Bayesian information criterion; *df*, degrees of freedom; *LogLik*, log likelihood; *L. ratio*, log-likelihood ratio statistic.