Determining Persistence with an Inhaled Corticosteroid in Asthma: Assessment Using an Objective Measurement vs the Self-Reported Foster Score

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\textbf{Introduction:} Adherence with controller medication is a major challenge in asthma management. Thus, a reliable method of measurement is mandatory to assess adherence.

\textbf{Aim:} To examine the test-retest reliability on adherence with inhaled corticosteroids in adults with asthma using a self-reported adherence score (Foster score).

\textbf{Methods:} Patients with asthma and >1 routine follow-up appointment at a university hospital outpatient clinic reported Foster scores. The objective Medication Possession Ratio (MPR) was calculated based on pharmacy redemption data and physician-prescribed doses of inhaled corticosteroids. The difference between Foster score and MPR at the first and second visit was assessed using a Bland–Altman plot, outcomes reported as limits of agreements and bias. Foster scores from both visits were used to calculate an intraclass correlation coefficient (ICC).

\textbf{Results:} Self-reported adherence with asthma controller medication measured by Foster score was significantly higher than the objective MPR (p < 0.0001). The Bland–Altman plot for MPR and Foster score at the first and second visit showed upper and lower limits of agreement of 83.5 – (−1.6) and 80.9 – (−6.9) and bias was 41.0 and 37.0, respectively. Of the included patients, 93.1% reported identical Foster scores between visits, resulting in an excellent ICC of 0.92. Absolute median difference between Foster scores and MPR at first and second visit was 8.7 percentage points (p = 0.049).

\textbf{Conclusion:} Foster score shows an excellent ICC; however, its poor agreement with objective measures of adherence suggests that clinicians should not rely on Foster scores alone to assess adherence with inhaled corticosteroids in patients with asthma.

\textbf{Keywords:} Foster score, medication possession ratio, controller medication, asthma, self-assessed adherence, self-reported outcome, adherence, persistence

\textbf{Introduction:} The goal of asthma management is to prevent asthma-related morbidity and mortality, such as exacerbations, persistent airflow limitation, asthma symptoms and reduce treatment side effects.\textsuperscript{1} Adherence to controller medication for asthma range from 30% to 70% as reported by the WHO.\textsuperscript{2} The Danish prevalence of asthma is 7500/100.000 citizens.\textsuperscript{3} Studies indicate that 30–70% of asthma patients have low adherence.\textsuperscript{4,5} Previous studies have calculated that patients should take 80% or more of their prescribed medicine to be adherent,\textsuperscript{6,7} hence 80% is a widely used...
Objective assessment of adherence can be calculated as Medication Possession Ratio (MPR), and is typically calculated as the total number of days supplied by medication, divided by the number of days in the period. MPR has previously been shown to correlate with asthma control. However, we have previously reported poor association between Foster score and MPR.

Adherence to medication may vary during the patients’ course of disease. The term persistency describes patients’ ability to withhold adherence to prescribed medication over time. In chronic diseases, persistency is a challenge, albeit a key feature for disease control. Although self-reported adherence has several potential pitfalls in persistency evaluation, it is often used given its advantages in clinical care, such as speed, efficiency, and low-cost. Using self-reported adherence to investigate persistency is, however, poorly investigated.

In further analyses of data from the cohort included in the previously published study from our group, we aim to investigate test-retest reliability of the Foster score over time, compared with MPR, in outpatient asthma patients.

Methods
This study is a cross-sectional, prospective study conducted at the respiratory outpatient clinics at the Department of Respiratory Diseases, Aalborg University Hospital (AaUH), Denmark (January 1-December 31, 2020) and Department of Respiratory Medicine, Copenhagen University Hospital-Hvidovre (CUHH), Copenhagen, Denmark (January 1-May 31, 2020).

Population
Patients diagnosed with asthma according to international guidelines were included by continuous enrolment at AaUH and CUHH, and patients with a routine follow-up appointment were screened for inclusion using electronic patient records. The inclusion criteria were i) more than one appointment at the outpatient clinic ii) age ≥18 years iii) diagnosed with asthma for at least 1 year prior to the index date. Exclusion criteria were i) prescribed ICS for less than one year prior to the index date ii) unclear dosage of medicine, that is prescriptions of multiple inhalers/changes in treatment regimen over a short period of time, where no reliable assessment of actual use of inhaled medicine could be obtained iii) receiving assisted medicine administration including living at a nursing home iv) inability to answer the questionnaire v) non-Danish residents.

Data Collection
Background characteristics were obtained on sex, age, Asthma Control Test (ACT), or Asthma Control Questionnaire (ACQ). Patients were considered highly symptomatic with an ACT ≤26 and an ACQ > 1.57. Spirometry data consisting of Forced expiratory volume in the first second (FEV\textsubscript{1}), FEV\textsubscript{1} in percent of predicted, Forced Expiratory Volume (FVC) and FVC in percent of predicted were collected through electronic patient records (Clinical Suite, CSC, Falls Church, Virginia, USA (AaUH) or Sundhedsplatformen, Epic Systems Inc., USA (CUHH)), and was obtained using Vyntus Spiro, Vyaire Medical, California, USA (AaUH) or Vitalograph Ltd., Buckinghamshire, UK (CUHH).

Foster scores were collected prior to or during physician consultation using either written questionnaires or verbally, as some appointments were conducted as telephone appointments due to the COVID-19 pandemic. Foster scores were obtained asking the question: “How many days, out of seven, do you take your medicine as recommended?”. The answer was subsequently divided by 7 and presented as percentages.

Pharmacy redemption data one year prior to the index date were obtained from the Common Medication Card (CMC) containing information on all of the redeemed medicine prescribed. Data included number of redeemed doses of SABA (short-acting β\textsubscript{2}-agonist), number of ICS doses redeemed, including combination therapy (ie, ICS/long-acting β\textsubscript{2}-agonist (LABA) or ICS/LABA/long-acting β\textsubscript{2}-agonist (LABA))
muscarinic antagonists (LAMA)). To account for inaccuracies in short prescription periods, any period shorter than 90 days was excluded. The MPR was calculated based on medication containing ICS, using the model described by Jensen et al.\textsuperscript{21}

Number of asthma exacerbations two years prior to the index date were assessed using number of redeemed prednisolone prescriptions from CMC, and number of hospitalizations due to asthma exacerbation, identified through ICD-10 discharge codes (J45.0-9) in the electronic patient records. Prescriptions of at least 37.5 mg P.O. prednisolone for at least 3 days, without concurrent hospitalizations equals a moderate asthma exacerbation, and hospital admission for over 24 hours and prescription of either P.O. or i.v. corticosteroids equals a severe asthma exacerbation.

**Adherence and Persistency**

Good adherence to prescribed inhalation medicine was defined as MPR > 0.8. Persistency was defined as the ability to maintain adherence >0.8 during the observation period.

**Ethics**

The study was approved by the Danish Patient Safety Authority (ref. 31–1521-118) and the Capital Region of Copenhagen’s Data Monitoring Board (ref. P-2020-648). The study was registered in the North Jutland Scientific Project Registry (ref 2020–101). All patients provided informed consent in accordance with the Declaration of Helsinki.

**Statistics**

Descriptive baseline characteristics were provided as means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on distribution. For categorical data, numbers and percentages were used. Non-normally distributed data were compared by Wilcoxon signed rank test, and a paired \( t \)-test if data were normally distributed. A p-value of 0.05 was considered statistically significant.

A Bland-Altman test was performed to compare the potential differences between MPR and Foster score at both visits. Data were reported as limits of agreement (LOA) and bias.\textsuperscript{28} A test retest, ICC (95% confidence intervals (CI)) was calculated for the Foster score and the Foster score/MPR-ratio, based on a mean-rating (k = 3), absolute-agreement, two-way mixed-effects model.\textsuperscript{29} All statistical work was conducted using IBM SPSS Statistics 27.0.

![Flowchart](https://doi.org/10.2147/JAA.S332756)

**Figure 1** Flowchart for in- and exclusion of patients in the population.

**Abbreviations:** AaUH, Aalborg University Hospital; CUHH, Copenhagen University Hospital Hvidovre.
Results

In total, 616 patients enrolled in this study, 58 had visited the out-patient clinic more than once and therefore met the inclusion criteria as shown in Figure 1. The mean period between Foster score assessments was 148.2 days (74.1SD).

Two-thirds of the population were female, and one-third had had a moderate- and one-fifth a severe exacerbation within the past two years prior to inclusion. Table 1 shows further baseline characteristics of the population.

Table 2 provides an overview of the different treatment regimens prescribed to the patients as well as their MPRs and Foster scores.

Persistence

There was no significant difference in Foster scores between first and second visit (p = 0.705), with 93.1% of patients reporting identical Foster scores and an ICC of 0.92 (0.86–0.95). A significant decline in MPR was observed from the first to the second out-patient visit (p = 0.046). Good adherence was recorded in 17.2% (10/58) of patients both at the first and the second visit, 10.3% (6/58) were persistently adherent, 7.0% (4/58) were adherent the first visit only, and 7.0% (4/58) at the second visit only.

Foster Score and MPR Agreement

Bland-Altman plots for MPR and Foster score at the first and second visit is shown in Figures 2 and 3. At the first visit, LOA was −1.6–83.5 and bias was 41.0. At the second visit, LOA was −6.9–80.9 and bias was 37.0.

MPR was significantly lower than Foster score at both first and second visit (both p < 0.0001). ICC for the Foster score/MPR-ratio was 0.84 (95% CI 0.73–0.91). Figure 4 shows the difference between first and second Foster score/MPR-ratio in the individual patients and, thereby, the variety of the discrepancy over time in a group of asthma patients. The absolute median difference between Foster score/MPR-ratios from first to second visit was 8.7 [2.9;17.5] percentage points (range 0 to 64.7), and the absolute mean difference between those was significantly different (p = 0.049).

Discussion

When assessed by Foster score (that is self-reported adherence to ICS), we found a significant over-estimation of adherence to ICS, compared to objectively assessed adherence calculated by MPR. Overall MPR improved by 7.7% between the two visits, while Foster score remained unchanged. Less than one-fifth of the included patients were adherent and only 10% were persistently adherent during the observational period.

Persistence

This study demonstrated a slight increase in overall MPR. However, the increase is well below clinically relevant improvements, typically estimated to approx. 25%. Similarly, due to the considerable variation in observation periods between subjects, any changes in adherence due to the increased clinical attention around the importance of adherence signaled by the questionnaire used are difficult to interpret, as interventions have mixed results in terms of lasting effects on adherence patterns and follow-up time being an important variable.

Overall persistence was low, even compared to other studies, reporting persistency rates of 20–30%. These studies comprised larger populations, which may make direct comparison difficult. However, it is intriguing to
see a low persistency in a group of patients followed in highly specialized units as the recruiting sites for this study. There are several plausible reasons for this, but use of more complex treatment regimens such as twice-daily or even twice-daily with multiple inhalers is known to influence adherence, and thus persistence, negatively.\(^{32,34}\) In the present study, patients were prescribed different inhalers. Second, the study period encompasses part of the COVID-19 pandemic, where the stance on ICS treatment and COVID-19 risk may possibly affect adherence, although trends to increase in adherence during the pandemic have been shown.\(^{35}\) It would be of interest to repeat the study at a larger scale. Nonetheless, the results underline the importance of focusing on persistency in patients followed in tertiary clinics.

**Foster Score and MPR Agreement**

In concordance with previous findings, this study demonstrated over-estimation of adherence when based on self-reporting.\(^{36–38}\) However, self-reported adherence is seemingly significantly higher in the present study, with approx. 94\% of patients claiming to be adherent to approx. 70\% in previously referred studies.\(^{29,30}\) There may be several explanations for this. For one, different self-reporting tools are used in these studies. Some enquire into greater detail and present different possible answers, which may be favorable compared to the simple, one-question Foster score, especially considering the multifaceted nature of controller adherence.\(^{34,39}\) Second, the methods for judging objective adherence differ between studies. The present study uses a nationwide register comprising all pharmacies in Denmark, allowing for complete follow-up in terms of MPR, making it a valid estimation for actual ICS purchase.\(^{40}\) Third, the statistical methods for evaluating the correlation between self-reported and objective adherence differ between studies.

A previous study on a larger patient population from the same cohort showed a weak, yet statistically significant association between Foster score and MPR.\(^{21}\) It may be

| Treatment and Adherence                                      | First Visit | Second Visit |
|--------------------------------------------------------------|-------------|--------------|
| **ICS Dose Prescribed**                                      |             |              |
| Low Dose                                                     | 9 (15.5\%)  |              |
| Moderate Dose                                                | 22 (37.9\%) |              |
| High Dose                                                    | 27 (46.6\%) |              |
| **Controller Therapy**                                       |             |              |
| ICS                                                          | 4 (7\%)     |              |
| ICS + LABA                                                   | 27 (46.6\%) |              |
| ICS + LAMA                                                   | 1 (1.7\%)   |              |
| ICS + LABA + LAMA                                            | 26 (44.8\%) |              |
| **Addition to Controller Therapy**                          |             |              |
| LTRA                                                        | 27 (46.6\%) |              |
| Theophylline                                                 | 2 (3.5\%)   |              |
| Yearly doses of SABA redeemed                                | 240 [0;800] |              |
| **Biologic Therapy**                                         |             |              |
| Foster score                                                 | 100 [100;100]| 100 [100;100]|
| Foster score of 7=100\%                                      | 54 (93.1\%) | 55 (94.8\%)  |
| **Medication Possession Ratio**                              |             |              |
| MPR in %.                                                    | 58.9 [40.48;71.92] | 63.42 [46.51;76.58] |
| MPR ≥80\%                                                    | 10 (17.2\%) | 10 (17.2\%)  |
| **Absolute differences in adherence in percentage points between:** |             |              |
| Foster score and MPR                                         | 40.95 (21.69) | 36.96 (22.39) |

**Note:** Treatment regimens of asthma and its medication adherence reported as Foster score and medication possession ratios for ICS.\(^*\) Dose size based on the NICE guidelines.

**Abbreviations:** ICS, inhaled corticosteroids; n, number of patients; SD, standard deviation; IQR, inter-quartile range; LABA, long-acting \(\beta\)_2-agonist; LAMA, long-acting muscarinic receptor antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting \(\beta\)_2-agonist; MPR, medication possession ratio.
argued that correlation and regression analyses are less suited when neither modality of measurement are deemed as gold standard. Based on these two studies, the use of Foster score only is not recommendable as there is a large discrepancy between patient assessed- and objective adherence.

In the present study, Bland-Altman testing revealed wide LOAs between Foster score and MPR with a skew towards increasing differences with lower MPR due to the remarkably large proportion of patients claiming perfect adherence. The imprecision of Foster scores, the resulting LOAs and large bias measurements suggest a significant risk of erroneous adherence assessment in a clinical setting when relying on Foster scores alone. The overall trend of imprecise self-reported adherence scores has resulted in multidimensional questionnaires regarding adherence, such as the Adherence Starts with Knowledge test, Test of Adherence to Inhalers, Medication Intake Survey-Asthma and the Medication Adherence Report Scale for Asthma that either directly incorporate objective adherence assessment or general recommendations to use both self-reported and objective measurements.

In conclusion, Foster score shows an excellent intra-class correlation coefficient, but poor agreement with objective measures of adherence clearly suggests that clinicians should not rely entirely on Foster scores alone to assess adherence. Furthermore, we find very poor persistency in adherence over time. This paper therefore underlines the importance of focusing on persistency when meeting the patient in a clinical setting.

Figure 2 Bland Altman plot of MPR plotted against the differences of Foster score minus MPR from the first visit. Green lines = Upper and lower limits of agreement, (−1.6 and 83.5). Red line = mean (41.0).

**Abbreviation:** MPR, medication possession ratio.

Figure 3 Bland Altman plot of MPR plotted against the differences of Foster score minus MPR from the second visit. Green lines = Upper and lower limits of agreement, (−6.9 and 80.9). Red line = mean (37.0).

**Abbreviation:** MPR, medication possession ratio.
Limitations
The use of MPR as a measurement of objective adherence is established as a valid form of assessing adherence but fails to reflect some forms of non-adherence such as redeemed but unused doses, and can be skewed by redemption in bulk or repeated redemptions in close intervals.45

Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure
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Figure 4 Difference between the differences of Foster score and Medication Possession Ratio from first to second visit.
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