ORIGINAL ARTICLE

Detection of exacerbations in asthma based on electronic diary data: results from the 1-year prospective BIOAIR study

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ABSTRACT

Background Objective measures are required that may be used as a proxy for exacerbations in asthma. The aim was to determine the sensitivity and specificity of electronic diary data to detect severe exacerbations (SEs) of asthma. A secondary aim was to identify phenotypic variables associated with a higher risk of exacerbation.

Methods In the BIOAIR study, 169 patients with asthma (93 severe (SA); 76 mild to moderate (MA)) recorded lung function, symptoms and medication use in electronic diaries for 1 year. Data were analysed using receiver-operator characteristics curves and related to physician-diagnosed exacerbations. Medical history and baseline clinical data were used to assess risk of exacerbation.

Results Of 122 physician-diagnosed exacerbations, 104 occurred in the SA group (1.1 per patient/year), 18 in the MA group (0.2 per patient/year) and 63 were severe using American Thoracic Society/European Respiratory Society criteria. During exacerbations, peak expiratory flow (PEF) and forced expiratory volume in 1 s significantly decreased, whereas day and night symptoms significantly increased. An algorithm combining a 20% decrease in PEF or a 20% increase in day symptoms on 2 consecutive days was able to detect SEs with 65% sensitivity and 95% specificity. The strongest risk factors for SEs were low Asthma Control Questionnaire score, sputum eosinophils ≥3%, body mass index >25 and low quality of life (St George's Respiratory Questionnaire), with ORs between 3.61 and 2.22 ($p<0.05$).

Conclusions Regular electronic monitoring of PEF and asthma symptoms provides an acceptable sensitivity and specificity for the detection of SEs and may be suitable for personal internet-based monitoring of asthma control.

Key messages

What is the key question?
- Which variables (symptoms, rescue medication use or lung function) represent the highest sensitivity and specificity to detect severe exacerbations in asthma patients?

What is the bottom line?
- Monitoring of PEF and symptoms of asthma gives the highest sensitivity and specificity for use as a proxy of severe exacerbations in asthma and may be used in personal, electronic or internet-based monitoring of asthma control.

Why to read on?
- The study identifies and validates objective criteria for the capturing of severe exacerbations.

INTRODUCTION

Asthma exacerbations involve episodes of acute worsening of the disease. The increase in symptoms (shortness of breath, cough, wheezing and chest tightness) results in a limitation of daily activities and the need for unscheduled healthcare intervention.[1 2] Exacerbations may also involve severe, life-threatening events, and they represent a great burden for the patients and for the healthcare systems. The level of asthma control is defined by clinical symptoms, and the treatment necessary to maintain this control and to avoid exacerbations.[1 3 4] Accordingly, definitions of severe, problematic or difficult-to-treat asthma incorporate exacerbations as a component to assess severity, in adults[5 6] and in children.[7] When testing the efficacy of new drug treatments in asthma, exacerbation frequency is often used as a primary outcome variable.[8] To identify exacerbations in everyday medical practise and in clinical trials, a wide range of unvalidated criteria have been applied.[8] Recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[8] defined severe exacerbations (SEs) according to the need for systemic corticosteroid use, a visit to an emergency department or hospital admission, whereas moderate exacerbations were defined by a deterioration in symptoms, decrease in lung function and increase in rescue medication use. However, the guidelines recognised that there is a remarkable absence of studies that have analysed and validated objective outcomes which may be used in the future to define exacerbations in asthma and thus can be regarded as a proxy for exacerbation.

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The primary goal of our study was to analyse the sensitivity and specificity of different variables to detect SEs in patients with asthma based on data collected during a 1-year follow-up with electronic diaries in the BIOAIR (Longitudinal Assessment of Clinical Course and Biomarkers in Severe Chronic Airway Disease) cohort of comprehensively examined patients. The electronic diary data included lung function (peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1)), use of a short-acting β agonist (SABA) as rescue medication, day and night symptoms, and limitation of daily activities. The analysis was performed to ascertain whether or not there were patterns in the electronic diary recordings that related to independently determined physician-diagnosed SEs. The overall aim of this analysis was to define the thresholds of various symptoms and lung function measurements that distinguish severe from moderate exacerbations at the time that they occur, as such values may be necessary for the future development of internet-aided personalised healthcare plans[9] or in clinical trials. The secondary goal of our study was to analyse potential risk factors for the development of SEs from medical history and baseline clinical data.

METHODS

Study design

The BIOAIR trial was a project on biomarkers and clinical outcomes partly supported by the European Union with a particular focus on severe asthma. Patients with asthma were screened and allocated to severe (SA) or mild to moderate asthma (MA) groups. After a 4-week period of treatment optimisation, patients were randomised to a systemic steroid versus placebo crossover intervention during the biomarker characterisation phase following which they were followed up for at least 1 year (figure 1). Information regarding lung function, biomarkers (induced sputum, peripheral blood, exhaled nitric oxide), atopy, medical history, asthma control (evaluated with the use of the Juniper Asthma Control Questionnaire (ACQ))[10] and quality of life (evaluated with the use of St Georges Respiratory Questionnaire (SGRQ))[11] was collected at baseline. In addition, lung function (PEF and FEV_1), rescue medication use (SABA), day and night symptoms, and limitation of activities were recorded daily using electronic diaries (Vitalograph Electronic PEF/FEV_1 Diary, XM version, Vitalograph Ltd, Buckingham, UK). For further details regarding the exact questions, scales used and definitions of asthma severity please refer to the online repository materials. The study was registered at clinicaltrials.gov (NCT00555607) and the protocol was approved by the local ethics committees and drug regulatory authorities in the 12 participating centres.[12]

Exacerbations

ATS/ERS recommendations[8] were used to define exacerbations as events clinically identified to be outside the patient's usual range of day-to-day asthma variation, and requiring a change in controller treatment. A SE was retrospectively defined as a worsening requiring at least 3 days' use of oral corticosteroids, or as an increase in systemic corticosteroids from an individual maintenance dose, or as a visit to the emergency room or hospitalisation. Likewise, a moderate exacerbation was defined as a period requiring a change in treatment, but not fulfilling the criteria of a SE. In line with the recommendations of the ATS/ERS task force,[8] mild asthma exacerbations were not identified as they could not be distinguished from a transient loss of asthma control. During the study, the patients were supplied with written cards advising them to contact the study physician or nurse immediately (all centres available 24 h/day and 7 days/week) in case of a troublesome loss of asthma control (increase in symptoms and rescue medication use, decrease in daily activities or quality of life). Based on medical history, symptoms, medication use and additional tests, the responsible physician then labelled the event as an asthma exacerbation. Day 1 of an exacerbation was defined as the day on which the subject visited the clinic due to an exacerbation (figure 1). For further details please refer to the online repository.

Data collection and statistical analysis

Data were entered into a central database through a web-based Case Record Form system developed specifically for the BIOAIR study. Patient baseline characteristics are expressed as mean±SEM. Analysis of variance, followed by Fisher's protected least significant difference test, was used to test differences between the groups. The values collected during exacerbations were compared with the same subject's baseline values, defined as the average of the last 10 days of the treatment optimisation period (figure 1). These values were selected as a reasonable approximation of 'best values'. Other comparators used were 2, 5 and 7 days respectively before the start of an exacerbation. Values during exacerbations were analysed in three different ways: on the day of reported exacerbation (values measured when the patient visited the clinic due to symptoms of an exacerbation); the average of the values from the two worst consecutive days (peak drop in PEF) during the 10-day exacerbation window after the first visit; and the average of 10 days from the start of the exacerbation. The results

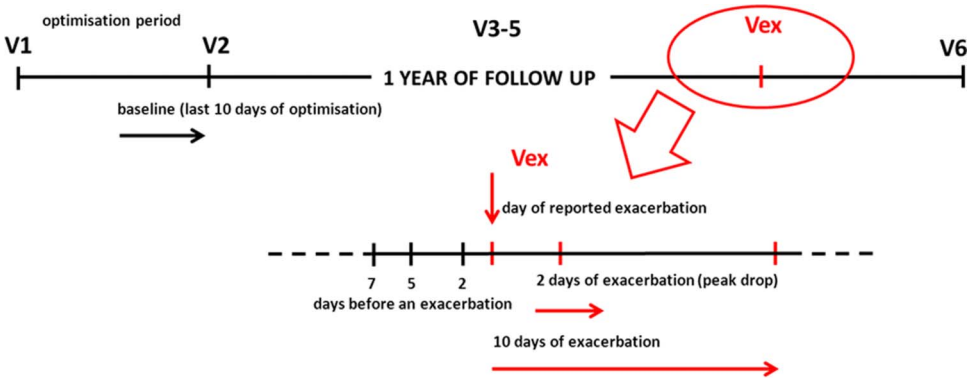


Figure 1 Study flow chart of the 1-year follow-up. Lower line represents illustration of how calculations were made during the exacerbation period requiring Vex. This figure is only reproduced in colour in the online version.

are presented as percentage change from baseline. To evaluate the statistical significance of the findings, the Mann–Whitney test was used. To study the sensitivity and specificity of different parameters for the detection of exacerbations, receiver-operator characteristics (ROC) curves were analysed. ROC curves usually compare a certain variable measured in 'controls' and 'cases' to determine the cut-off values for this variable that give the optimal specificity and selectivity for defining a particular disease. Here 'cases' were represented by the change in a certain variable measured on the first 2 days of a doctor-diagnosed exacerbation compared with baseline. 'Controls' were represented by the change in a certain variable measured on all normal days outside of the exacerbation period compared with baseline, to provide an indication of normal fluctuations in the relevant variable. The variables studied were PEF, FEV_1, day and night symptoms, and rescue medication use, and change in these values, either on the first 2 days of the exacerbation or on all days outside of the exacerbation period, were compared with baseline (patient's best as a mean of the last 10 days of the optimisation period).

To identify potential factors associated with the development of exacerbations, subjects with reported exacerbations were compared with those who did not have exacerbations during the 1-year follow-up period. A multivariate logistic regression model including all potential predictors with a univariate p value <0.1 was built, and adjusted for atopy, sex, age and smoking status. SPSS V.17.0 software was used for statistical analysis. A p value <0.05 was considered a statistically significant difference for all tests.

RESULTS

Patient characteristics

A total of 169 subjects were screened and included in the BIOAIR study.[12] Table 1 displays their demographic data and baseline characteristics. In comparison with MA, patients with SA were older (50 vs 42.2 years), had a higher body mass index (BMI) (28.5 vs 25.0 kg/m^2), lower lung function (FEV_1 % of predicted: 70.4% vs 88.7%) and poorer asthma control (Juniper ACQ score 2.03 vs 1.03). Comprehensive data on the patient cohorts are reported elsewhere.[12] As many as 53 patients with SA (56.9% of those screened and randomised) and 53 with MA (69.7%) completed 1-year of follow-up. Mean adherence to the study protocol regarding daily measurements with the electronic diaries reached 86.6% in patients with SA and 79.4% in those with MA. Only events for which >60% of days were completed in patient diaries have been used for further calculations.

Number of exacerbations

During the 1-year follow-up, 68 patients (40.2% of the whole asthma cohort) had a total of 122 exacerbations in the range of one to six events per year. Figure 2A displays the distribution of exacerbations in the whole asthma cohort and figure 2B the monthly distribution over the 1-year follow-up. The average number of exacerbations per patient per year was 0.72 for the whole asthma cohort.

The vast majority of exacerbations occurred in the SA group (n=93 patients) in which a total of 104 exacerbations were recorded. The average number of exacerbations per patient per year was 1.12 in the SA group, although 41 of 93 patients in the SA group did not have any exacerbations. Out of patients who did have exacerbations, the true number of exacerbations per year was therefore 2.0 (104/52). Forty-four exacerbations in the SA group (42.3%) were severe but did not require hospitalisation, and in 14 cases (13.7%) hospitalisation was necessary.

In contrast to SA, only 16 patients in the MA group (22.2%) had a total of 18 exacerbations during the 1-year follow-up. The number of exacerbations per patient per year was 0.24. Five exacerbations were severe (27.8%). No hospitalisations due to asthma exacerbations were reported in the MA group.

Table 1 Demographic data and baseline characteristics of the study cohort (mean values (±SEM), unless stated differently)

	Severe asthma	Mild to moderate asthma	p Value
Patients in the BIOAIR cohort (n)	93	76	ND
Age (years) (min–max)	**50.0±1.3 (18–72)**	**42.2±1.5 (20–70)**	**0.001***
Women (%)	58	61	0.982†
FEV_1 (% pred)	**70.4±2.1**	**88.7±2.1**	**<0.0001***
FEV_1 (litres)	**2.04±0.08**	**2.79±0.08**	**<0.0001***
FEV_1/FVC	0.67±0.01	0.70±0.01	0.093*
Reversibility (% of change)	9.4±0.8	10.6±0.7	0.192*
ICS (median (mean±SD)) Beclomethasone eq.	**1600 μg* (2064±939.7)**	**800 μg (614±218.6)**	**<0.0001***
OCS (median (mean±SD; min–max)) prednisolone eq.	10 mg (14.15±11.8; 2–50)	–	ND
BMI (kg/m^2)	**28.5±0.6**	**25.0±0.4**	**<0.0001***
ACQ (Juniper)	**2.03±0.1**	**1.03±0.7**	**<0.0001***
QoL (SGRQ)	**45.9±2.1**	**22.5±2.0**	**<0.0001***
CRP (mg/litre)	6.1±0.9	3.5±0.6	0.092*
Atopy (%)	43	48	0.642†
F_ENO (ppb)	46.3±6.2	40.1±4.1	0.962*
Sputum cells ($\times 10^6$)	3.34±1.02*	1.83±0.34	0.455*
Sputum eosinophils (%)	**16.7±3.49***	**5.79±1.71**	**0.018***
Sputum neutrophils (%)	42.2±3.7	44.2±4.4	0.338*

Atopy defined as at least one positive skin prick test. **p<0.05**
*Mann–Whitney U test.
†χ^2 test.[12]
ACQ, Asthma Control Questionnaire; BIOAIR, Longitudinal Assessment of Clinical Course and Biomarkers in Severe Chronic Airway Disease; BMI, body mass index; CRP, serum C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; ND, not determined; OCS, oral corticosteroid; QoL, quality of life; SGRQ, St George's Respiratory Questionnaire.

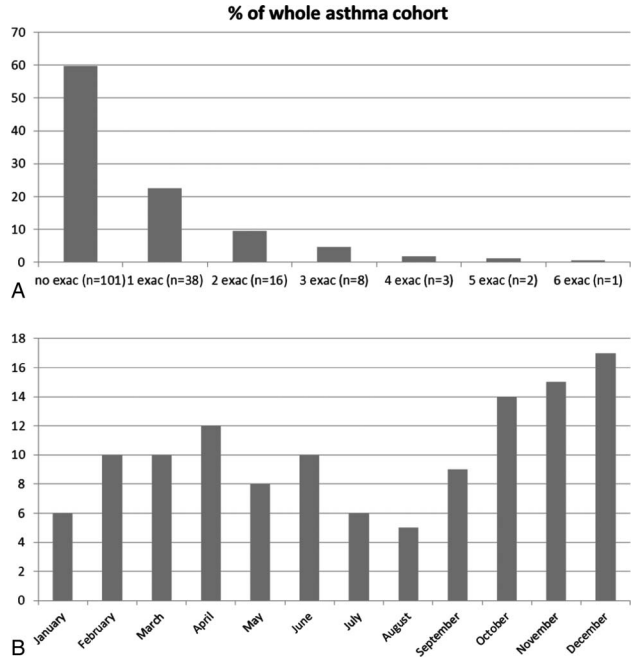


Figure 2 Percentage and number (n) of patients with asthma exacerbations (exac) during 1 year of follow-up in the whole asthma cohort ((A) n=169), and the monthly distribution of exacerbations over the 1-year period (B).

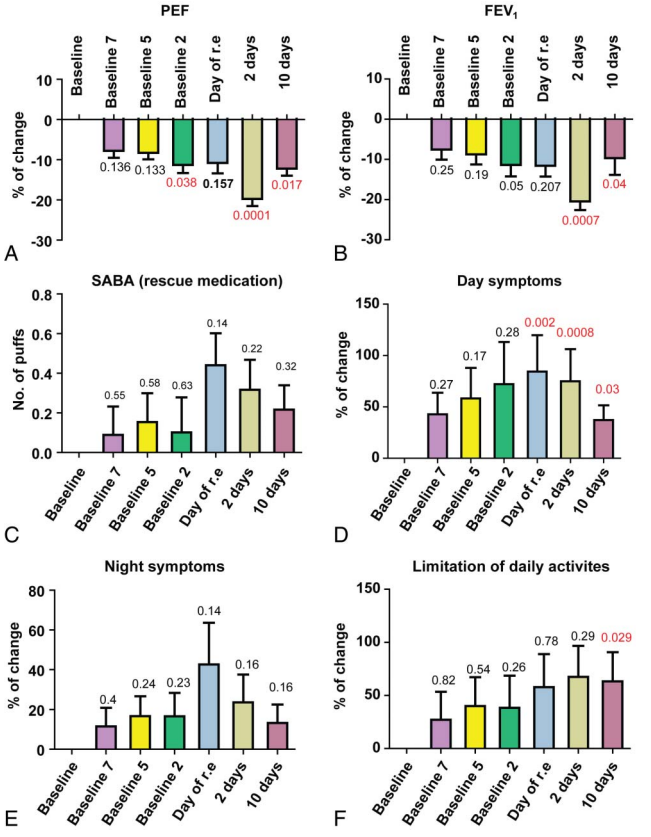


Figure 3 Percentage of change from baseline (=personal best during optimisation phase of the study, calculated as average of the last 10 days of the treatment optimisation period) for the different studied variables during exacerbations in patients with severe exacerbations. (A) Peak expiratory flow (PEF), (B) forced expiratory volume in 1 s (FEV_1), (C) rescue medication (change in number of puffs), (D) day symptoms, (E) night symptoms and (F) limitation of daily activities; error bars represent SEM, Mann–Whitney test. Day or r.e.: the day of reported exacerbations which represents values measured during an unscheduled visit to the clinic due to symptoms of exacerbations (1 day); 2 days: the average of the values from the two worst consecutive days during exacerbation; 10 days: the average of 10 days during exacerbations; 2, 5, 7 days baseline: the average of −2, −5 or −7 days before an exacerbation. SABA, short-acting β agonist. This figure is only reproduced in colour in the online version.

In total, 63 exacerbations were classified as severe based on ATS/ERS criteria.[8] In the current report, data regarding all SEs in both groups (severe and mild-to-moderate groups combined) are reported. Complete data on all exacerbations are displayed for the whole asthma group, and for SA and MA groups separately, in the online repository.

Changes recorded during SEs

Figure 3 displays changes in the studied variables during different periods in relation to the day of exacerbation. The data are expressed as a percentage of the personal best value recorded after treatment optimisation at the beginning of the study (figure 1 shows how calculations have been made). For all variables, there was a gradually increasing change from 7 days before an exacerbation until 2 days before.

The maximal drop in PEF (the average of the values from the two worst consecutive days vs baseline) was 19.8% (p=0.0001). During the 10-day period following an exacerbation, a 12.2% decrease in PEF was observed (p=0.017) (figure 3A). During the 2 days of maximum deterioration, FEV_1 decreased by 20.4% (p=0.0007), and there was a 9.7% decrease in FEV_1 during the 10 days of an exacerbation (p=0.04) (figure 3B).

There were no significant changes in the use of SABAs before or during the exacerbations (figure 3C), although the numerical value was 0.44 puffs higher on the day of the reported exacerbation.

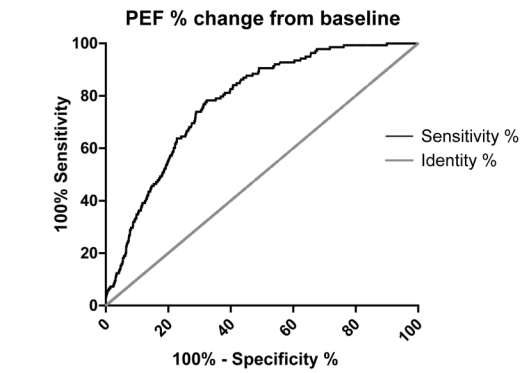
With respect to day and night symptoms, there was a significant increase (41.0%) in day symptoms on the day of the reported exacerbation compared with baseline (p=0.002) but no change in night symptoms (p=0.14; figure 3D,E).

For the variable 'limitation of daily activities', a significant increase was observed (63.1%, p=0.029) when the whole 10-day period of exacerbation was analysed.

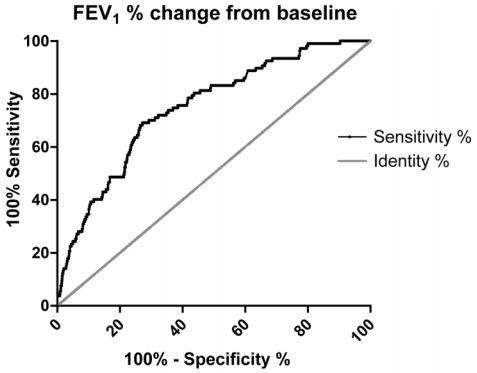
Sensitivity and specificity of evaluated outcome variables to detect a SE

ROC curves for the percentage decrease in PEF and FEV_1 versus baseline values in SEs are presented in figure 4. Testing previously used cut-off points, such as a 30% or 20% decrease in PEF,[8] resulted in a sensitivity of 29% and 45% respectively, and a specificity of 92% and 85% respectively (table 2). A 30% or 20% decrease in FEV_1 resulted in a sensitivity of 31% and 49% respectively, and a specificity of 92% and 82% respectively. The sensitivity and specificity of different cut-off points for other tested variables (change in FEV_1, increase in rescue drug use, increase in day and night symptoms) for the whole study group are presented in table 2.

We also assessed whether the combination of two or more variables increased the sensitivity and specificity of a given definition to detect exacerbations. Based on the analyses of single variables (see above), combinations that were most likely to increase the sensitivity and specificity were selected. Thus, the combination of a 20% decrease in PEF on 2 consecutive days and/or a 20% increase in day symptoms on 2 consecutive days (combined predictors



AUC	Std. error	95% CI	p
0.78	0.32	0.88 – 0.96	<0.0001



AUC	Std. error	95% CI	p
0.75	0.52	-0,26 – 1.76	<0.0001

Figure 4 Receiver-operator characteristic curves for change in peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1) as variables to detect physician-diagnosed exacerbations in the whole asthma group. To build receiver-operator characteristics curves, change in a certain variable measured on the first two days of a doctor-diagnosed exacerbation vs baseline was compared to the change in a certain variable measured on all normal days outside of the exacerbation period vs baseline for all studied variables (PEF, FEV_1, day and night symptoms, and rescue medication use). AUC, area under the curve.

used), and the combination of a 20% decrease in FEV_1 and/or a 20% increase in day symptoms on 2 consecutive days (combined predictors used) were evaluated (table 3). The highest sensitivity and specificity were found when an exacerbation was defined as a combined 20% decrease in PEF on 2 consecutive days and a 20% increase in day symptoms on 2 consecutive days. This definition was able to detect a SE with a sensitivity of 65.0% and a specificity of 94.9%. Using FEV_1 instead of PEF as a lung function variable in combination with day symptoms gave the same specificity but a slightly lower sensitivity (60.4%).

Baseline subject characteristics associated with the development of exacerbations

The univariate analysis of factors (baseline patient characteristics) associated with the development of SEs, or any exacerbations, in the whole asthma group and SA group are presented in online repository table E5. When adjusted for possible confounding factors (age, smoking, atopy and gender) in multivariate logistic regression models (table 4), Juniper ACQ score >1.36, sputum eosinophils ≥3%, BMI >25 and SGRQ score >34.6 were associated with an increased risk of SEs. Factors associated with an increased risk of developing any exacerbation in our asthma cohort were a history of smoking, SGRQ score >34.6, Juniper ACQ score >1.36, atopy and reversibility ≥12%. In the SA group a history of smoking, female gender, age <65 years and Juniper ACQ score >2.14 were associated with an increased risk of developing an exacerbation. Having a BMI >30 was associated with a decreased risk for the development of exacerbations in SA.

Table 2 Sensitivity and specificity of selected cut-off points for the parameters evaluated to detect severe exacerbations

	Severe exacerbations	
Parameter	**Sensitivity % (95% CI)**	**Specificity % (95% CI)**
Decrease in PEF (% change vs baseline)		
30	29 (21.6 to 37.0)	92 (91.5 to 92.0)
20	45 (36.0 to 53.6)	85 (84.8 to 85.7)
15	54 (45.6 to 62.8)	80 (79.6 to 81.0)
Decrease in FEV_1 (% change vs baseline)		
30	31 (22.3 to 40.5)	92 (91.0 to 92.0)
20	49 (38.8 to 82.0)	82 (81.3 to 82.7)
15	63 (53.7 to 72.6)	75 (74.0 to 75.7)
Increase in SABA use (number of puffs)		
2	4 (2.2 to 5.7)	97 (96.6 to 97.3)
1	4 (2.4 to 5.9)	96 (95.5 to 96.3)
Increase in day symptoms (% change vs baseline)		
30	44 (34.5 to 53.0)	84.6 (84.6 to 86.0)
20	46 (37.0 to 55.6)	84.9 (83.4 to 84.7)
Increase in night symptoms (% change vs baseline)		
30	34 (25.8 to 44.0)	85 (84.2 to 85.5)
20	41 (31.6 to 50.4)	82 (81.3 to 82.7)

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; SABA, short-acting β agonist.

DISCUSSION

Guidelines recognise the prevention of asthma exacerbations as a major goal of asthma treatment.[1] The ATS/ERS Task Force on asthma control and exacerbations highlighted the absence of studies aimed at validating objective criteria for the capturing of

Table 3 Sensitivity and specificity of combined parameters to detect severe exacerbations

	Severe exacerbations in the whole asthma cohort	
Definition of exacerbation	**Sensitivity (%)**	**Specificity (%)**
20% decrease in **PEF** on 2 consecutive days **and** 20% increase in **day** symptoms on 2 consecutive days	13.3	99.5
20% decrease in **PEF** on 2 consecutive days **or** 20% increase in **day** symptoms on 2 consecutive days	**65.0**	**94.9**
20% decrease in **FEV_1** on 2 consecutive days **and** 20% increase in **day** symptoms on 2 consecutive days	13.2	99.3
20% decrease in **FEV_1** on 2 consecutive days **or** 20% increase in **day** symptoms on 2 consecutive days	**60.4**	**94.8**

Bold used to underline the most significant parts of the definition. FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow.

Table 4 Adjusted ORs in multivariate logistic regression models for factors associated with the development of severe exacerbations and any exacerbations in the whole asthma cohort and severe asthma group

Factor	OR	95% CI	p Value	Comments
Severe exacerbations				
Juniper ACQ >1.36 (median)	3.61	1.7 to 7.65	0.001	Adjusted for age, gender, smoking and atopy
Sputum eosinophils ≥3%	3.27	1.13 to 9.42	0.028	As above
BMI >25	2.9	1.3 to 6.5	0.01	As above
SGRQ >34.6 (median)	2.22	1.03 to 4.8	0.042	As above
Whole study group				
Smoking history	3.69	1.66 to 8.21	0.001	Adjusted for age, gender and atopy
SGRQ >34.6 (median)	3.09	1.41 to 6.76	0.005	Adjusted for age, gender, smoking and atopy
Juniper ACQ >1.36 (median)	3.07	1.49 to 6.29	0.002	Adjusted for age, gender, smoking and atopy
Atopy	2.06	1.01 to 4.19	0.047	Adjusted for age, gender and smoking
Reversibility ≥12%	2.04	1.0 to 4.14	0.049	Adjusted for age, gender, smoking and atopy
Sputum eosinophils ≥3%	2.39	0.89 to 6.37	0.081	As above
FEV_1 ≤80%	1.93	0.95 to 3.93	0.071	As above
Severe asthma				
Smoking history	9.14	2.47 to 33.87	0.001	Adjusted for age, gender and atopy
Female gender	4.47	1.55 to 12.84	0.005	Adjusted for age, smoking and atopy
Age <65 years	4.28	1.03 to 17.82	0.046	Adjusted for gender, smoking and atopy
Juniper ACQ >2.14 (median)	3.58	1.14 to 11.29	0.029	Adjusted for age, gender, smoking and atopy
BMI >30	0.28	0.09 to 0.87	0.028	As above
SGRQ >44.1 (median)	2.465	0.85 to 7.17	0.098	As above

There were no statistically significant factors found in the mild to moderate asthma group.
ACQ, Asthma Control Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SGRQ, St George's Respiratory Questionnaire.

exacerbations.[8] In this study, we analysed electronic diary data collected over a 1-year period from 169 patients with asthma. We assessed how changes in the recorded outcomes related to 122 physician-diagnosed exacerbations determined during the study period, independently of the information provided by the patients in the diaries. We found that when evaluating individual outcomes changes in lung function (PEF and FEV_1) gave the highest sensitivity and specificity as a proxy for exacerbations, whereas day and night symptoms, and in particular use of rescue medication, were less suitable as indicators of an exacerbation (table 2). Moreover, the combined criteria of a 20% decrease in PEF on 2 consecutive days or a 20% increase in day symptoms on 2 consecutive days, further increased sensitivity and specificity to close to 65% and 95%, respectively (table 3).

The strength of the study lies in the careful patient selection, prospective design and 1-year follow-up period. Strict diagnostic criteria were applied to recruit a group of patients in whom comorbidities and poor compliance with treatment were unlikely to confound the study results. In addition, all patients underwent a 4-week treatment optimisation period with high doses of inhaled corticosteroids and long-acting β agonists before the follow-up year, making it highly likely that each subject's personal best lung function and asthma control were determined. Moreover, all information was collected using electronic diaries and the data were related to the time points for independently physician-diagnosed exacerbations. This approach was recommended by the ATS/ERS Task Force,[8] and significantly increases the quality of the database compared with paper diaries and other strategies in which data are usually collected retrospectively, and therefore more likely to contain errors.[8 13–15]

Previous definitions of exacerbations have used a wide panel of unvalidated or partly validated criteria.[8] Most commonly, a decline in PEF of 20–30% has been applied. Usually at least 2 consecutive days with a lower PEF are required; however, in some studies a single day with a low PEF measurement was accepted.[16] Furthermore, changes from baseline PEF, rather than from on-treatment PEF values, have been used. In our study, the average PEF value obtained after 2 weeks of treatment optimisation were used as a baseline for further analyses. Gelb *et al*[17] evaluated the use of lung function parameters for identifying patients with asthma at higher risk of exacerbation and found that using an FEV_1 value of 76% predicted as a cut-off value resulted in a sensitivity of 91% and a specificity of 50%. However, we found that a change in PEF provides a somewhat higher sensitivity and specificity than FEV_1, and moreover, is easier to measure outside the hospital setting. Using a 20% decrease in PEF compared with the baseline personal best gave a higher sensitivity than using 30% as a cut-off point. This agrees with the findings of Tattersfield *et al*,[18] in which a fall of at least 20% in PEF was seen in 69% of all exacerbations, whereas a fall in PEF of at least 30% only occurred in 45%. Similarly, Chan-Yeung *et al*[19] found that a 30% decrease in PEF was too stringent a criterion for defining an acute exacerbation.

In our study, all electronic diary card data started to change a week before the recorded exacerbation (figure 3), supporting our strategy of recording personal best values to increase sensitivity. In the trial by Tattersfield *et al*[18] a similar pattern of changes in PEF, symptoms and β-agonist use prior to exacerbations was found, suggesting that none of these measures provides an earlier warning of an approaching exacerbation. In our study, an increase in day symptoms gave a higher sensitivity and specificity than night symptoms, thus this variable was incorporated into the combined definition. To our surprise, rescue medication (SABA) use gave the lowest sensitivity and specificity of all factors studied. This result is presumably due to changes in clinical practice in Europe during the last decade with widespread use of LABAs. This has caused a significant decrease in the use of SABAs as a rescue drug in patients with SA. The results of our study suggest that an increase in SABA use, due to

its low sensitivity, should not be recommended as a variable for detecting exacerbations in asthma. However, it needs to be acknowledged that self-reported inhaler use poorly reflects actual use as determined by electronic monitoring with a tendency to under-report, especially regarding overusage.

The use of mathematical correlations and distribution properties of electronic lung function data have previously been used to define the probability of exacerbations.[20 21] Thamrin *et al*[22] proved that lung function history quantified by fluctuation analysis provides additional information and may help characterise the current state of asthma control. Taking into account the results of our study, we propose that monitoring of electronic lung function data together with other variables such as symptoms, may further increase the prediction of exacerbations in real time. In the future, such strategies incorporated into specific software for smartphones could be integrated into an asthma self-management plan to improve the quality of healthcare and optimise the level of asthma control.[23] The current finding of high sensitivity for the combination of 20% decrease in PEF or 20% increase of symptoms supports use of such an algorithm to define a SE and thus to serve as a signal for the patient to contact the healthcare provider. Perhaps the addition of baseline patient profiles to such strategies may further enhance the effectiveness of monitoring by providing individualised levels of alert. For example, in our SA cohort, the multivariate statistics indicated that women with low baseline asthma control were particularly exacerbation prone.

One of the limitations of our study may be the possibility that not all exacerbations were captured and reported during the 1-year follow-up. Thus, some events might have been treated at home without contact with the supervising clinical centre, as some patients may have occasionally followed their own pre-study personalised asthma action plans. To address this issue we performed a post hoc analysis of the data from the electronic diaries. With the application of our 20%PEF+20%Sx (symptoms) exacerbation definition, we found 155 additional events in the SA group and 6 in the MA group that could be regarded as possible non-reported exacerbations. It is remarkable, however, that all those possible missed events were found in the very same patients who had already been identified as having exacerbations in the SA and MA cohorts. No extra events were identified in subjects who did not have physician-verified exacerbations, and the allocation to the analysed groups was the same. Thus, we believe that this has not had any impact on our analysis of the specificity and sensitivity of different indicators, but is more likely to have resulted in an underestimation of the number of exacerbations per patient. Taken together, the post hoc analysis supports the validity of the '20%PEF+20%Sx' algorithm and also supports previous indications that patients with exacerbations represent one specific phenotype.[24]

In conclusion, the results of our study indicate that monitoring of PEF and symptoms of asthma gives the highest sensitivity and specificity for use as a proxy of SEs in asthma. Increased use of rescue medications (SABA) was of little value for capturing exacerbations, presumably due to recent changes in therapeutic routines.

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Contributors Primary data aggregation and statistical analyses were done by MK, SH and SED, and then discussed and interpreted with the other coauthors at face-to-face meetings. MK wrote the first draft of the manuscript. Revisions were made by MK together with SED and in an interactive process including all coauthors. All authors participated in the study design, conduction of the trial, collection and interpretation of data, and critical review of the draft versions of the report.

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Online repository materials

Kupczyk M et al.

Detection of exacerbations in asthma based on electronic diary data - results from the one year prospective BIOAIR study

METHODS

Study design

The BIOAIR study was a multicentre trial, consisting of an initial cross-sectional comparison of patients with severe, mild-to-moderate asthma, followed by an optimisation of treatment, double-blind oral steroid intervention and a longitudinal (1 year) follow up.

Subjects

Patients selected by 12 European centres were recruited to the study. They were 18 to 80 years of age, and after screening they were allocated to an appropriate subject group, either mild-to-moderate or severe asthma. By definition all reports resulting from the BIOAIR trial share the same methodology of the cohort selection and the baseline characteristics of the included patients.

Diagnosis of asthma had to have been confirmed by a pulmonary specialist, and the patients had to fulfill at least one of the four criteria for reversible airway obstruction as documented during the last 5 years before the study or at screening visit, namely:

1) an increase in FEV_1 (Forced Expiratory Volume in 1 second) ≥ 9% of predicted (or improvement of 200 ml) after administration of four puffs of 100 μg salbutamol dose-aerosol

inhaled via a spacer, or after additional inhalation of four puffs of 20 μg ipratropium bromide administered through a large volume spacer;

2) mean diurnal variation in Peak Expiratory Flow (PEF) of ≥ 15% on ≥ 4 days/week for at least 2 weeks, as calculated by the following equation: (highest PEF – lowest PEF)/mean PEF;

3) an increase in FEV_1 of at least 400 ml after a course of prednisolone 0.5 mg/kg/day for 14 days;

4) in patients with a FEV_1 ≥ 70% predicted, a demonstrated bronchial hyperresponsiveness to histamine, methacholine, isocapnic hyperventilation, exercise or other indirect challenges (according to established local methods).

Patients included in the severe asthma (SA) group had to have been under specialist treatment for at least one year and to have experienced at least one exacerbation during the year preceding the study start. Severe asthmatics had to require continuous treatment with high doses of inhaled steroids (at least 1600 μg/day budesonide or beclomethasone, 800 μg/day fluticasone or equivalent). For those taking oral steroids, the inhaled dose of steroids had to be at least 800 μg/day budesonide or beclomethasone, 400 μg/day fluticasone or equivalent. In addition, the patients had to require continuous treatment with long-acting β-agonists or oral theophylline, as documented for at least one year (E1). Patients in the MA group had stable disease, received daily treatment with a maximum of 800 μg/day budesonide, used short-acting β-agonists (SABA) as needed but did not require treatment with LABA and had not experienced either exacerbations or hospitalisations in the last year.

Patients were excluded if they were pregnant, had a history of alcohol or illicit drug abuse, had other acute or chronic pulmonary disorders or had clinically relevant psychiatric disease. Current smokers or patients who had smoked for more than 5 pack years were also excluded. Patients were not allowed to be taking immunosuppressants other than corticosteroids, or undergoing immunotherapy. Patients receiving chronic oxygen therapy were also excluded. All exacerbations and adverse events during the study were recorded in the study case report form for further analysis.

Upon inclusion in the study, all patients underwent a four-week treatment optimisation period. Fixed minimal doses of medications used by patients during the optimisation are presented in Table E1. Degree of the control of asthma was evaluated in all patients on a personal basis at the clinical centre. The endpoints used were: symptoms, quality of life, asthma control (ACQ), lung function and exacerbations' number. In case the control was found to be suboptimal (in opinion of the study physician) the dose of controller medications could be increased or other controllers (oral corticosteroids) could be added. Maintenance therapy was determined by all study centres. None of study patients was under follow up in the primary care provided. In our study an effort has been made to improve adherence by repeated education, training of inhalation techniques, and individual plan for asthma prepared for patients at all centres involved. Compliance was enhanced by repeated phone calls and a question ("Did you take your prescribed inhaled steroid medication (corticosteroid) in the last 24 hours?") included in the electronic diary that all patients filled every day during the whole follow up period. Accordingly, patients' compliance with the electronic diary was on average 66.3% and self-reported compliance with the asthma medications reached 94.3%. In another

sub-study of the BIOAIR trial (not reported in this paper) oral steroid (OCS) intervention in severe asthmatics was evaluated. Good compliance with the intervention was confirmed by indirect measures. A significant increase in white blood cells was found only in those patients who received OCS in contrast to the placebo group.

Exacerbations

In the event of a troublesome loss of asthma control (an increase in symptoms and rescue medication use, or a decrease in daily activities or quality of life) patients were advised to contact the study coordinator/physician. If, on the basis of medical history, symptoms, medication use and additional physiological tests, a physician considered this event to be outside the patient's usual range of day-to-day asthma variation and required a change to the controller regimen (either a start/increase in OCS therapy or increase in any other controllers (ICS, LABA, theophylline) in line with GINA recommendations), this event was labelled an asthma exacerbation according to ATS/ERS guidelines. In the second step exacerbations were defined as either severe or moderate by the use (or increase in dose) of systemic corticosteroids and necessity to be hospitalized. In line with the study protocol, all exacerbations should have been recorded in the CRF section on exacerbations, however, as in all "real life studies" some events were reported in the sections on adverse events, hospitalizations or change in medication use. Thus, to increase the quality of the database for the purposes of the current analyses, all exacerbations reported as adverse events, hospitalisations or change in medication use (the initiation of a course of oral steroid (OCS) therapy in those individuals on regular inhaled corticosteroid (ICS) treatment, or for those on regular OCS therapy, a significant temporary increase in their dose of oral steroids for an acute

deterioration in their disease control) were carefully analysed, and if in line with ATS/ERS criteria, included for further evaluation. This approach is in line with ATS/ERS recommendations (E2), which state that all events clinically identified to be outside the patient's usual range of day-to-day asthma variation, which are troublesome for patients and require a change in treatment, should be regarded as exacerbations of asthma.

Those events that did not require patients to begin, or increase their OCS or systemic steroid treatment, were defined as moderate exacerbations. Day 1 of an exacerbation is the day the subject visits the clinic due to an exacerbation, and the 10 day average is calculated from values obtained over the next 10 days. Two days with minimal values – these are 2 consecutive days over 10 days of the exacerbation period. A study flow chart and the definitions used for further statistical analyses are presented in Figure 1.

Pulmonary function

Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and forced inspiratory volume in 1 second (FIV_1) were measured at each visit with spirometers calibrated on a daily basis according to previously published guidelines (E3,E4). Patients were asked to withhold the use of short- and long-acting β-agonists for 6-10 hours before the measurements. The highest value of three technically satisfactory attempts was recorded, and predicted values were calculated according to established formulas (E3). A reversibility test was performed at the screening visit. After the measurement of FEV_1, patients inhaled four puffs of 100 µg salbutamol (MDI via spacer) and after 15 min, FEV_1 was measured again and reversibility was calculated as percent predicted. If an improvement of 9% was not achieved, four puffs of 20 µg

ipratropium bromide by MDI via a large volume spacer were administered, and as before, FEV_1 was measured after 15 min and reversibility calculated.

Atopy and inflammatory markers

In addition to a complete physical examination, skin prick tests to common aeroallergens were performed in all patients at the screening visit. Patients were tested with six standard allergens (*Dermatophagoides pteronyssinus*, mixed grasses, cat, dog, *Alternaria* and *Aspergillus fumigates*) and two regional allergens (Southern Europe: parietaria and olive, Ferrara: parietaria and birch, Northern Europe: birch and mugwort, hazel or alder). Allergens were compared to a positive control (histamine) and a negative control (allergen diluent). ALK Soluprick (Soluprick™, ALK lab, Copenhagen, Denmark) solutions were used and the results were expressed as mean diameter in millimetres of two right angle measurements. A wash-out period of 3 days for short-acting, and 5 days for long-acting anti-histamines was required prior to the skin prick test. A positive response was taken as a wheal ≥ 3 mm in comparison to the negative control. Patients were considered atopic when at least one allergen showed a positive result. Total wheal size was calculated in mm as the total of the 8 allergens.

At each visit, arterial blood gases were determined and venous blood samples were taken for routine blood chemistry and haematology (including total and differential white blood cell count (WBC)), according to the normal routine at each clinic.

Induced sputum was obtained at all centres according to recommendations made by the ERS (European Respiratory Society) task force on induced sputum (E5). Patients with a post-bronchodilator FEV_1 < 60% predicted, a peak flow (PEF) variability of > 30% during the four days preceding the sputum induction, or who had experienced severe bronchoconstriction or other

adverse reactions at previous attempts, were excluded from sputum induction. The procedure was stopped if the patient displayed more than a 15% fall in FEV_1 at 2 minutes after inhalation of saline (0,9% NaCl) during the induction of sputum. Differential cell counts were expressed as a percentage of non-squamous cells. Samples with more than 20% squamous cells or with a viability of less than 40% were excluded.

Exhaled NO

Exhaled nitric oxide (eNO) was measured using a NIOX analyser (Aerocrine AB, Solna, Sweden) according to ATS guidelines (E6) at a flow rate of exhaled air of 50 mL/second. For each patient at least three correctly executed exhalations with the device were required and the mean value was recorded.

Electronic diaries

Lung functions (PEF and FEV_1), rescue medication use (SABA), day and night symptoms, and limitation of activities were recorded daily using electronic diaries (Vitalograph Electronic PEF/FEV_1 Diary – XM version, Vitalograph Ltd., Buckingham, UK). Rescue medication (SABA) use was recorded as number of puffs used daily (the question from the diary read: “How many puffs of the short-acting bronchodilator (e.g. Ventoline) did you take during the last 24 hours?”). Day and night symptoms (“How severe were your respiratory symptoms during the day/night?”) were recorded on a scale from 0 to 4 where 0 = no symptoms; 1 = mild symptoms present, but they caused little or no discomfort; 2 = moderate symptoms that caused discomfort, but did not affect my normal daily activities; 3 = severe symptoms that interfered with my normal daily activities at least once during the day; 4 = symptoms so severe that I could not go to work/school or carry out the activities that were scheduled for this day (for example

holiday/weekend events). Limitation of daily activities ("Did you stay away from work/school or scheduled activities (for example weekend or holiday activity) yesterday because of your respiratory symptoms?") was recorded as a yes/no answer.

Statistical analysis

To study the sensitivity and specificity of different parameters for the detection of exacerbations, Receiver-Operator Characteristics (ROC) curves were analysed.

Univariate and multivariate logistic regression models

Odds ratios (OR) and risk ratios (RR) in univariate analysis were calculated. The following baseline variables were studied: age (65y), smoking history, childhood (<16 years) onset of asthma, sex, BMI, reversibility, FEV_1, FEV_1/FVC, quality of life (SGRQ), asthma control (ACQ), atopy (defined as at least 1 positive skin prick test with any allergen), ASA hypersensitivity, sputum eosinophils, sputum neutrophils, blood eosinophils and FeNO. For numerical variables, medians with 25^{th} and 75^{th} percentiles as possible cut-off values were evaluated. Chi-squared tests (or Fisher's exact test wherever appropriate) were also applied.

RESULTS

Ten patients with SA (11.8% of the group) and 2 with mild-to-moderate disease (3%) reported respiratory symptoms after ingestion of aspirin (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs). Thirty patients had BMI over 30.

Information from 82 exacerbations (78.8% of exacerbations were reported in the SA group) from 44 SA patients was used for further calculations. In the MA cohort, data from all of the 18 exacerbations was available for analysis, whereas in the SA cohort the database was scattered in eight patients due to insufficient compliance with the electronic diaries (n=2

patients) or length of follow- up (n=3). Non reliable data (mistakes during recording, n=3) were also excluded from the analyses.

There were 44 ex-smokers included with a number of pack-years history in a range from 1 to 36. No current smokers were included in the study. There were 3 patients included with a history of more than 5 pack-years which was a violation of the study inclusion criteria.

The mean values of analyzed variables (PEF, FEV_1, SABA use, day and night symptoms, and limitation of daily activities) at baseline and during exacerbations, are presented in Table E2. When SA were compared to MA, the pattern and range of changes of the analysed variables was similar for PEF, FEV_1 and rescue medication use, but not for day and night symptoms and limitation of daily activities.

Changes recorded during exacerbations in severe and mild-to-moderate asthmatics

On the day of the reported exacerbation, a 13.6% decrease in PEF was found in SA ($p<0.0001$) (Fig E1a). During the maximum drop in PEF (the average of the values from the two worst consecutive days during exacerbation), the decrease was 23.0% ($p<0.0001$). During the 10 day period, a decrease in PEF of 15.0% was observed ($p<0.0001$). Furthermore, for FEV1, there was 12.5% decrease on the day of the reported exacerbation ($p<0.0001$). During the two days of maximum deterioration, FEV1 decreased by 20.4% ($p<0.0001$), and there was a 12.0% decrease in FEV1 during the 10 days of exacerbation ($p<0.0001$)(Fig E1b). On the day of the reported exacerbation, an increase of 0.42 puffs of SABAs was found ($p<0.0001$) while during the 10 day period of exacerbation, an average increase of 0.2 puffs of SABAs was observed ($p<0.0001$) (Fig E1c). With respect to day and night symptoms, there was a clear increase

(41.0% and 52.0% for day and night symptoms, respectively) on the day of the reported exacerbation compared with baseline ($p<0.0001$) (Fig E1d,e). For the variable "limitation of daily activities", there was a non-significant increase of 77.0% on the day of the reported exacerbation ($p=0.215$)(Fig E1f).

On the day of a reported exacerbation, a 12.7% decrease in PEF was observed in MA ($p<0.0001$)(Fig E2a). The maximal decrease in PEF (the average of the values from the two worst consecutive days during exacerbation) reached 18.2% ($p<0.0001$). During the 10 days of an exacerbation, a 9.0% decrease in PEF was found ($p<0.0001$). For FEV1, on the day of reported exacerbation, there was a decrease of 11.0% ($p=0.0006$). The average of 2 days of minimal FEV1 values reached 14.0% ($p<0.0001$), and a 7.2% decrease in FEV1 was observed during the 10 days of exacerbation ($p<0.0001$)(Fig E2b). On the day of reported exacerbations, an increase of 0.35 puffs in SABA use was recorded ($p=0.03$)(Fig E2c). With respect to day symptoms, a non-significant increase of 202.6% was observed on the day of the reported exacerbation ($p=0.253$)(Fig E2d). However, the increase in night symptoms on the day of the reported exacerbation was 31.8% ($p=0.026$)(Fig E2e). On the day of reported exacerbations, a 9.0% increase in limitation of daily activities was recorded ($p=0.488$)(Fig E2f).

Sensitivity and specificity of evaluated outcome variables for detecting an exacerbation

ROC curves for % decrease in PEF vs baseline values in all asthmatics, SA and MA are presented in Figure E3. Testing of some previously used cut-off points such as a 30% or 20% decrease in PEF (8), resulted in a sensitivity of 31.4% and 50.6% respectively, and a specificity of 93.2% and 87.8% respectively for the whole asthma cohort (Table E3). The sensitivity and

specificity of different cut-off points for other tested variables (change in FEV1, increase in rescue drug use, increase in day and night symptoms) for the whole study group are presented in Table E3. The testing of some previously used cut off points (8), decreases in PEF of 30% and 20% in the SA cohort, resulted in a specificity of 90.5% and 83.3 % respectively, and a sensitivity of 35% and 52.8%, respectively (Table E3). Similarly, in MA, cut off points of 30% and 20% resulted in a specificity of 99.7% and 98.6%, and a sensitivity of 13% and 40%, respectively (Table E3). The sensitivity and specificity of different cut off points for other tested variables (change in FEV1, increase in rescue drug use, increase in day and night symptoms) for SA and MA are presented in Table E3. Limitation of daily activities was excluded from the analysis due to the lack of significant changes in this variable when compared to baseline data. Sensitivity and specificity of combined parameters to detect exacerbations in the whole asthma group, SA and MA groups are presented in Table E4.

For the severe exacerbations ROC curves the thresholds with the greatest Jaeger statistic are as follows:

PEF: -7.7%, sensitivity 78.3%, specificity 67.7%

FEV1: -13.75%, sensitivity 69.16%, specificity 72.79%

Day symptoms: 4.7%, sensitivity 59.83%, specificity 71.64%

Night symptoms: 5.6%, sensitivity 48.67%, specificity 76.11%

Rescue medication use: 0.2 puffs, sensitivity 94.8%, specificity 40.87%

Results of the univariate analysis of factors potentially associated with the development of severe exacerbations and any exacerbations in SA, MA and the whole study group are presented in Table E5. Major risk factors for the whole study group included Juniper ACQ >1.36, SGRQ >34.6, sputum eosinophils ≥3%, FEV_1≤80%, smoking history, atopy and reversibility ≥12%. A FEV_1/FVC ratio<0.7 was associated with a lower risk of developing an exacerbation in the whole study group. Major risk factors in the SA group included age <65years, Juniper ACQ >2.14, SGRQ >44.1, smoking history and female sex. There were no statistically significant factors associated with the development of exacerbations in the MA group. By definition MA patients were identified by the lack of exacerbations in the past year. Therefore this group will have a low risk of exacerbation (as discussed above) and the number of events during 1 year of follow up is small. Given the relatively small sample size the power to see associations of any parameters with risk of exacerbation is also small.

A medical history of at least 1 exacerbation in the preceding year (an inclusion criterion for severe asthma) represents a significant risk factor for the development of exacerbation during one year of follow up in the whole asthma group : OR 4.7 (CI: 2.4 – 9.5), RR 2.67 (CI1.7 – 4.2), p<0.0001.

DISCUSSION

The BIOAIR study was a European, multicentre trial, consisting of an initial cross-sectional comparison of patients with severe, mild-to-moderate asthma, followed by an optimisation of treatment, double-blind oral steroid intervention and a longitudinal (1 year) follow up. We believe that the intervention (oral steroid treatment, 0.5 mg/kg of body weight

for 14 days) does not affect results of our sub- study due to the cross over design. Those patients who received placebo during the first 2 weeks of the intervention received 2 weeks course of oral steroids before the second phase of the BIOAIR study which was 1 year of follow up. Thus all patients were characterized by the same background treatment before 1 year of follow up.

We analysed whether various phenotypic characteristics of the patients were potential risk factors for exacerbations. Smoking history, Juniper ACQ and SGRQ scores at baseline were positively associated with a higher risk of exacerbations, both in severe asthma, and in the whole asthma group. Female gender, and age <65 years were identified as risk factors in SA, whereas atopy and reversibility ≥12% were also significant risk factors in all asthmatics. The negative impact of smoking on the airways and on disease control in asthma patients is not surprising and has been reported in several studies (E7, E8, E9). We have shown that the level of asthma control and quality of life evaluated using the SGRQ and Juniper ACQ respectively, are associated with the risk of exacerbation. This finding has clinical implications as both SGRQ and Juniper ACQ represent validated and widely used questionnaires in our practice. Female gender as a risk factor for asthma exacerbations has already been reported. The reason why women are more prone to exacerbations is not completely clear. This may be explained partly by the fact that asthma among adults is more common in women (E10), and women are more likely to be admitted to the hospital with asthma (E11). Moreover, it has been showed that women with asthma report more severe symptoms and a worse quality of life in comparison to men with a similar lung function (E12). We found that BMI negatively correlates with the risk of asthma exacerbation in the SA group. This is in contrast to previous studies showing that

obesity is associated with worse asthma outcomes and an increased risk of asthma-related hospitalisations (E13). However, others did not find a correlation between BMI and asthma severity (E14). One possible explanation of this phenomenon may be that in our study cohort, the majority of exacerbations were due to allergic factors (see seasonal distribution of events in Figure 2B), and thus may be associated with atopic asthma which is more common among younger patients with a lower BMI. Further studies are needed to fully elucidate possible impact of obesity on asthma exacerbations.

Ninety three severe asthmatics (100% of the study group) and 18 mild-to-moderate asthmatics (23.7% of the study group) used LABA on the entry to the study. Among those majority used formoterol (61 patients) and 50 subjects used salmeterol. Sixteen patients used Symbicort. The SMART regime has not been recommended by the study protocol of the BIOAIR trial, however might have been used by some centres.

It needs to be acknowledge that our analysis does not allow estimation of the frequency of the specified falls in FEV1/PEF or increase in symptoms that occurred in the setting of an exacerbation as that was not the aim of the study.

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Table E1. Fixed doses of medications used by patients during treatment optimisation period (V1-V2a). In the case of a severe asthma patient taking oral corticosteroids the dose remained unchanged.

	Severe asthma	**Mild-to-moderate asthma**
inhaled steroids	1600 µg budesonide or 1500 µg beclomethasone, or 1000 µg fluticasone	800 µg budesonide or beclomethasone, or 500 µg fluticasone
LABA	formoterol 9-24 µg b.i.d. or salmeterol 50 µg b.i.d	formoterol 9-24 µg b.i.d. or salmeterol 50 µg b.i.d.
other	short-acting β-agonists as needed	short-acting β-agonists as needed

Table E2. Mean (or median when appropriate) values of analyzed variables (PEF, FEV_1, SABA use, day and night symptoms, and limitation of daily activities) at baseline and during exacerbations.

	SEVERE ASTHMA				**MILD-TO-MODERATE ASTHMA**			
	baseline	day of reported exacerbation	2 days of exacerbation	10 days of exacerbation	baseline	day of reported exacerbation	2 days of exacerbation	10 days of exacerbation
PEF (mean, L/min)	393.3	321.2	294.5	325.4	526.9	405.2	396.3	470.9
FEV_1 (mean, L/s)	2.08	1.84	1.71	1.87	3.19	2.57	2.56	2.87
SABA (median, number of puffs)	1.8	2.0	2.0	2.0	0.0	1.0	1.0	0.4
day symptoms (median, 0-4 scale)	1.2	2.0	2.0	1.83	0.14	2.0	2.0	0.66
night symptoms (median, 0-4 scale)	0.5	1.0	1.0	0.73	0.0	1.0	0.5	0.2
limitation of daily activities (median, 1-yes, 0-no)	0.0	0.0	0.0	0.07	0.0	0.0	0.0	0.0

Table E3. Sensitivity and specificity of selected cut off points for the parameters evaluated to detect exacerbations (proxy for exacerbation) in the whole asthma group, severe and mild-to-moderate asthma (for MA group day and night symptoms *cut off defined as 67% and # cut off defined as 17%).

	WHOLE ASTHMA		SEVERE ASTHMA		MILD-TO-MODERATE ASTHMA	
parameter	**sensitivity % (95% CI)**	**specificity % (95% CI)**	**sensitivity % (95% CI)**	**specificity % (95% CI)**	**sensitivity % (95% CI)**	**specificity % (95% CI)**
Decrease in PEF (% change vs baseline)						
30%	31.4% (24.5 – 38.9)	93.2% (92.8 – 93.5)	35.0% (27.4 – 43.7)	90.5% (90.0 – 91.0)	13.0% (3.7 – 30.7)	99.7% (99.5 – 99.8)
20%	50.6% (42.9 – 58.3)	87.8% (87.3 – 88.3)	52.8% (44.3 – 61.25)	83.3% (82.6 – 84.0)	40.0% (22.7 – 60.0)	98.6% (98.2 – 99.0)
15%	62.8% (55.1 – 70.0)	83.0% (92.4 – 83.6)	63.4% (54.9 – 71.3)	77.5% (76.8 – 78.3)	60.0% (40.6 – 77.3)	96.1% (95.5 – 96.7)
Decrease in FEV_1 (% change vs baseline)						
30%	25.2% (18.4 – 33.0)	93.2% (92.8 – 93.6)	28.6% (20.7 – 37.6)	91.0% (90.5 – 91.6)	10.7% (2.3 – 28.0)	99.2% (98.9 – 99.0)
20%	39.5% (31.5 – 47.8)	84.6% (84.0 – 85.2)	46.2% (37.0 – 55.6)	80.0% (79.2 – 80.7)	10.7% (2.3 – 28.0)	96.9% (96.3 – 97.0)
15%	55.1% (46.7 – 63.3)	77.9% (77.2 – 78.6)	58% (48.6 – 67.0)	72.2% (71.4 – 73.1)	42.9% (24.5 – 62.8)	93% (92.1 – 93.8)
Increase in SABA use (number of puffs)						
2	17.2% (10.9 – 25.4)	97.0% (96.7 – 97.3)	9.8% (5.15 – 16.4)	98% (98.0 – 98.25)	8.0% (1.0 – 26.0)	97.6% (97.1 – 98.1)
1	20.7% (13.7 – 29.2)	95.8% (95.4 – 96.1)	24.4% (17.1 – 33.0)	90.4 (90.0 – 91.0)	16.0% (4.5 – 36.1)	96.8% (96.2 – 97.3)
Increase in day symptoms (% change vs baseline)						
30%	39.9% (31.9 – 48.2)	85.9% (85.3 – 86.4)	35.8% (27.3 – 45.0)	84.4% (83.7 – 85.1)	56.0% (34.9 – 75.6)*	90.0% (89.0 – 90.9)
20%	41.9% (33.8 – 50.3)	84.9% (84.3 – 85.5)	38.2% (29.6 – 47.4)	83.1% (82.4 – 83.8)	60.0% (38.7 – 78.9)#	89.9% (88.9 – 90.1)
Increase in night symptoms (% change vs baseline)						
30%	29.7% (22.5 – 37.8)	87.7% (87.1 – 88.2)	30.1% (22.1 – 39.0)	84.0% (83.4 – 84.8)	24.0% (9.4 – 45.1)*	96.8% (96.2 – 97.3)
20%	34.5% (26.8 – 42.7)	85.4% (84.8 – 85.9)	35.8% (27.3 – 45.0)	81.4% (80.0 – 82.1)	28.0% (12.1 – 49.4)#	96.5% (95.9 – 97.1)

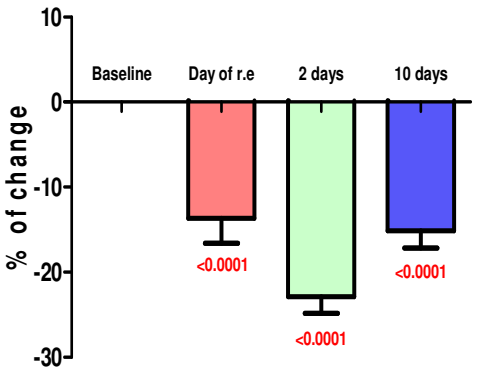
Table E4 Sensitivity and specificity of combined parameters to detect exacerbations in the whole asthma group, SA and MA groups.

Asthma cohort / Definition of exacerbation	**WHOLE ASTHMA**		**SEVERE ASTHMA**		**MILD-TO-MODERATE ASTHMA**	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
20% decrease in PEF on 2 consecutive days **AND** 20% increase in **DAY** symptoms on 2 consecutive days	12.8%	99.5%	12.5%	99.4%	14.3%	99.95%
20% decrease in PEF on 2 consecutive days **OR** 20% increase in **DAY** symptoms on 2 consecutive days	**67.9%**	**94.2%**	**68.75%**	**96.0%**	**64.3%**	**97.65%**
20% decrease in PEF on 2 consecutive days **AND** 20% increase in **NIGHT** symptoms on 2 consecutive days	12.8%	99.55%	14.1%	99.4%	7.1%	99.95%

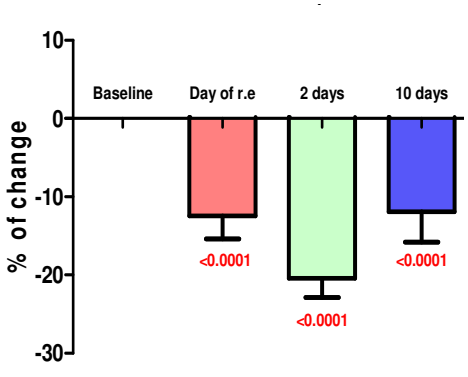
20% decrease in PEF on 2 consecutive days **OR** 20% increase in **NIGHT** symptoms on 2 consecutive days	**61.5%**	**97.1%**	**64.1%**	**96.5%**	**50.0%**	**99.1%**

Table E5. The univariate analysis of baseline characteristic factors associated with the development of severe exacerbations and any degree of exacerbations in the whole study group and SA. There were no statistically significant factors found in the MA group.

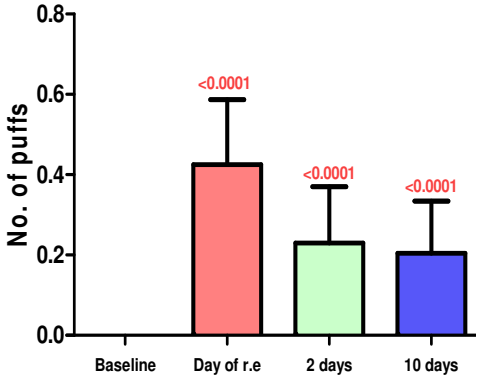
factor	OR	95% CI	RR	95% CI	p
SEVERE EXACERBATIONS					
Sputum eosinophils ≥ 3%	3.84	1.37-10.8	2.65	1.22-5.74	0.009
ACQ>1.36 (median)	3.68	1.77-7.65	2.39	1.43-4.0	0.0004
BMI>25	2.27	1.08-4.78	1.8	1.03-3.16	0.029
SGRQ>34.6 (median)	2.08	1.0-4.31	1.66	1.0-2.76	0.047
WHOLE STUDY COHORT					
Juniper ACQ > 1.36 (median)	3.57	1.77 – 7.18	2.03	1.35 – 3.05	0.0003
SGRQ > 34.6 (median)	2.66	1.32 – 5.34	1.76	1.16 – 2.66	0.005
Sputum eosinophils ≥ 3%	2.65	1.07 – 6.57	1.78	1.03 – 3.08	0.033
FEV1 ≤80% (median)	2.22	1.18 – 4.19	1.59	1.1 – 2.31	0.013
Smoking history	2.21	1.1 – 4.44	1.55	1.08 – 2.22	0.024
atopy	2.08	1.08 – 3.99	1.5	1.05 – 2.17	0.027
Reversibility ≥ 12%	2.03	1.04 – 3.97	1.5	1.04 – 2.2	0.04
$FEV_1/FVC < 0.7$	0.43	0.22 – 0.83	0.63	0.44 – 0.89	0.0011
SEVERE ASTHMA					
Age < 65y	5.27	1.34 – 20.7	2.65	0.97 – 7.27	0.01
Juniper ACQ > 2.14 (median)	3.46	1.29 – 9.26	1.6	1.09 – 2.34	0.012
SGRQ > 44.1 (median)	3.04	1.21 – 7.68	1.63	1.07 – 2.47	0.017
Smoking history	2.79	1.08 – 7.23	1.49	1.07- 2.1	0.03
Female sex	2.38	1.02 – 5.55	1.49	0.99 – 2.23	0.04
atopy	*2.46*	*0.96 – 6.3*	*1.41*	*1.0 – 1.99*	*0.06*



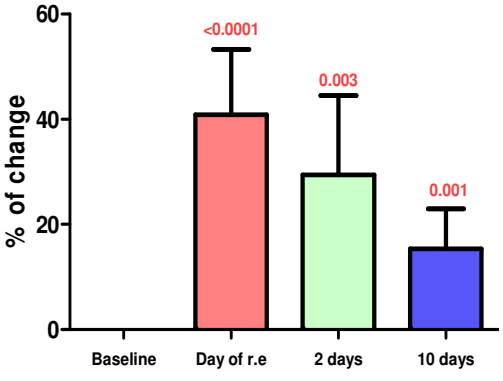
a) PEF



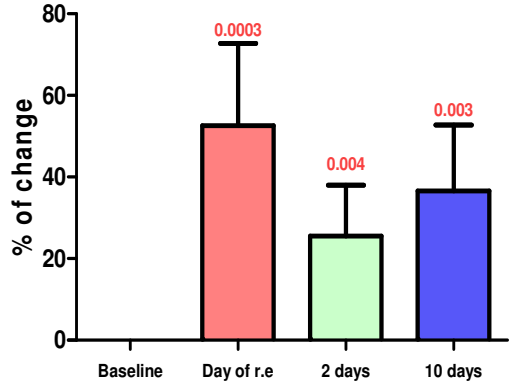
b) FEV_1



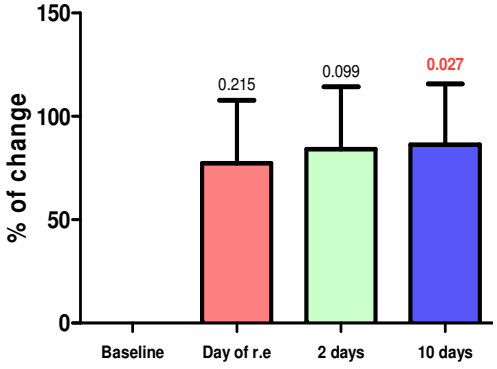
c) SABA (rescue medication)



d) day symptoms



e) night symptoms



f) limitation of daily activities

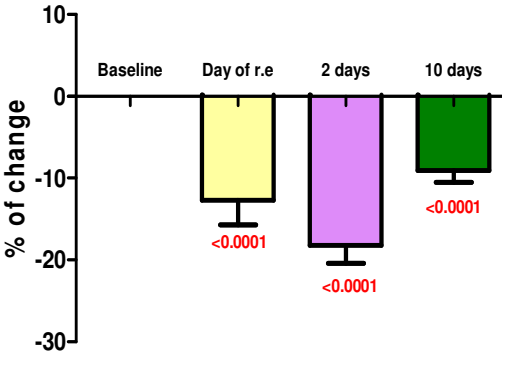
Figure E1. Percent change from baseline for the different variables studied (average of the last 10 days of the treatment optimisation period) during exacerbations in SA cohort. (a) PEF, (b) FEV_1, (c) rescue

medication (change in no. of puffs), (d) day symptoms, (e) night symptoms and (f) limitation of daily activities. Error bars represent SEM.

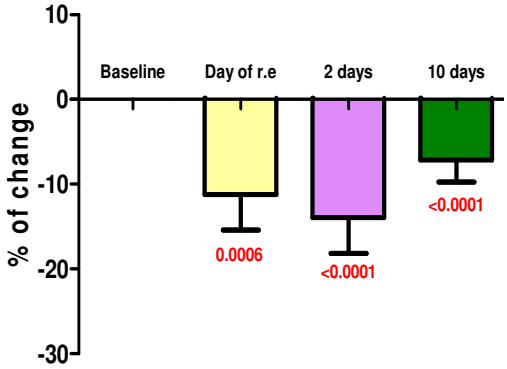
Day of r.e : the day of reported exacerbations represent values measured during unscheduled visit to the clinic due to symptoms of exacerbations (one day.)

2 days : the average of the values from the two worst consecutive days during exacerbation.

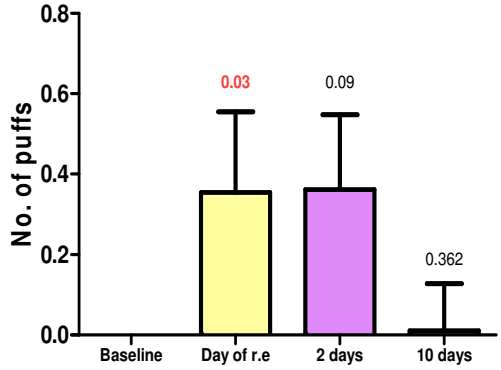
10 days : the average of 10 days during exacerbations.



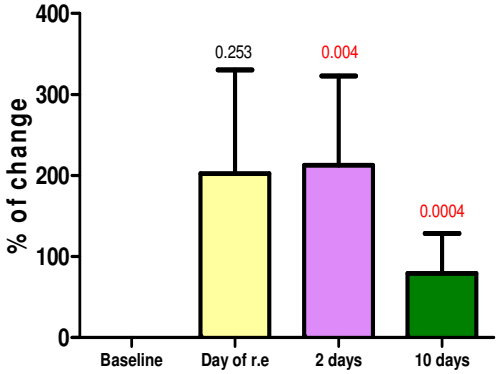
a)PEF



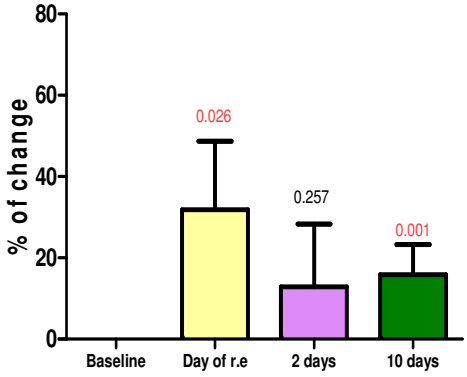
b) FEV_1



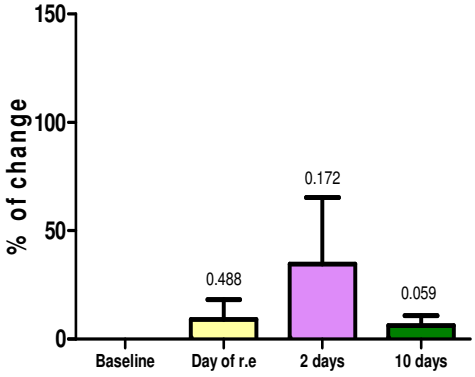
c) SABA (rescue medication)



d) day symptoms



e) night symptoms



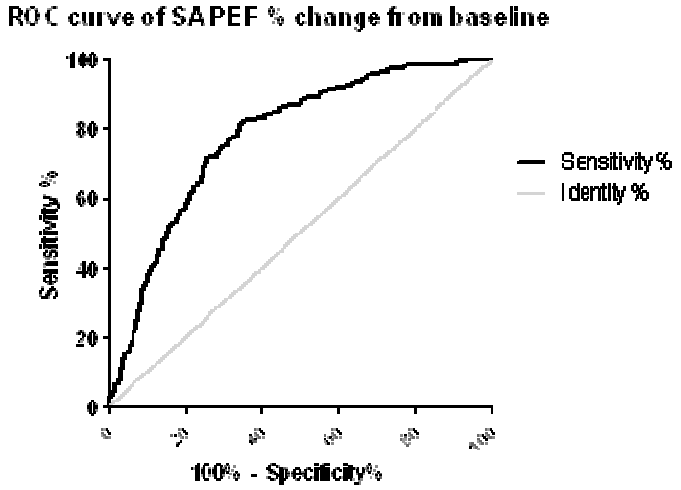
f) limitation of daily activities

Figure E2. Percent change from baseline for the different variables studied (average of the last 10 days of the treatment optimisation period) during exacerbations in MA cohort. (a) PEF, (b) FEV_1, (c) rescue medication (change in no. of puffs), (d) day symptoms, (e) night symptoms and (f) limitation of daily activities. Error bars represent SEM.

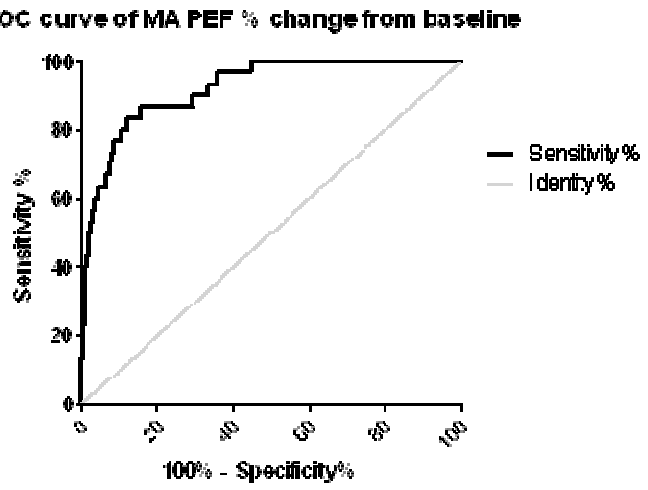
Day of r.e : the day of reported exacerbations represent values measured during unscheduled visit to the clinic due to symptoms of exacerbations (one day.)

2 days : the average of the values from the two worst consecutive days during exacerbation.

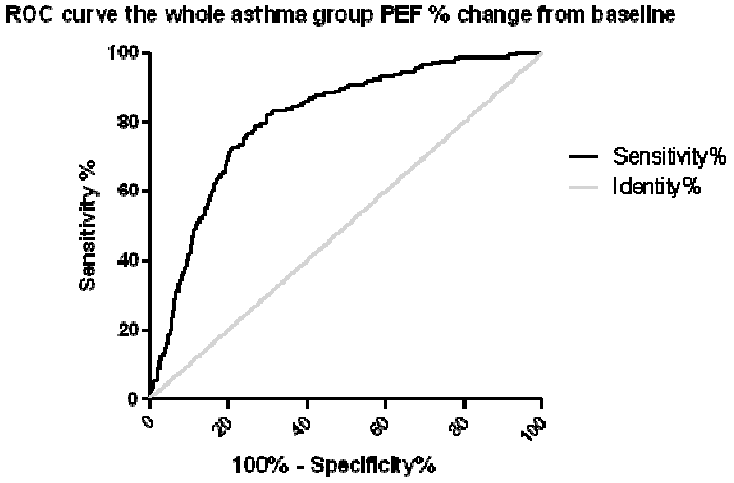
10 days : the average of 10 days during exacerbations.



AUC	Std. error	95% CI	p
0.77	0.41	-0.025 – 1.58	<0.0001



AUC	Std. error	95% CI	p
0.92	0.02	0.88 – 0.96	<0.0001



AUC	Std. error	95% CI	p
0.81	0.02	0.88 – 0.96	<0.0001

Figure E3. Receiver operator characteristic curves for the change in PEF as a variable to detect exacerbations in SA, MA and the whole asthma cohorts.