Online supplement

Methods

Spirometries with bronchodilator test were performed according to international recommendations [S1,S2]. In hospital Vmax 22 (Vmax 22, Viasys Healthcare, Palm Springs, CA) was used and in GP offices M9426 spirometer (Medikro, Kuopio, Finland) was most often used. The quality of primary care spirometry in the study area has been previously analysed in detail and has been found good [S3]. Finnish reference values were used [S4]. Only spirometries of steroid-naïve patients were chosen, i.e. spirometries measured during glucocorticoid medication or <1 month from discontinuation were excluded as well as those with insufficient medication data (n=270). Also spirometries without bronchodilator test were excluded (n=129). Bronchodilator test was made by salbutamol 200 μg according to guidelines [S2,S5].

eTable 1. Inclusion & exclusion criteria used in SAAS study[S6]

Inclusion criteria	• a diagnosis of new-onset asthma made by a respiratory specialist • diagnosis confirmed by at least one of the following objective lung function measurements[1]: ○ FEV_1 reversibility in spirometry of at least 15% and 200 ml ○ diurnal variability (≥ 20%) or repeated reversibility (≥ 15%/60 L/min) in PEF-follow-up ○ a significant decrease in FEV_1 (15%) or PEF (20%) in response to exercise or allergen ○ a significant reversibility in FEV_1 (at least 15% and 200 ml) or mean PEF (20%) in response to a trial with oral or inhaled glucocorticoids • symptoms of asthma • age ≥ 15years
Exclusion criteria	• physical or mental inability to provide signed informed consent • of note: ○ patients with comorbidities, either other lung disease or any other significant disease were not excluded ○ patients were not excluded because of smoking, alcohol use or any other lifestyle factor

eTable 2 Three most common methods to calculate the immediate FEV_1 BDR discussed in the recommendations, reports and guidelines for asthma and spirometry measurements

	Unit	Calculation formula
Absolute volume change (ΔFEV_1)	litres (L) or millilitres (mL)	$postbd\ FEV1 - initial\ FEV1$
ΔFEV_1 % of the initial FEV_1	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{initial\ FEV1} * 100$
ΔFEV_1 % of the predicted FEV_1*	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{predicted\ FEV1} * 100$

postbd = post-bronchodilator, FEV_1= forced expiratory volume in 1 second

* Can also be expressed as the percent predicted FEV_1 after bronchodilator administration minus the percent predicted FEV_1 before bronchodilator administration

eTable 3. Diagnostic criteria fulfilled by the patients in the SAAS-cohort.

Diagnostic criteria fulfilled	n=219
Positive BDR (ΔFEV_1% of the initial FEV_1 ≥15% and ≥200 mL) at least in one spirometric measurement n (%)	72 (32.9%)
if not Diurnal variability (⩾20%) or repeated reversibility (⩾15%/60l/ min) in peak flow monitoring	119 (54.3%)
if not Variable bronchial obstruction shown in exercise, allergen exposure or as a steroid treatment response	28 (12.8%)

[a]*Practically all patients underwent one or more spirometric evaluations and 2 week peak flow monitoring. Other tests were performed if considered necessary. Only the major diagnostic feature per patient is shown using a hierarchical evaluation in which positive bronchodilator response on FEV_1 was considered first, if negative, then peak flow changes were considered and if negative, the other tests were considered.*

eTable 4. Proportion of steroid-naïve patients (n=219) fulfilling at least one of the BDR thresholds among 369 study spirometries

Absolute change ≥200 mL of ΔFEV_1	128 (58.4%)
ΔFEV_1% of the predicted FEV_1 ≥8%	95 (43.6%)
ΔFEV_1% of the predicted FEV_1 ≥9%	79 (36.1%)
ΔFEV_1% of the initial FEV_1 ≥12% and 200 mL	78 (35.6%)
ΔFEV_1% of the predicted FEV_1 ≥10%	65 (29.8%)
ΔFEV_1% of the initial FEV_1 ≥15% and 200 mL	58 (26.5%)
Absolute change ≥400 mL of ΔFEV_1	53 (24.2%)
ΔFEV_1% of the initial FEV_1 ≥12% and 400 mL	46 (21.0%)
ΔFEV_1% of the initial FEV_1 ≥15% and 400 mL	40 (18.3%)
None of the criterion was fulfilled	91 (41.6%)

Data is shown as n (%)

eTable 5 Differencies of the subgroups of patients fulfilling absolute volume of ΔFEV1% 200mL and either ΔFEV1% of the initial FEV1 ≥12% or ΔFEV1% of the predicted FEV1 ≥9%

	ΔFEV$_1$% of the initial FEV$_1$ ≥12%	**ΔFEV$_1$% of the predicted FEV$_1$ ≥9%**	**P value**
	n=9	n=10	
Male gender	5 (55.6%)	7 (70.0 %)	0.650
Age	50 (10)	39 (11)	**0.032**
BMI	25.3 (23.6-30.3)	25.0 (23.5-28.2)	0.842
Smoking history	5 (55.6%)	7 (70%)	0.650
Current smoker	1 (11.1%)	4 (40%)	0.303
Pack years	15 (4.5-31.5)	5 (3.5-11)	0.343
Atopic	2 (25%)	4 (50%)	0.608
Pre-BD FEV$_1$ (%ref)	52 (14)	92 (8)	**<0.001**
Post-BD FEV$_1$ (%ref)	59 (15)	102 (9)	**<0.001**
Pre-BD FVC (%ref)	65 (13)	102 (10)	**<0.001**
Post-BD FVC (%ref)	71 (15)	106 (8)	**<0.001**
Pre-BD FEV$_1$ (L)	1.90 (0.49)	3.91 (0.81)	**<0.001**
Post-BD FEV$_1$ (L)	2.18 (0.54)	4.34 (0.89)	**<0.001**
Pre-BD FVC (L)	2.96 (0.57)	5.22 (1.19)	**<0.001**
Post-BD FVC (L)	3.22 (0.58)	5.40 (1.05)	**<0.001**
Pre-BD FEV$_1$/FVC	0.64 (0.10)	0.76 (0.07)	**0.008**
Post-BD FEV$_1$/FVC	0.68 (0.09)	0.80 (0.06)	**0.002**
FEV1 reversibility, ml	283 (67)	428 (88)	**0.001**
FVC reversibility, ml	261 (196)	179 (200)	0.380
FEV1 reversibility, % of initial value	15.2 (3.0)	11.0 (0.8)	**<0.001**
FVC reversibility, % of initial value	9.1 (7.0)	4.4 (5.6)	0.125
FEV1 reversibility, % of predicted	7.6 (1.4)	10.1 (1.1)	**0.001**
Blood eosinophils x10^9/L	0.50 (0.16-0.73)	0.34 (0.11-0.60)	0.604
Total IgE kU/L	74 (23-107)	71 (44-331)	0.481
Fulfills COPD criteria (≥10 pack years and post-FEV$_1$/FVC<0.7)	2 (22.2%)	0	0.211

Data is shown as n (%)

eTable 6. Baseline characteristics of the patients with pre-bronchodilator FEV1/FVC ≥0.7 vs. FEV1/FVC<0.7

	pre-BD FEV_1/FVC ≥0.7	**pre-BD FEV_1/FVC <0.7**	
	n=151	n=68	
Age	45 (15)	50 (15)	**0.028**
Female gender	95 (62.9 %)	31 (45.6 %)	**0.019**
BMI	27.1 (24.1-30.9)	27.2 (23.6-30.1)	0.695
Smoking history	70 (46.4 %)	43 (63.2 %)	**0.028**
Current smokers	30 (19.9 %)	15 (22.1 %)	0.720
Pack years	11 (4-20)	15 (9-26)	0.098
Blood eosinophils $x10^9$/L	0.24 (0.18-0.40)	0.30 (0.17-0.50)	0.935
Total IgE kU/L	99 (34-198)	71 (29-111)	0.160
Atopic	51 (37.5 %)	16 (27.1 %)	0.190
Pre-BD FEV_1 (L)	2.9 (2.4-3.5)	2.1 (1.7-2.8)	**<0.001**
Post-BD FEV_1 (L)	3.1 (2.5-3.7)	2.5 (2.0-3.2)	**<0.001**
Pre-BD FVC (L)	3.6 (3.0-4.4)	3.5 (2.8-4.4)	0.508
Post-BD FVC (L)	3.7 (3.2-4.6)	3.8 (3.2-4.6)	0.859
Pre-BD FEV_1 (%ref)	84 (14)	64 (15)	**<0.001**
Post-BD FEV_1 (%ref)	91 (15)	74 (17)	**<0.001**
Pre-BD FVC (%ref)	88 (16)	84 (17)	0.129
Post-BD FVC (%ref)	93 (15)	90 (17)	0.207
Pre-FEV_1/FVC, ratio	0.79 (0.75-0.84)	0.64 (0.59-0.67)	**<0.001**
Post-FEV_1/FVC, ratio	0.82 (0.79-0.87)	0.69 (0.62-0.74)	**<0.001**
Fulfills COPD criteria (≥10 pack years and post-FEV_1/FVC<0.7)	3 (2 %)	21 (32.3 %)	**<0.001**

Data is shown as n (%)

eTable 7. Diagnostic criteria fulfilled by the obstructive and non-obstructive patients[a] in the SAAS-cohort.

	pre-BD FEV_1/FVC ≥0.7	**pre-BD FEV_1/FVC <0.7**	**P value**
Subjects	151	68	
Positive BDR (ΔFEV_1% of the initial FEV_1 ≥15% and ≥200 mL) at least in one spirometric measurement n (%)	39 (25.8%)	33† (48.5%)	0.001
if not Diurnal variability (⩾20%) or repeated reversibility (⩾15%/60l/ min) in peak flow monitoring	94 (62.3%)	25† (36.8%)	
if not Variable bronchial obstruction shown in exercise, allergen exposure or as a steroid treatment response	18 (11.9%)	10 (14.7%)	

† p<0.05 vs. group with pre-BD FEV_1/FVC ≥0.7, BD=bronchodilator, BDR=bronchodilator response

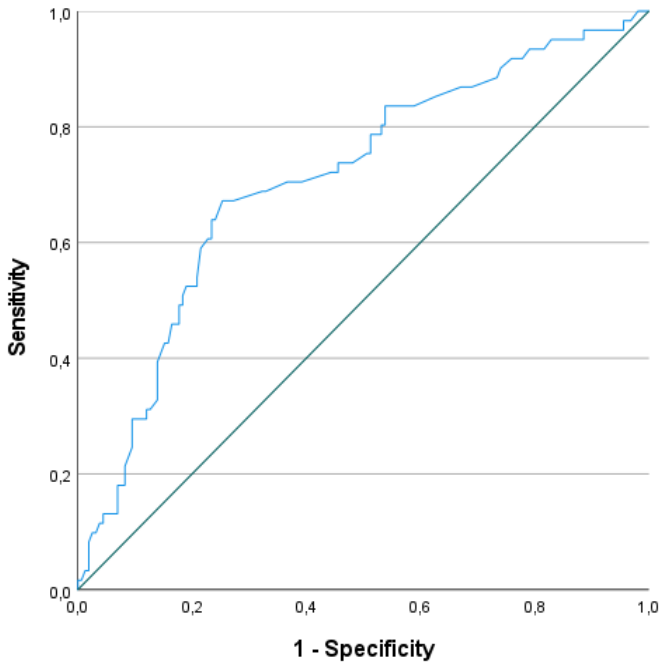
eTable 8. Predicting fulfilling threshold of 12% and 200ml FEV_1 reversibility by pre-BD FEV_1/FVC ratio

AUC	0.71 (fair)
p-value	<0.001
Lower AUC boundary (of 95% CI)	0.632
Upper AUC boundary (of 95% CI)	0.788
Cut-off point	0.7205
Sensitivity %	67.2
Specificity %	74.7

	Predicted positive	Predicted negative	Total
Actual positive	41 (67.2%)	20 (32.8%)	61 (100%)
Actual negative	40 (25.3%)	118 (74.7%)	158 (100%)

Accuracy 41+118 / (41+20+40+118) = 72.6%

eFigure 1. Receiver-operation characteristic (ROC) curve for the performance of FEV_1/FVC for predicting fulfilling FEV_1 reversibility threshold 12% and 200 mL



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