AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: NA
ACTIVE INGREDIENT: NA

Study No: NIS-RSE DUM 2008/1
A descriptive study to explore certain characteristics of patients at risk for COPD in a primary care setting.

Developmental Phase: NA. NIS (Non Interventional Study)
Study Completion Date: 13 April 2010
Date of Report: 5 April 2011

OBJECTIVES:

Primary objective

The primary objective of the present study, was to explore if certain characteristics, easily detected within a regular primary care setting, may indicate that a patient at risk for COPD ($45 \leq$ age ≤ 80 and a smoking history of ≥ 15 pack years) is prone to have a diagnosis of COPD according to MPA guidelines (Information from Läkemedelsverket 4:2002, or later if released).
These found characteristics, together with results from COPD 6 measurement, will be a part of a method developed during the study, which will help the primary care to diagnose COPD earlier than today.

Secondary objective

The secondary objective was to describe the costs of finding a patient with COPD.
The objectives were achieved by describing the following symptoms, risk factors and historical medical events within the selected population:

- COPD symptoms evaluated by questionnaires.
- Sick leave.
- Occupational status.
- Results from COPD 6 measurement.

- Results from spirometry.
- Smoking history.
- Presence of, and number of health care contacts, regarding infection in the upper air way passage recorded in medical records during the last 24 months prior to visit 1.
- Presence of, and number of health care contacts, regarding pneumonia recorded in medical records during the last 24 months prior to visit 1.
- Presence of, and number of health care contacts, regarding acute bronchitis recorded in medical records during the last 24 months prior to visit 1.
- Presence of, and number of health care contacts, regarding other relevant respiratory condition recorded in medical records during the last 24 months prior to visit 1.
- Relevant medical history (co-morbidity).
- Current medical treatment.

Time spent by health care personnel when performing different procedures such as spirometry was measured outside the study in order to calculate costs for finding a COPD patient.
A questionnaire was sent to participating centres after the study in order to evaluate if the method most effective according to the result is feasible in clinical praxis.

METHODS:

Information concerning symptoms was collected using the Clinical COPD questionnaire (CCQ) and the Modified Medical Research Council dyspnoea scale (MMRC).
Information about smoking habits, BMI and medical history was also gathered.

Lung function was measured in all subjects by two separate methods according to below order:

- **COPD 6** – a mini-spirometer (Vitalograph, Ireland), indicating lung function by FEV1 and FEV6 (forced expiratory volume in 1 and 6 seconds, respectively) in liters and percent of predicted value and FEV1/FEV6 ratio.
- **Standard spirometry** – FEV1, VC (vital capacity) FVC (forced vital capacity) and FEV1/VC ratio were registered pre- and post bronchodilation. Reversibility was tested using a short acting ß-agonist. Spirometry was performed according to each participating center's routine.

Standard spirometry was used for the establishment of COPD diagnosis (FEV1/VC ratio post bronchodilation < 70 % reflecting the GOLD (Global initiative of Obstructive Lung Disease) criteria.

The evaluation of diagnostic sensitivity and specificity of COPD 6 was performed by comparing the COPD 6 results with the spirometry outcome (golden standard). FEV1/VC was used according to study protocol to establish the COPD diagnosis.

Statistical methods

Univariate logistic regression for predicting the COPD diagnosis was performed including all variables at baseline. For variables with a low p-value in the logistic regression, receiver operating characteristic (ROC) curves were utilized and sensitivity and specificity were calculated.

The subjects with a verified COPD disease were assigned to a '1' value and subject without a COPD disease were assigned with a '0'. Descriptive variables were eligible for entry into a multiple logistic regression model if they significantly were associated with prediction of COPD at a $p < 0.25$ and at least 5% of the population exhibited this factor. Estimated coefficients and their standard errors (SEs) were calculated using the method of maximum likelihood. Variables were eliminated from the model one at a time based on likelihood ratio tests using a 'backward' statistics principle. A sensitivity analysis using the 'forward' principle was also applied.

The baseline characteristics of all subjects, and divided into COPD and non-COPD subjects, are presented using descriptive statistics and simple tests were used to compare the groups at baseline. T-test was used for continuous variables and χ^2 test was calculated for categorical variables. All analysis was done using SAS.

Cost calculations

The incremental cost of detecting a COPD patient was calculated from a health care provider perspective by applying national average nurse wage (year 2009) from official statistics.
An exchange rate of 1 SEK = € 0.109 was used.

RESULTS:

In all, 305 patients from 21 Swedish primary care centers were included. Baseline characteristics including symptoms for the study population are presented in Table 1.

Table 1 Demographic and baseline characteristics

		COPD	Non-COPD	Total
Age (years)		63.8 (7.8)	60.3 (8.4)	61.2 (8.4)
Female (%)		51.9	58.3	56.7
BMI (kg/m^2)		26.1 (4.8)	27.6 (4.7)	27.2 (4.8)
Packyears		32.9 (13.2)	29.4 (10.7)	30.3 (11.5)
CCQ[1]	Function	0.7 (0.7)	0.6 (1.0)	0.6 (0.8)
	Mental	0.7 (1.1)	0.7 (1.0)	0.7 (1.0)
	Symptom	1.8 (1.0)	1.6 (1.0)	1.6 (1.0)
	Total	1.1 (0.8)	1.0 (0.8)	1.0 (0.8)
MCR[2]		0.8 (0.9)	0.8 (0.8)	0.8 (0.8)

Classification according to GOLD criteria. Data presented as mean values (standard deviation) unless otherwise stated. 1 Clinical COPD Questionnaire; 2 Medical Research Council dyspnoea scale.

COPD was diagnosed in 77 patients (25.2 %) by standard diagnostic spirometry. Out of these, 35 patients (45.5%) with Stage I (mild disease), 41 patients (53.2%) with Stage II (moderate disease) and 1 patient (1.3%) with Stage III (severe disease). None were in stage IV.

Patients with COPD had a mean (standard deviation, SD) FEV1/FVC ratio of 63.6 % (5.9) and patients without COPD had 79.0 % (5.6). COPD patients had a FEV1/FEV6 ratio of 68.0 % (8.0) and patients without COPD had a FEV1/FEV6 ratio of 78 % (10.0) as presented in Table 2.

The FEV1/FEV6 ratio measured by COPD 6 was the best predictor of COPD using a logistic regression ($p<0.0001$).

Table 2 Lung function parameters for a) standard spirometry, and b) COPD 6

	COPD	Non-COPD	Total
a) Standard spirometry			
FEV1, % of predicted pre-bronchodilation	76.1 (17.4)	96.2 (16.1)	91.1 (17.8)
FVC, % predicted pre-bronchodilation	89.9 (17.4)	96.2 (16.0)	94.6 (16.6)
VC, % predicted pre-bronchodilation	91.2 (13.1)	93.9 (16.8)	93.3 (16.0)
FEV1, % of predicted post-bronchodilation	79.7 (16.5)	98.2 (14.6)	93.5 (17.1)
FVC, % of predicted post-bronchodilation	96.5 (21.6)	96.1 (15.5)	96.2 (17.1)
VC, % of predicted post-bronchodilation	94.0 (14.6)	94.3 (17.4)	94.2 (16.7)
FEV1/FVC, % pre-bronchodilation	64.4 (7.2)	77.0 (5.9)	73.8 (8.3)
FEV1/FVC, % post-bronchodilation	63.6 (5.9)	79.0 (5.6)	75.1 (8.8)
Reversibility-ß2-agonist, %	5.1 (10.9)	2.5 (5.9)	3.2 (7.5)
b) COPD 6			
FEV1, % predicted pre-bronchodilation	75.5 (16.0)	92.5 (19.2)	88.2 (19.9)
FEV6, % predicted pre-bronchodilation	90.4 (18.3)	97.8 (17.9)	95.9 (18.2)
FEV1/FEV6, %	68.0 (8.0)	78.0 (10.0)	75.3 (10.2)

FEV1=forced expiratory volume in 1 second; FVC=forced vital capacaty; VC=vital capacity; FEV6=forced expiraory volume in 6 seconds. * GOLD= (Global initiative of Obstructive Lung Disease) Classification according to GOLD criteria (1). Data presented as mean values (standard deviation).

In the logistic regression model, COPD 6 screening significantly predicted COPD, in a descending order according to significance, by FEV1/FEV6, $p<0.0001$; FEV1 (% of predicted), $p<0.0001$; FEV1 (L), $p<0.0001$; FEV6 (L), $p=0.02$; and FEV6 (% of predicted), $p=0.04$.
The other collected information e.g. gender, BMI, pack years, medication, CCQ and MRC were not found to predict COPD in the present study population.

COPD 6 sensitivity and specificity were analysed using a ROC curve analysis (Figure 1). Each plotted value on the ROC curve corresponds to a FEV1/FEV6 ratio cut off value. The FEV1/FEV6 cut off ratio affects the sensitivity and specificity of COPD diagnosis, see Table 3. At a selected FEV1/FEV6 cut off of 73.0 %, the highest sensitivity with an acceptable specificity in the study, the COPD 6 device showed a sensitivity (percent of patients with COPD identified by COPD 6) of 79.2 % and a specificity of 80.3 % (i.e. 19.7 % of the patients are erroneously identified as COPD patients by COPD 6).

Figure 1 **Receiver operating characteristics (ROC) curve for COPD 6 FEV1/FEV6**

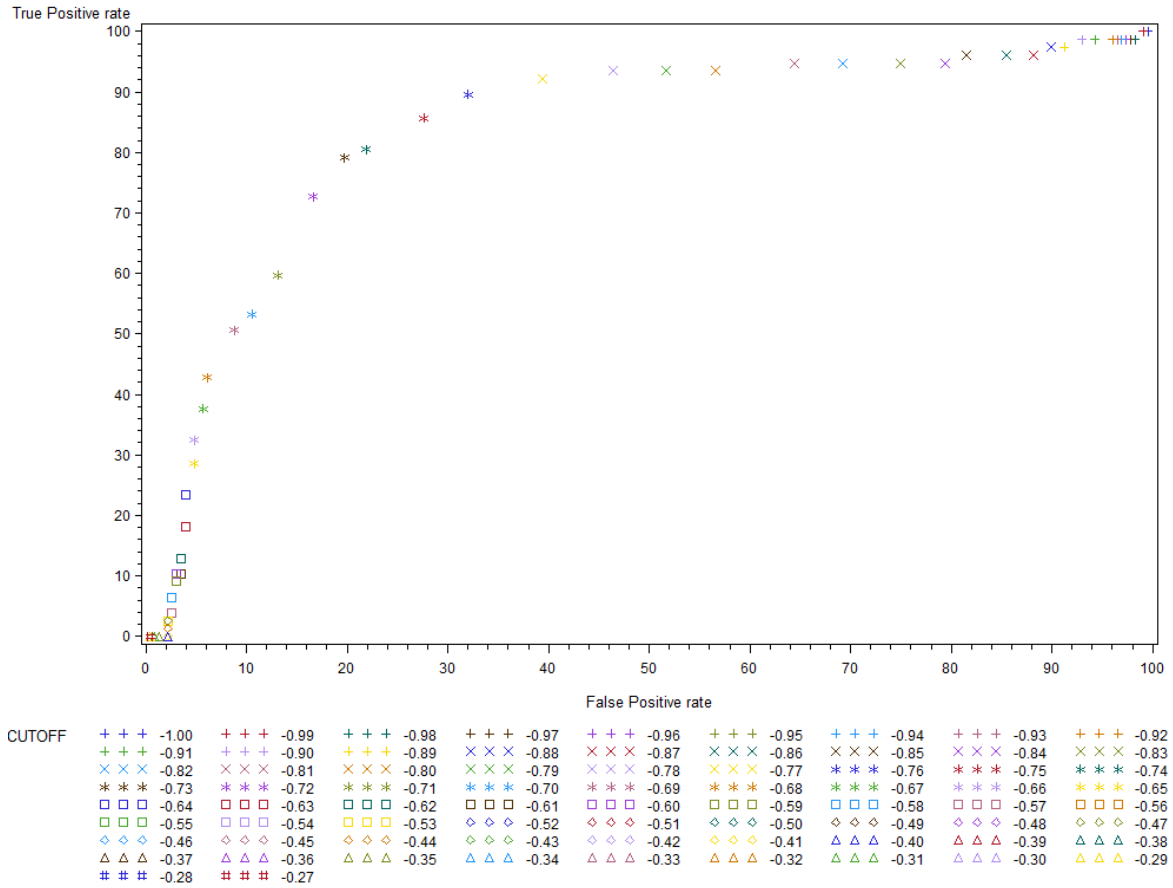

Table 3 **Sensitivity and specificity at different FEV1/FEV6 cut off ratios**

FEV1/FEV6 cut off (%)	Sensitivity (%)	Specificity (%)
70.0	53.3	89.5
73.0	79.2	80.3
75.0	85.7	72.4
77.0	92.2	60.5
80.0	93.5	43.4

The average time for a COPD 6 measurement and a standard spirometry were 4:17 and 32:31 minutes, respectively. Within Swedish healthcare these procedures are usually performed by a nurse. The national average full-time nurse wage year 2009 was € 3064 per month. Social benefit payments in the health-care sector were 41.93 % year 2009. For full-time employment assumptions of 220 working days per year, 8 hours of work per day were made. This resulted in cost estimations of € 2.12 and € 16.07 per COPD 6 measurement and standard spirometry, respectively. (COPD 6 devices and spirometers are assumed to be available. Acquisition costs are not included in the analysis.)

Incremental cost-effectiveness ratios (ICERs) reflecting the cost per additional COPD case detected by screening without COPD 6 versus screening with COPD 6 at different FEV1/FEV6 cut off ratios are presented in Figure 2.
The maximum ICER (€ 279) per additional COPD case detected by ordinary health care routines (i.e. without COPD 6) was found at a COPD 6 FEV1/FEV6 cut off of 78.0 %.

Figure 2 ICER curve showing ICERs of COPD screening without COPD 6 versus screening with COPD 6 at different FEV1/FEV6 cut off ratios