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How representative are clinical study patients with asthma or COPD for a larger ''real life'' population of patients with obstructive lung disease?

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Summary Evidence-based medicine is a corner stone in treatment decision making and large randomised, clinical trials are usually designed in order to provide highly significant results. This study was conducted in order to find out to what extend a ''real life'' patient population with obstructive lung disease could fit into criteria commonly used in clinical research trials. As a secondary aim of the study, we wanted to compare the OLD population recruited from GP's and specialist out-patient clinics, respectively. Eight-hundred and seventy prospective OLD patients were included. Criteria's for selecting asthma patients to a clinical trial were, absence of co-morbidity, FEV 50–85% of predicted, present or historical reversibility 12% last year, non-smoke or if ex-smoke a smoke burden less then 10 pack years. Only 5.4% of the study asthma patients met with these criteria. Additional criteria's as being symptomatic and regular use of inhaled corticosteroids reduced the numbers of eligible asthma patients to 3.3% representing 1.3% of the entire population. The same procedure was applied for the COPD patients, requesting a $FEV_1 < 70\%$ of predicted normal, significant smoke history (>15 pack years) and absence of atopy. This selected 17% of the COPD population, representing 7% of the entire population. We conclude that ''evidence based'' treatment decisions for OLD are based on studies which include a very small and highly selected fraction of this patient population. It is questionable whether such data can extrapolated to a larger, ''real life'' population of patients with obstructive lung disease. Moreover, we found surprisingly minor differences between the Specialist and GP populations.

Introduction

During recent years, clinical decision making has been directed away from the doctor's clinical experience towards a more evidence-based

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approach. The latter is exemplified by a number of treatment guidelines with recommendations graded according to the strength of scientific evidence. The strongest category of evidence is based on randomised controlled trials (RCTs), including a large number of patients. However, most of these clinical trials have been performed in highly selected patient populations. The argument for this strict selection of study subjects is to secure that confounding factors do not conceal the effect of the actual treatment. On the other hand, a strictly selected patient population may not necessarily allow extrapolation of the treatment results to larger, unselected patient populations. This is a major problem when treatment guidelines are to be implemented in the everyday practice of medical doctors.

Several guidelines for management of obstructive lung diseases (OLD) have been published.[1,2] These guidelines are the result of thorough studies of the current literature in the field of bronchial asthma and chronic obstructive pulmonary disease (COPD). The treatment recommendations are mainly based on well-designed RCTs. However, it is not known how representative these study patients are for the majority of patients with obstructive airway diseases. The aim of the present study was to investigate what proportion of an outpatient population with obstructive lung disease that could actually have been included in a typical randomised clinical trial on either asthma or COPD patients. This might be of interest since, in everyday medicine; the results of such trials are implemented on a much broader spectre of patients than the populations from which these results are obtained.

All outpatients with obstructive lung disease were consecutively recruited for the study from three pulmonary specialist clinics and nine GP's. All participating doctors had previously recruited asthma and/or COPD patients for clinical trials. The investigators were asked to classify the patients as having either asthma or COPD on a 10 cm free-graded visual analogue scale (VAS). After being classified as having either asthma or COPD the patients were subjected to regularly employed selection criteria used in RCTs. Subsequently, the number of patients suitable for such clinical trials was calculated. Our hypothesis was that the typical study patients represent a small minority of the "real life" population of patients with obstructive lung disease. If so, the trials providing high-grade evidence for global treatment recommendations might be questioned as a tool for guiding the treatment of a larger population of patients. As a secondary aim of the study, we wanted to compare the OLD population recruited from GP's and specialist out-patient clinics, respectively.

Materials and methods

Patients

Nine GP's and three hospital out-patient clinics recruited consecutive out-patients with OLD for the study. The centres were trained in an investigator meeting to make sure that all the investigators followed the same study procedure. Patients over age 18 and a history of OLD were recruited following an oral consent. All patients fulfilling these criteria were prospectively included during the period August 2001–January 2002. The patients could only be included once.

Methods

All patients were interviewed by the investigator following a structured questionnaire, and the results were plotted in a form with tick boxes, easy to complete.

Demographic data were collected, age, height, gender and duration of OLD, smoke history and history of hay fever and other significant co-morbidity. Disease activity data included number of awakenings due to respiratory symptoms last month, use of rescue medication and other anti-obstructive medication and also use of oral corticosteroids last 12 months. Baseline spirometry values including reversibility data were registered. The investigating physicians were asked to grade the relative purity of disease by using a 10 cm free-graded visual analogue scale (VAS) with bronchial asthma and COPD as the extremes. A VAS score 0–$<$2.5 was regarded as bronchial asthma and a score $>$7.5 as COPD. The group VAS 2.5–7.5 was classified as intermediate, non-classified OLD (Table 1).

The study was approved by the National Regional Ethic Committee.

Statistical analysis

Comparison of subgroups (GP vs. Hospital, asthma vs. COPD) for categorical variables, were tested using Fisher's exact test. Comparison of the same subgroups regarding continuously distributed variables was tested using the unpaired *t*-test. All tests were performed two-sided, and a significance level of 5% was used in all tests.

Table 1 Descriptive data from 870 prospective patients classified on a VAS scale as being pure asthma (VAS <2.5), COPD (VAS >7.5) or having a mixed disease (VAS 2.5–7.5).

	Asthma VAS 0–2.49 ($n = 334$)		Mixed group VAS 2.5–7.49 ($n = 170$)		COPD VAS 7.5–10 ($n = 366$)		ALL Total ($n = 870$)	
	n	%	*n*	%	*n*	%	*n*	%
Age (mean and SD)	43.7	16.8	58.6	15.1	67.1	11.0	56.2	17.7
Gender (male)	124	37.1	59	34.7	182	54.2	365	42.0
History of hay fever	174	52.1	57	33.5	42	12.5	273	31.4
Current smoke	65	19.5	64	37.6	153	45.5	282	32.4
Previous smoker	75	22.5	60	35.3	172	51.2	307	35.3
Smoke burden >10 pack year	49	14.7	90	52.9	255	75.9	394	45.3
Baseline spirometry $FEV_1<70\%$ of pred	57	17.1	88	26.3	295	87.8	440	50.6
Baseline spirometry FVC $<70\%$ of pred	23	6.9	36	10.8	172	51.2	231	26.6
Baseline spirometry FEV_1 51–85% of pred	124	37.1	100	29.9	157	46.7	381	43.8
Baseline spirometry FVC 51–85% of pred	88	26.3	94	28.1	215	64.0	397	45.6
Historical reversibility 12% within 12 m	94	28.1	38	11.4	49	14.6	181	20.8
Significant co-morbidity	104	31.1	87	51.2	222	60.7	413	47.5
Cor Pulmonale	0	0.0	1	0.6	18	4.9	19	2.2
Hypertonia	27	8.1	29	17.1	66	18.0	122	14.0
Ischemic heart disease	13	3.9	17	10.0	74	20.2	104	12.0
Diabetes	11	3.3	14	8.2	23	6.3	48	5.5
Anxiety	15	4.5	18	10.6	26	7.1	59	6.8
Depression	12	3.6	16	9.4	31	8.5	59	6.8
Interstitia lung disease	5	1.5	4	2.4	6	1.6	15	1.7
Oral steroid courses last 12 months	86	25.7	45	26.5	130	35.5	261	30.0
Use of ihaled GCS	242	72.5	129	75.9	255	69.7	626	72.0
$<400\,\mu g$/day	34	10.2	8	4.7	23	6.3	65	7.5
400–800 μg/day	151	45.2	83	48.8	152	41.5	386	44.4
$>800\,\mu g$/day	46	13.8	36	21.2	65	17.8	147	16.9
Use of short-acting β 2 agonist	204	61.1	96	56.5	211	57.7	511	58.7
Average use <1 dose/day	97	29.0	25	14.7	44	12.0	166	19.1
Average use 1–2 doses/day	53	15.9	31	18.2	48	13.1	132	15.2
Average use >2 doses/day	46	13.8	35	20.6	101	27.6	182	20.9
Use of long-acting β 2 agonist	168	50.3	93	54.7	182	49.7	443	50.9
Regular use	126	37.7	71	41.8	173	47.3	370	42.5
Treatment PRN	29	8.7	13	7.6	13	3.6	55	6.3
Nocturnal awakening last month								
None	240	71.9	113	66.5	269	73.5	622	71.5
1–2 night weekly	53	15.9	30	17.6	48	13.1	131	15.1
>2 nights weekly	39	11.7	24	14.1	46	12.6	109	12.5

Results

Study population

Eight-hundred and seventy out-patients were included, 420 investigated by GP's and 450 by lung specialists. Three-hundred and thirty four patients were diagnosed by the clinicians as having mainly bronchial asthma (VAS <2.5), and 366 patients were diagnosed as mainly COPD patients (VAS >7.5). The remaining 170 patients were regarded as being less clear-cut with regard to type of obstructive lung disease (VAS 2.5–7.5) (Table 1). More patients were diagnosed as having

COPD among the lung specialists than among the GPs (52.4% vs. 31%, $P<0.05$) with a trend towards more asthma patients in the GP population (30 vs. 47.4%). Significant co-morbidity was found in 31% of the asthmatics and among 61% of the COPD patients. While 52% of the patients with asthma had a baseline FEV_1s exceeding 85% of predicted, this was found only in 3% of the COPD patients. In contrast, 15% of the COPD patients had FEV_1s less than 30% of predicted compared to none among the asthmatics. Seventy-three per cent of the asthmatics were using regular inhaled corticosteroid therapy and 50% where using long-acting beta-2 agonist compared to 70% and 50% among the COPD patients. Twenty-six per cent of the asthmatics had taken at least one course of oral steroids last 12 months compared to 36% among the COPD patients. Thirty-two per cent of the patients were current smoker, 19.3% among the asthmatics, 42% among the COPD patients and 37.8% among those with mixed disease. Twenty-five per cent of all current smokers also had a history of hay fever, 48% in the asthma group, 10% in the COPD group and 36% among those with mixed disease.

Selection of asthma patients for a typical RCT

The inclusion criteria were applied on the group of patients defined by the clinical investigator as having asthma on the VAS scale (<2.5). The selection criterion excluding most patients was a requested FEV between 50% and 85% of predicted excluding 62.9% of the asthma population, with 124 patients remaining (Table 2, Fig. 1). Other selection criteria used in order of discriminating significance, were historical reversibility of FEV_1s $>12\%$ last 12 months (50 patients remaining), absence from significant co-morbidity (32 patients remaining), no current-smoking or for ex-smokers request of a smoke burden of less then 10 pack-years (One pack-year $=$ 20 cigarettes daily for 1 year.)(18 patients left $=5.4\%$ of those with VAS $<2.5\%$ and 2.1% of all patients) (Table 3, Fig. 1). When the selection criteria were further stressed demanding patients on regular use of inhaled corticosteroids and having symptomatic asthma (nocturnal symptoms at least once weekly or use of beta-2 agonist at least once daily) the numbers of eligible patients were reduced to 15 and 11, respectively (3.3% left of those with VAS $<2.5\%$ and 1.3% of all patients).

Selection of COPD patients for a typical RCT

The inclusion criteria were applied on the group of patients defined by the clinical investigator as having COPD on the VAS scale (>7.5). The selection criterion excluding most patients was absence of

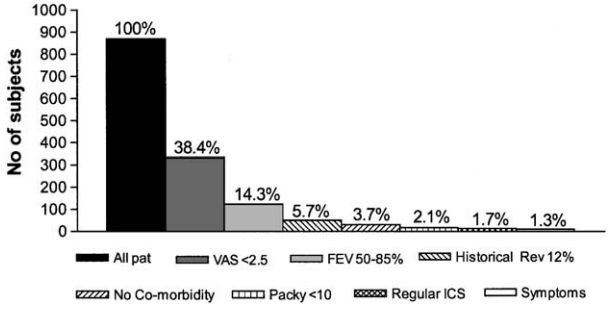

Figure 1 Number of subjects remaining as eligible asthma clinical trial patients, after applying various selection criterias. (1) VAS <2.5 defining pure asthma patients on a visual analogue scale from 0–10. (2) FEV between 50% and 85% of predicted normal. (3) Historical reversibility in FEV 12% within last 12 months. (4) Absence of significant co-morbidity. (5) Non-smoker or if previous smoker, a smoke burden less than 10 pack-years. (6) Regular use of inhaled corticosteroids. (7) Symptomatic asthma defined as either use of short acting β2-agonist daily or nocturnal awakening due to asthma at least once weekly.

Table 2 No. of eligible asthma patients after different selection criterias.

	Asthma patients (VAS <2.5) GP		Specialist		Total	
All patients	No 199	%	No 135	%	No 334	%
No co-morbidity	137	68.8	90	66.7	227	68.0
FEV_1 50–85% of pred	72	36.2	52	38.5	124	37.1
Rev 12% last year	42	21.1	52	38.5	94	28.1
Pack year <10	140	70.4	87	64.4	227	68.0
Regular use of ICS	149	74.9	93	68.9	242	72.5
Symptomatic asthma	135	67.8	96	71.1	231	69.2

Table 3 No. of asthma patients remaining after stepwise introduction of selection criterias.

	Asthma patients (VAS <2.5) GP		Specialist		Total	
All patients	No 199	%	No 135	%	No 334	%
FEV_1 50–85% of pred	72	36.2	52	38.5	124	37.1
Rev 12% last year	26	13.1	24	17.8	50	15.0
No co-morbidity	16	8.0	16	11.9	32	9.6
Pack year <10	11	5.5	7	5.2	18	5.4
Regular use of ICS	10	5.0	5	3.7	15	4.5
Symptomatic asthma	6	3.0	5	3.7	11	3.3

Table 4 No. of eligible COPD patients after different selection criterias.

	COPD patients (VAS 7.5–10) GP		Specialist		Total	
All patients	No 130	%	No 236	%	No 366	%
No co-morbidity	41	31.5	91	38.6	132	36.1
Smoke or X-smoke	122	93.8	203	86.0	325	88.8
Pack year >15	118	90.8	175	74.2	293	80.1
No hay fever	117	90.0	192	81.4	309	84.4
FEV_1 30–70%	87	66.9	154	65.3	241	65.8
FEV <30	13	10.0	41	17.4	54	14.8

Table 5 No. of COPD patients remaining after stepwise introduction of selection criterias.

	COPD patients (VAS 7.5–10) GP		Specialist		Total	
All patients	No 130	%	No 236	%	No 366	%
No co-morbidity	41	31.5	91	70.0	132	36.1
FEV_1 30–70%	29	22.3	59	45.4	88	24.0
Smoke or X-smoke	28	21.5	52	40.0	80	21.9
Pack year>15	25	19.2	46	35.4	71	19.4
No hay fever	23	17.7	40	30.8	63	17.2

significant co-morbidity excluding 65.9% of the COPD population, with 132 patients remaining (Table 4). The patients should have an FEV exceeding 30 and being less than 70% of predicted normal (88 patients remaining). They should also have a smoke history (current or past smoke) with at least 15 pack years (71 patients remaining). Moreover, the patient should not have a history of hay fever (63 patients remaining; 17.2% of patients with VAS >7.5% and 7.2% of all patients (Table 5, Fig. 2)). If the smoke criterion was strengthened requesting ongoing smoking, no further patients were excluded.

Intermediate group (VAS 2.5–7.5), selection for a typical RCT

The intermediate group represented as may be expected an intermediate group of patients between COPD and asthma (Table 1). Thirty-eight per cent of the patients were current smoker

compared to 19.5 of the asthmatics and 45.5 of the COPD patients. Co-morbidity was present in 51% of the patients compared to 31% of the asthmatics and 61% of the COPD patients.

When the same selection criteria's was used for this group as was done for the asthma and COPD patients, 14 (8.2%) the fulfilled the COPD RCT criteria's and 2 (1%) fulfilled the asthma RCT criterias. When the additional asthma criteria, regular use of inhaled corticosteroids and presence of nocturnal symptoms or daily use of rescue beta-2 agonist, was applied, only one patient was left.

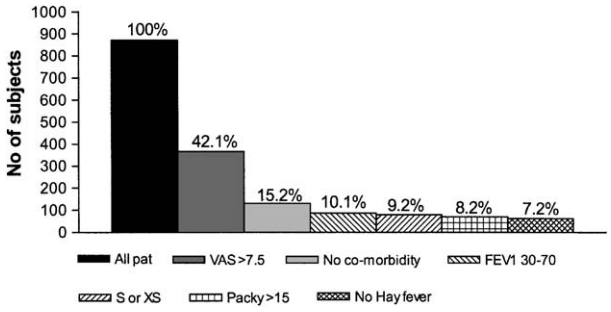

Figure 2 Number of subjects remaining as eligible COPD clinical trial patients, after applying various selection criterias. (1) VAS >7.5 defining pure COPD patients on a visual analogue scale from 0–10. (2) Absence of significant co-morbidity. (3) FEV between 30% and 70% of predicted normal. (3) Smoker or previous smoker. (4) A smoke burden of at least 15 pack-years. (5) No history of hay-fever indicating presence of atopy.

OLD population; GP's vs. specialist out-patient clinics

Asthma patients (VAS <2.5)

One hundred ninety-nine GP patients and 135 specialist patients were judged to having mainly asthma (VAS <2.5) (Table 6). Significantly, more specialist patient had taken at least one oral steroid course during the last 12 months (35% vs. 20%, $P<0.004$). The specialist patients also more frequently used rescue beta-2 agonist. Seventy-nine per cent of the specialist patients compared to 66% of the GP patients used rescue beta-2 agonist at least once daily ($P<0.02$) and 20.7 vs. 9.5% used >2 doses daily ($P=0.006$). The specialist patients also more often reported more frequent nocturnal awakening due to asthma, with 17% vs. 8% ($P<0.05$) having >2 nights per week with nocturnal awakening. Reversibility to beta-2 agonist ($>12\%$) during the last 12 months was also more frequently reported among the specialist patients (53% vs. 24%, $P<0.001$).

Table 6 Characteristics of asthma patients seen by general practitioners compared to those seen by specialists.

	Asthma						
	GP ($n=199$)		Specialist ($n=135$)		All ($n=334$)		P
	n	%	n	%	n	%	
Age (mean and range)	43.9	18–84	43.5	19–89	43.7	18–89	Ns
Gender (male)	69	34.7	55	40.7	124	37.1	Ns
History of hay fever	103	51.8	71	52.6	174	52.1	Ns
Current smoke	38	19.1	27	20.0	65	19.5	Ns
Smoke burden <10 pack year	140	70.4	87	64.4	227	68.0	Ns
Smoke burden >15 pack year	45	22.6	34	25.2	79	23.7	Ns
Baseline spirometry FEV_1 51–85%	72	36.2	52	38.5	124	37.1	Ns
Baseline spirometry FVC 51–85%	46	23.1	42	31.1	88	26.3	Ns
Historical reversibility	42	21.1	52	38.5	94	28.1	0.0001
Significant co-morbidity	51	25.6	40	29.6	91	27.2	Ns
Oral steroid courses last 12 months	39	19.6	47	34.8	86	25.7	0.004
Use of ihaled GCS	149	74.9	93	68.9	242	72.5	Ns
$<400\,\mu g$/day	21	10.6	13	9.6	34	10.2	
400–800 μg/day	97	48.7	54	40.0	151	45.2	Ns
$>800\,\mu g$/day	21	10.6	25	18.5	46	13.8	
Use of short-acting β 2 agonist	122	61.3	82	60.7	204	61.1	Ns
Average use >2 doses/day	19	9.5	28	20.7	47	14.1	0.006
Use of long-acting β 2 agonist	97	48.7	71	52.6	168	50.3	Ns
Nocturnal awakening last month	49	24.6	45	33.3	94	28.1	Ns
1–2 night weekly	33	16.6	20	14.8	53	15.9	
>2 nights weekly	16	8.0	25	18.5	41	12.3	

Table 7 Characteristics of COPD patients seen by general practitioners compared to those seen by specialists.

	COPD VAS >7.5						
	GP ($n = 130$)		Specialist ($n = 236$)		All ($n = 366$)		P
	n	%	n	%	n	%	
Age (mean and range)	67.8	36–88	66.7	24–91	67.1	24–91	Ns
Gender (male)	68	52.3	114	48.3	182	49.7	Ns
History of hay fever	12	9.2	30	12.7	42	11.5	Ns
Current smoke	62	47.7	91	38.6	153	41.8	Ns
Smoke burden >15 pack year	118	90.8	175	74.2	293	80.1	Ns
Baseline spirometry FEV_1<70%	100	76.9	195	82.6	295	80.6	Ns
Historical reversibility	14	10.8	35	14.8	49	13.4	0.004
Significant co-morbidity	51	39.2	40	16.9	91	24.9	Ns
Oral steroid courses last 12 months	42	32.3	88	37.3	130	35.5	Ns
Use of ihaled GCS	89	68.5	166	70.3	255	69.7	Ns
<400 μg/day	3	2.3	20	8.5	23	6.3	
400–800 μg/day	50	38.5	102	43.2	152	41.5	
>800 μg/day	29	22.3	36	15.3	65	17.8	
Use of short-acting β 2 agonist	74	56.9	137	58.1	211	57.7	Ns
Average use >2 doses/day	39	30.0	62	26.3	101	27.6	Ns
				0.0			
Use of long-acting β 2 agonist	72	55.4	120	50.8	192	52.5	Ns
Nocturnal awakening last month	39	30.0	58	24.6	97	26.5	Ns
1–2 night weekly	25	19.2	23	9.7	48	13.1	
>2 nights weekly	13	10.0	33	14.0	46	12.6	

Significant co-morbidity was equally reported among the specialist compared to the GP patients (30% vs.26%, $P>0.05$).

COPD patients

One hundred twenty-eight GP patients and 234 specialist patients were judged to having mainly COPD (VAS >7.5) (Table 7). Significantly more GP patient had a smoke history with a smoke burden exceeding 15 pack years (92 vs. 79%, $P<0.001$). In all other aspects, the profile of the GP and specialist patients was fairly the same.

Discussion

The current study shows that typical clinical study patients with asthma or COPD represent a very small fraction of the patient population being treated by clinicians in everyday practice, regardless of whether the doctors are pulmonary physicians or GPs.

The most important selection criterion regarding COPD patients seems to be the presence of co-morbidity, with more than 60% of the patients having a disease potentially interfering with the treatment. Thus, in addition to suffering from other diseases, these patients are often using other medication than anti-obstructive drugs. This might have an impact on the risk of side effects, but also on the clinical effect of the actual study drug per se. The compliance will also be influenced by the number of drugs being prescribed.[3] Another important selection criterion was severely reduced lung function, i.e. FEV_1 less than 30% of predicted.[4–8] Little is known about how these patients react on the various anti-obstructive drugs, but one might anticipate that such patients could experience less effect of inhaled drugs due to their reduced ventilation of the peripheral airways.[9]

COPD patients with atopy are often excluded from clinical trials. It has been shown that the lung function of these patients deteriorates faster than in non-atopic COPD patients,[10] and it has been claimed that the underlining pathology in these two groups of COPD patients, and thus, the effect of drug treatment may be dissimilar.[11] Even if most studies on COPD patients are performed on patients with a heavy smoking burden, patients who have smoked less are treated with the drugs tested in these clinical trials.

Eight per cent of all patients were recognised as being smokers with concurrent atopy and 25% of all smokers were recognised as atopic. Of those subjects, 49% were regarded as pure asthmatics,

10% as COPD and 41% as having a non-classified OLD. Also in those patients being regarded as pure asthmatics, it is a reasonable assumption that the inflammation triggered by smoke exposure influenced by the atopic sensitisation in one way or an other may represent a mixed pathology demanding special treatment strategies. Indeed, it has been shown that, asthmatic patients who smoke seems to respond less to inhaled corticosteroid therapy compared to those who do not smoke.[12–14]

In many studies looking at lung function improvement as a primary outcome, a sub-optimal lung function is often required in order to allow further lung function improvement. We have chosen 85% as a commonly used criteria for upper limit of predicted FEV, even though also a lower upper limit, i.e. 80% of predicted, is commonly used.[15–17] In the present study nearly 65% was excluded because of a FEV exceeding 50–85% of predicted. In clinical practice, these patients are also treated with anti-asthmatic drugs; targeting asthma symptoms like exercise intolerability, nocturnal symptoms etc. and the documentation regarding treatment effect on these patients are thus limited. Reversibility was defined as improvement in FEV_1s of more than 12% following inhalation of a beta-agonist. This criterion was more frequently positive among the patients examined by pulmonary physicians. One reason is probably that reversibility testing was more frequently performed among specialists than by GPs. Reversibility should not be regarded as a static phenomenon, and it has been shown that repeated reversibility testing in the same patient over several days increases the probability of getting at least one positive test.[18]

More specialist asthma patients had been taken at least one course of oral steroids during the last 12 month. Moreover, they tended to use more rescue beta-2 agonists and more frequently reported nocturnal awakenings. This indicates a slightly more severe disease in the group of patients seen by the specialists. On the other hand, the medications used were similar between the groups both regarding regular use of glucocorticosteroid and long acting beta agonists. Moreover, the lung function profile and the percentage of patients with co-morbidity, was the same for both groups (data not shown). Taken all this together, we found surprisingly minor differences between the two populations.

Most recent guidelines for COPD and asthma treatment are referring the recommendations to evidence collected from large RTC and or systematic reviews. Even though a large randomised trial, containing a large number of patients, provide highly statistical significances, in favour of one drug before the other, this does not necessarily imply that the results can be extrapolated to a larger, less selected patient population. The question also remains, to what extent strictly selected RTC really provides information that justifies the investments made. The more strict, the criteria, the easier it will be to predict the outcome, and a sufficient number of patients will in most instances secure enough power for to reach statistical significant differences.

Before stating ''high grade of evidence'' we need to consider to what extend the results are of clinical significance as well as statistical significance. And still, the important question remains; can the results obtained in a strictly selected RCT be applied to the entire target population, i.e. to the patients we meet in our ''every day'' clinical practice.

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