Optimizing health care for patients with COPD or asthma in Dutch general practice

Tjard Schermer
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This thesis has been prepared by the Department of General Practice of the Radboud University Nijmegen Medical Centre, the Netherlands, and within the programme Chronic Diseases in General Practice of the Nijmegen Centre for Evidence Based Practice (NCEBP), one of the approved research institutes of the Radboud University Nijmegen. The Department of General Practice participates in the Netherlands School of Primary Care Research (CaRe), which has been acknowledged by the Royal Netherlands Academy of Arts and Sciences (KNAW) in 1995.

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Optimizing health care for patients with COPD or asthma in Dutch general practice

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen
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Tjaarda Roland Jacob Schermer

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Prof. dr. P.M. Calverley, University Hospital Aintree, Liverpool, UK
It’s all about air ...
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Preface

In developed countries like the Netherlands health care for patients with chronic diseases is of a high standard compared with many other, less fortunate countries around the world. The typical structure of the Dutch health care system, with general practitioners (GPs) as the gatekeepers towards medical specialist and paramedical care facilities provides a rather transparent and efficient health care infrastructure. The GP gatekeeper structure is intended to reduce costs while maintaining or improving the quality of care by increasing coordination and preventing and reducing duplicative or inappropriate care. This is especially important for patients with chronic diseases, many of whom are dependent on medical care and seek contact with health care providers on a regular basis.

Two chronic diseases that are highly prevalent in the population are asthma and chronic obstructive pulmonary disease (COPD). Until about 1997, the two conditions were often described jointly by the overarching term chronic non-specific lung disease (CNSLD, or ‘CARA’). Nowadays, asthma and COPD are recognized as two separate disease entities, although individual patients may well exhibit features of both diseases. Even specific histopathological features in endobronchial biopsy specimens are not always sufficient to discriminate between COPD and asthma. This means that –even with extensive diagnostic testing- the two conditions cannot always be strictly separated, which may complicate the appropriate choice of treatment. Moreover, underdiagnosis in the general population appears to substantial for both conditions.

The subdivision of CNSLD into asthma and COPD has had (and still has) important consequences for the way patients in the Netherlands are diagnosed and managed by GPs. Over the next few years it is expected that in many countries a sharp increase will occur in the prevalence of both asthma and COPD. Especially patients with COPD will make steadily increasing demands on available primary and secondary health care services. One of the major challenges for the near future is to achieve efficient use of available health care services for patients with COPD and asthma. This means propagating effective treatment in patients for whom this is indicated, while at the same time reducing unnecessary and ineffective treatment and counteracting barriers that restrain optimal delivery of care. These goals should preferably be attained on the basis of scientific evidence, to which this thesis makes a modest contribution.

The thesis contains chapters that pertain to COPD, to asthma, or to both conditions simultaneously. The Introduction consists of the summary of a comprehensive literature review regarding the efficacy and (cost-)effectiveness of a range of health care interventions.
for COPD and asthma, which was performed as a part of the 1997 Public Health Status and Forecasts (PHSF) project enforced by the National Institute of Public Health and the Environment (RIVM)\textsuperscript{11}. Possible barriers towards attaining optimal health care for patients with COPD and asthma were also identified and discussed in this PHSF contribution. The subsequent chapters mainly comprise two topics that were also considered in the PHSF, and which are particularly relevant for the primary care management of patients with COPD and asthma, i.e. (1) spirometric testing in the general practice setting, and (2) treatment with inhaled corticosteroids in different study populations of subjects with -or at high risk of- chronic respiratory disease. Chapter 1 is a review of the literature on different aspects of spirometry in general practice. Because the accessibility of spirometry for GPs has substantially improved over the last couple of years, evidence-based information needs to be established in order to critically assess the applicability of spirometry as a tool for diagnosis and monitoring in the general practice setting. In Chapters 2 through 4 the results of two original studies regarding the validity of spirometric tests performed in Dutch general practices are reported. Chapter 5 explores the impact of spirometry on GPs’ diagnostic differentiation and decision making, whereas Chapter 6 reflects on the current status and organisation of spirometry in primary care. Chapter 7 reports a qualitative study in which the views of pulmonologists with regard to efficient referral and consultation in patients with COPD or asthma are explored. In chapters 8 to 11 the effects of regular treatment with inhaled corticosteroids, one of the most prescribed classes of drugs in COPD and asthma, is studied in three different populations: adult patients with asthma (Chapters 8 and 9), subjects with early signs and symptoms of COPD (Chapter 10), and patients with COPD or chronic bronchitis (Chapter 11). In asthma the position of inhaled corticosteroids is no longer a matter of dispute.\textsuperscript{12} However, the role of inhaled steroids in the management of COPD is less clear\textsuperscript{13}, although evidence is accumulating that supports a preventive effect on the occurrence of acute exacerbations\textsuperscript{14-16}, deterioration of health status\textsuperscript{14}, and maybe the progression of airflow limitation.\textsuperscript{16} Finally, Chapter 12 focuses on the occurrence and costs of acute exacerbations in patients with COPD or chronic bronchitis. Prevention of exacerbations is generally considered as one of the main treatment goals in these patients\textsuperscript{18,19}, because exacerbations are known to have a significant impact on the quality of life\textsuperscript{20,21} and are responsible for the majority of COPD-related health care costs.\textsuperscript{22,23} Moreover, exacerbation rate is increasingly used as an outcome measure in long-term clinical COPD studies.\textsuperscript{24} The data presented in Chapters 11 and 12 are from a randomised controlled trial, the COOPT (‘COPD on Primary Care Treatment’) study, in which the long-term effects of regular treatment with N-acetylcysteine
and the inhaled corticosteroid fluticasone propionate are investigated in a primary care population of patients with COPD. The results of this study were not timely available for inclusion in this thesis.

References


Introduction

Published as: The Public Health Status and Forecast 1997.
Chapter 8. Chronic Non-Specific Lung Disease,
National Institute of Public Health and the Environment (RIVM), 1997
CHRONIC NON-SPECIFIC RESPIRATORY DISEASE (CNSLD)

1. Introduction

This chapter gives a summary of a comprehensive literature review on the efficacy and effectiveness of health care interventions for COPD and asthma and barriers associated with the primary process of care delivery. These barriers comprised: contact with the health care system, diagnosis of the disease, indications for intervention, the execution of care and treatment compliance (Schermer et al. 1997). To justify the contents and the majority of literature references, the reader is referred to the background report.

In contrast with the usual approach taken in the 1997 Public Health Status and Forecasts (PHSF), this literature study categorized chronic non-specific respiratory disease (CNSLD) into chronic obstructive pulmonary disease (COPD, chronic bronchitis and emphysema) and asthma. Chronic bronchitis is characterised by the hypersecretion of mucus in the bronchial tree that manifests itself as a chronic or recurrent productive cough. By definition, these symptoms must be present on most days, for a minimum of three months per year and for at least two consecutive years. Emphysema is defined as anatomical changes in the lungs, characterised by abnormal enlargement of the air-containing spaces distal to the terminal, non-respiratory bronchioli, without any evidence of fibrosis. Asthma is described as inflammation of the respiratory tract that is accompanied by reversible narrowing of the bronchi and increased bronchial responsiveness to various trigger factors.

COPD and asthma have different pathogeneses and pathophysiologies. In this chapter, it is particularly important to distinguish between COPD and asthma, because there are diagnostic and therapeutic consequences and also consequences regarding the outcome of the disease processes. In section 1.2, this distinction receives further elaboration.

1.1 Methods

A literature review was performed in which the efficacy of health care interventions was judged on the basis of systematic literature reviews, meta-analyses and original studies, such as randomised clinical trials (RCTs). Information was obtained via the Cochrane Collaboration, MEDLINE (period 1981-1996), references in relevant literature, the Nederlands Tijdschrift voor Geneeskunde, Huisarts & Wetenschap, Tijdschrift voor Sociale Geneeskunde and Dutch theses. The quality of the original reports was assessed using the criteria formulated by Guyatt et al. (Guyatt, et al., 1993). Preference was given to randomised controlled studies. When these were unavailable, use was made of non-randomised studies. Information on the effectiveness of interventions and the primary process of care was obtained from the same sources, except for the Cochrane Collaboration. When necessary, additional information was obtained from experts in the fields of COPD and asthma.

To review the literature on economic evaluations of COPD/asthma, extensive searches were made in MEDLINE (1968-1996), diverse bibliographies, editions of journals on health economics and cross-references.
1.2 Epidemiology, pathogenesis, disease course and prognostic factors

On the basis of general practice registries, it was estimated that 172,500 persons were suffering from asthma in 1994, while 290,000 persons were suffering from COPD (see Theme Report I, Part B2, Section 4). In that year, an estimated 60,500 persons were newly diagnosed with asthma, while 34,600 were newly diagnosed with COPD. In 1994, data showed that 54 patients died from asthma, while 5643 died from COPD. This means that approximately 50,100 years of life were lost (see Theme Report I, Part B1, Section 3.1).

COPD is characterised by pathophysiological changes in gas exchange, ventilation and pulmonary circulation. Chronic bronchitis is associated with increased numbers of mucus-producing goblet glands, while these glands, in contrast with the normal situation, can also be found in the more peripheral airways. Cellular inflammatory infiltrates are present in the mucus membrane and also around the goblet glands. Inhalation of cigarette smoke and viral or bacterial respiratory infections cause increases in mucus production and decreases in mucus drainage.

Viral infections and inhalation of tobacco smoke, ozone, nitrogen dioxide and other irritating agents are largely responsible for the increases in oxygen radical level and enzymes that are harmful to lung tissue. It is assumed that the natural anti-oxidative protection mechanisms of the body against these oxygen radicals fails in COPD patients. The combination of the relative excess of harmful enzymes and damaged support tissue of the lungs and alveolar walls ultimately leads to emphysema. Interaction between oxygen radicals and immune defence cells may increase the risk of recurrent respiratory infections in COPD.

Asthma is characterized by infiltration of various types of inflammatory cells into the walls of the bronchi, which damages the bronchial mucosa and causes oedema and thickening of the basal membrane. The combination of increased mucus production and contraction of the smooth muscle in the bronchial walls leads to bronchial constriction. An important difference between asthma and COPD is that the bronchial constriction in asthma is reversible, either spontaneously or due to treatment. The bronchial hyperresponsiveness (BHR) typical of asthma is caused by genetic factors and environmental factors (such as exposure to allergens). BHR is a strong determinant of the severity and degree of bronchial constriction.

Although the natural course of COPD cannot be followed in its pure form, because diverse care interventions will have already been applied, it is possible to make an approximation of lung function deterioration over time by recording sequential measurements of the forced expiratory volume in 1 second (FEV1). The results of various epidemiological studies performed within this framework on COPD patients indicated irreversible deterioration of the FEV1 of 48-91 ml per year (Burrows, 1991). This decrease is about two to three times more rapid than in healthy persons of the same age and sex. Owing to the fairly gradual deterioration in lung function and the only moderate correlation between FEV1 and symptoms, many patients do not consult their GP until they are in a rather advanced stage of the disease (Van Weel 1996).

A wide range of prognostic factors determine the (clinical) course in individual COPD and asthma patients. A number of these prognostic factors might form suitable targets for health care interventions. These include: failure to quit smoking, continuous use of/poor response to
bronchodilatory medication (Van Schayck & Van Herwaarden 1993), airway infections and hypersecretion of mucus in the lungs, hypoxaemia and nocturnal desaturation, malnutrition, poor functional status, reduced exercise tolerance, cardiac dysfunction and congestive heart failure, alpha-1-antitrypsin deficiency, bronchial hyperresponsiveness, occupational exposure factors.

Outcome measures that are relevant to COPD and asthma are: mortality, quality of life, functional status, illness-related absenteeism from work or school and incapacity to work. All these aspects are less favourable than in the general population. Intermediary outcomes for COPD and asthma are: FEV\textsubscript{1} (as predictor of mortality and functional status) and BHR (as indicator of the severity of bronchial inflammation), respectively. Peak flow measurements can be used in asthma patients to monitor treatment effects.

2. Outcomes and process assessment

2.1 Contact with the health care system
Dutch screening programmes on the general population revealed that 306 per 1000 persons aged 25-70 years, after exclusion of patients with congestive heart failure and chronic pulmonary diseases other than COPD or asthma, had symptoms or lung function abnormalities consistent with COPD or asthma (Tirimanna et al., 1996a). In 65%, the GP was not aware of this, while in the group with severe symptoms or severely compromised lung function, the GP was not aware in 7%. As mentioned above, many patients do not consult their GP until a late stage of the disease. Explanations for this are the gradual deterioration in lung function, the moderate correlation between lung function (FEV\textsubscript{1}) and symptoms, and different perceptions of dyspnoea (Tirimanna et al., 1996b; Tirimanna, 1997; Van Weel, 1996).

2.2 Diagnosis
One year after the primary diagnosis of asthma had been made by the GP, the diagnosis was still recorded by the GP in only 60% of the cases; ten years later, this was only 20% (Bottema 1993). Apparently, the symptoms had diminished to such an extent that the diagnosis was no longer justifiable. It is possible that over-diagnosis played a role. Besides evidence of over-diagnosis, there is also evidence of under-diagnosis (Bottema 1993). Furthermore, it has been suggested that the ineffectiveness of health care interventions in a proportion of the patients can be attributed to insufficient differentiation between asthma and COPD. This differentiation can be made to a certain extent using lung function tests, while the (clinical) course of asthma and COPD can be monitored by recalling the patient for regular lung function tests.

2.3 Health care interventions
Tables 1 and 2 give overviews of health care interventions for COPD and asthma, their efficacy, effectiveness, indications, barriers reported in relation with their administration and (if applicable) treatment compliance.
The tables show that a large number of health care interventions are effective. These interventions influence outcomes such as symptoms, physical functioning, quality of life, FEV\textsubscript{1} and mortality. The size of the effects and the outcome measures differed between studies. Judgements of efficacy were chiefly made on the basis of randomised controlled trials. However, for a number of health care interventions, no data were available from such trials. For example, no experimental research was available on influenza vaccination in COPD patients, but assessments of efficacy were derived from studies on the elderly; in the case of lung transplantation, judgement was based on comparisons between patients who had undergone a lung transplant and the patients on the waiting list who acted as controls.

Information on the effectiveness of health care interventions was often lacking, or effectiveness assessments were made on the basis of research from other countries. Consequently, it was impossible to draw any conclusions about the health benefit that might be gained from specific health care interventions by comparing studies on efficacy under ideal circumstances to studies performed in daily practice.

Information about barriers in the process of care was scarce and partly based on foreign research. Nevertheless there were indications that some of the barriers also applied to the Dutch situation (see table 1). Solving these problems can lead to greater health benefit.

**COPD**

By solving the barriers in *treatment indications* for COPD, more health benefit can be achieved if:

- GPs advise more patients to quit smoking and repeats this advice often
- more patients are vaccinated against influenza
- more consideration is given to anticholinergic medication as the first choice instead of β\textsubscript{2}-agonists
- oral corticosteroids are indicated more often as experimental treatment for severe, stable, therapy-resistant COPD
- fewer prescriptions are written for antibiotics and are based more on further diagnostics into the cause of exacerbation. A short course of corticosteroids might form an alternative
- more indications are recognised for (outpatient) pulmonary rehabilitation or home care
- ventilatory support with oxygen is started at home at an earlier stage and is based more often on existing indication criteria
- non-invasive ventilatory support is offered (at home) to the small subgroup of COPD patients who might benefit from it
- more attention is paid to (preventive) measures and advice relevant to the working environment of patients who are active in the employment process.
Table 1. Health care interventions for COPD: efficacy, effectiveness and barriers in the process of care delivery.

<table>
<thead>
<tr>
<th>Health care intervention</th>
<th>Efficacy(^b)</th>
<th>Effectiveness(^b)</th>
<th>Indication for treatment(^c)</th>
<th>Execution(^c)</th>
<th>Treatment compliance(^c)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Trials in smokers</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>? to +</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>n.a.</td>
<td>No trials specifically in COPD, but in healthy/elderly subjects</td>
</tr>
<tr>
<td>Preventive measures with surgical interventions</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>No trials in COPD, but in major (abdominal) surgery, recommendation according to guideline</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Preferred above (\beta_2)-agonists</td>
</tr>
<tr>
<td>(\beta_2)-agonists</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Compared to placebo</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>Trials with probable case-mix with asthma</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>Compared to placebo, not to (\beta_2)-agonists</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Reduced risk of exacerbation, anti-oxidative effect is being investigated</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>One trial for one drug</td>
</tr>
<tr>
<td>Mucolytics and cough preparations</td>
<td>? to +</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>Not effective compared to oral steroid courses, effective compared to placebo. Cause of exacerbations often unclear in trials</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>- to +</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>(Outpatient) pulmonary rehabilitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>(Multidisciplinary) home care, after-care, transmural care</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>In other countries effect on mortality by deploying respiratory nurses</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>- to +</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Depending on the nature of the treatment</td>
</tr>
<tr>
<td>Home oxygen therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Chronic intermittent ventilatory support</td>
<td>- to +</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lung transplants and lung volume reduction surgery</td>
<td>? to +</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>n.a.</td>
<td>Before-after comparison or waiting list controls, mixture of pulmonary diseases</td>
</tr>
<tr>
<td>Patient education and self-management</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>Effect on hospital admissions</td>
</tr>
</tbody>
</table>

\(^a\) efficacy unknown for pneumococcal and staphylococcal vaccination, alpha-antitrypsine supplementation and nutritional supplementation.

\(^b\) + = proven, - = inefficacious or ineffective, ? = unknown or unclear, \(\ldots\) to \(\ldots\) = dependent on subgroup or specific intervention.

\(^c\) + = barrier present, ? = unknown.

n.a. = not applicable.
The execution of health care interventions for COPD can be improved by:

- providing more intensive guidance and after-care following smoking-cessation advice
- giving better instruction about the inhalation technique of diverse respiratory drugs
- monitoring the effects and side-effects of a trial treatment with corticosteroids more closely
- providing adequate supervision and after-care following outpatient or clinical pulmonary rehabilitation in order to prevent relapse
- prescribing oxygen at home for a sufficiently long duration, providing better instruction about its use, supplying modern equipment and making closer evaluations of the treatment effect
- improving the feasibility of ventilatory support treatment and its administration by means of intermittent ventilatory support at home
- increasing the uptake of influenza vaccination, for instance by providing better patient education and organising special vaccination consulting hours.

Improvements in treatment compliance to a large number of health care interventions for COPD can also lead to greater health benefit.
Table 2. Health care interventions for asthma: efficacy, effectiveness and barriers in the process of care delivery.

<table>
<thead>
<tr>
<th>Health care intervention</th>
<th>Efficacy</th>
<th>Effectiveness</th>
<th>Indication for treatment</th>
<th>Execution</th>
<th>Treatment compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>n.a.</td>
</tr>
<tr>
<td>Domestic allergen avoidance measures</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+ e</td>
</tr>
<tr>
<td>Allergen immunotherapy</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Preventive measures in case of surgical interventions</td>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
<td>- to + g</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>β-agonists</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Methyloxanthines</td>
<td>- to + i</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>+ j</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>+ k</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Nedocromil and cromones</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>(Multidisciplinary) home care, after-care, transmural care</td>
<td>? m</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>+ n</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Patient education and self-management</td>
<td>- to + o</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

a) for pneumococcal and staphylococcal vaccination the preventive efficacy has not been established sufficiently in clinical trials; no placebo-controlled trial has been reported for antibiotics.
b) + = proven, - = ineffective, ? = unknown or unclear, ... to ... = depends on the subgroup or type of intervention.
c) + = barrier present, ? = unknown, n.a = not applicable.
d) trials in smokers.
e) proportion that takes avoidance measures is rather limited; it is unknown to what extent advices given by physicians or paramedical professionals are followed.
f) no trials in patients with asthma, but from preventive measures in major (abdominal) surgical procedures.
g) in adults no long-term additional value compared with β-agonists; in children additional value when combined with β-agonists in exacerbations.
h) in a foreign region with a low β-agonists prescription rate more asthma-related hospital admissions.
i) no additional value in treating exacerbations compared with β-agonists and systemic corticosteroids, short-term effect of regular treatment.
j) in a foreign region with a low prescription rate more asthma-related hospital admissions.
k) short course in case of exacerbation; reduction of hospital admissions and improved exacerbation recovery.
l) in a foreign region with a low prescription rate more hospital admissions for asthma.
m) multidisciplinary home care efficacious in a randomised trial in CNSLD; no effect of CNSLD-nurse supervision at home in a randomised study.
n) relaxation exercises.
o) in adults not in children.

ASTHMA

Determining treatment indications for asthma can be enhanced by:

- improving the diagnosis of allergies and causes of exacerbations
- encouraging patient education and self-treatment/self-management in adult patients
- advising more patients to quit smoking and repeating this advice more often
- making more recommendations about domestic allergen avoidance measures following adequate allergy diagnostics
- conducting more allergen-immunotherapy in specific subgroups (after adequate allergen diagnostics)
- prescribing more prophylactic medication, such as nedocromil, cromoglycine acid or inhaled
corticosteroids

- prescribing inhaled corticosteroids (if necessary in higher dosages) instead of systemic corticosteroids
- giving more consideration to $\beta_2$-agonists than to anticholinergics for bronchodilatory treatment
- limiting the use of methylxanthines as regular treatment
- using systemic corticosteroids and $\beta_2$-agonists more often and at an earlier stage during exacerbations and avoiding the use of methylxanthines
- using systemic corticosteroids more often for therapy-resistant asthma
- exercising moderation in the prescription of antibiotics during asthma exacerbations
- encouraging relaxation training
- paying more attention to (preventive) measures and advice in relation with the work situation of patients who are active in the employment process.

The execution of health care interventions for asthma can be improved by:

- providing more intensive guidance and after-care following smoking-cessation advice
- encouraging the use of $\beta_2$-agonists "as required" instead of continuously
- emphasizing "continuous" use of inhaled corticosteroids
- monitoring serum concentrations after the prescription of methylxanthines
- closely monitoring patients on oral corticosteroids for early detection of side-effects.

Encouraging treatment compliance to achieve health benefit also applies to asthma patients.

3. Economic evaluations

Table 3 shows the results of a literature study on economic evaluations of health care interventions for COPD and asthma. Not all health care interventions were subjected to economic evaluation. A total of 87 studies were traced that applied to 24 health care interventions, including several cost-of-illness studies and partial economic evaluations. No studies at all were found on seven health care interventions. In ten of the health care interventions, it was possible to make some degree of judgement about cost-effectiveness, albeit with the greatest of caution. Another important finding was that the study designs varied widely, which made mutual comparisons practically impossible and no conclusions could be drawn on actual differences in cost-effectiveness between health care interventions.
### Table 3. Literature review on economic evaluations in COPD and asthma

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of studies</th>
<th>Results</th>
<th>Comments</th>
<th>C-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>6</td>
<td>2xLYS, 1xQALY, 1xCOI, 2xother</td>
<td>Various interventions, non-CNSLD specific, mainly modelling studies</td>
<td>?+</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>7</td>
<td>2xLYS, 3xQALY, 2xCBA</td>
<td>mainly modelling studies, on high-risk populations probably cost-effective</td>
<td>+</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>4</td>
<td>3xLYS, 1xCBA</td>
<td>Results of modelling studies differed substantially, not all relevant cost was included</td>
<td>?+</td>
</tr>
<tr>
<td>Allergen immunotherapy</td>
<td>1</td>
<td>CBA</td>
<td>Only part of direct cost was estimated</td>
<td>?</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>4</td>
<td>1xCVM, 1xCBA, 2xO</td>
<td>Compared to various alternatives, not C/E in asthma or case of acute exacerbation</td>
<td>?+</td>
</tr>
<tr>
<td>β2-agonists</td>
<td>8</td>
<td>1xEFD, 3xO, 2xCMA, 2xCBA</td>
<td>Differences in study design, perspective and outcome measures</td>
<td>?</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>2</td>
<td>1xCFM, 1xO</td>
<td>Limited indication</td>
<td>?-</td>
</tr>
<tr>
<td>Inhaled corticosteroids (children)</td>
<td>3</td>
<td>1xO, 1xSFD, 1xCBA</td>
<td>Dutch study regarding costs and savings, good quality design</td>
<td>?+</td>
</tr>
<tr>
<td>Inhaled corticosteroids (adults)</td>
<td>5</td>
<td>1xCOL, 3xO, 1xCBA</td>
<td>Dutch study regarding costs and savings, good quality design, asthma only, increase of dose not C/E</td>
<td>?+</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>1</td>
<td>1xO</td>
<td>Insufficient data</td>
<td>?</td>
</tr>
<tr>
<td>Cromones</td>
<td>1</td>
<td>1xCBA</td>
<td>Insufficient data</td>
<td>?</td>
</tr>
<tr>
<td>Alpha-1 antitrypsine supplementation</td>
<td>1</td>
<td>1xLYS</td>
<td>Modelling study, appears to quite expensive</td>
<td>?-</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>3</td>
<td>1xWY, 1xCBA, 1xO</td>
<td>Probably C/E in a selected target population, insufficient good-quality data</td>
<td>?+</td>
</tr>
<tr>
<td>Home care, after-care, transmural care</td>
<td>5</td>
<td>1xO, 4xCBA</td>
<td>Improved integration between care echelons may be C/E, additional good-quality studies are needed</td>
<td>?+</td>
</tr>
<tr>
<td>Home oxygen therapy</td>
<td>9</td>
<td>9xO</td>
<td>None of the traced studies were full economic evaluations</td>
<td>?</td>
</tr>
<tr>
<td>Home mechanical ventilation</td>
<td>6</td>
<td>6xO</td>
<td>None of the traced studies were full economic evaluations</td>
<td>?</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>2</td>
<td>2xQALY</td>
<td>Good-quality Dutch study, results positive compared with other studies</td>
<td>?-</td>
</tr>
<tr>
<td>Patient education and self-management (children)</td>
<td>5</td>
<td>3xCBA, 2xO</td>
<td>Diverse interventions, different cost categories included</td>
<td>?+</td>
</tr>
<tr>
<td>Patient education and self-management (adults)</td>
<td>8</td>
<td>7xCBA, 1xO</td>
<td>Mainly asthma, diverse interventions and cost categories, no cost-effectiveness analyses</td>
<td>?+</td>
</tr>
</tbody>
</table>

*a* no economic evaluations could be traced for: allergen avoidance measures, prophylactic measures in surgery, N-acetylcysteine, expectorants, antibiotics, nutritional interventions, physiotherapy

**Abbreviations used:**
- CEA = Cost-effectiveness analysis
- CBA = Cost-benefit analysis
- CMA = Cost-minimisation analysis
- LYS = CEA based on Life Years Saved
- QALY = CEA based on Quality Adjusted Life Years
- COI = Cost of Illness study
- CFM = CEA based on Complication-Free Month
4. Future developments

Over the next few years, it will become clear whether early detection of COPD and/or asthma is desirable. Diagnostic procedures to discriminate COPD from asthma will undergo further refinement. In the field of pathophysiology, the role of free radicals will become more definite. In the longer-term, more insight into the pathophysiology of asthma and COPD might yield new medication that focuses specifically on the pathogenetic mechanism. The effect of inhaled corticosteroids on COPD should become apparent in the short-term, as well as insight into the effect of N-acetylcysteine (NAC) on COPD. In the field of patient care, pulmonary rehabilitation will gain importance and it will be necessary to pay more attention to after-care.

5. Discussion

A large number of health care interventions exist for COPD and asthma. These interventions have proved to be efficacious in improving a wide range of outcome measures, such as respiratory complaints, exacerbations, physical functioning, quality of life, FEV₁ and mortality. Studies vary strongly on the size of the effects and the type of outcomes for which effects have been demonstrated.

Only limited knowledge is available on the degree to which existing health care interventions yield health benefits in daily practice. It was impossible to calculate the level of health benefit that could be gained on the basis of direct comparisons between studies on effectiveness in daily practice and studies in which the intervention was applied under ideal circumstances.

Economic evaluation studies proved to be limited in number, quality, comparability and applicability to the Dutch situation. There is a particular need for more, better quality studies that are relevant to Dutch health care practice.

Insight into barriers in the primary process of care is partly based on foreign study data and partly lacking. Nevertheless a large number of barriers have been demonstrated in areas such as: patient contact with the health care service, diagnostic procedures, determination of treatment indications, execution of health care interventions and treatment compliance.

A large proportion of persons with (mild) COPD or asthma never consult health care services about these complaints. There are indications that health benefit can be achieved in this group. A randomised, double-blind trial was conducted on the effects of inhaled corticosteroids in subjects with respiratory complaints and impaired lung function and/or bronchial hyperresponsiveness (BHR) (Tirimanna, 1997). These subjects were detected in the general population and were not registered as having COPD or asthma by their GP. After one year of treatment with an inhaled corticosteroid, improvements in lung function and BHR were observed. The diagnosis can be improved by making use of lung function tests, so that COPD can be distinguished from asthma. Assessment of treatment indications also requires supplementary investigations, such as allergy testing and evaluation of the cause of exacerbations. It seems likely
that improvements can be made in the determination of indications for preventive health care interventions, regular treatment and treatment for exacerbations. In addition, health benefit may be achieved by broadening the indications to enable non-invasive and non-pharmaceutical-based health care interventions, in particular patient education and self-management. Greater health benefit can be achieved not only through better determination of treatment indications, but also through better execution of the health care interventions by professionals. Treatment compliance to many health care interventions is far from perfect, which offers further scope for improving health benefit. It is difficult to quantify the amount of health benefit that can be gained by overcoming these barriers. One reason for this is that the relationship between the current process of care in practice and the outcomes has received little or no research attention. Another reason is that selection occurs in the determination of treatment indications. For example, the group of patients with severe asthma will be the first to receive inhaled corticosteroids. Broadening the indications for inhaled corticosteroids will indeed lead to health benefit, but it cannot be expected that the health benefit achieved in the remainder of the patients with milder asthma will be as high as that in the more severe group.

In the overview of barriers, suggestions have been made regarding aspects that need to be improved within the primary process of health care delivery. Ways in which to achieve these improvements have never been studied, although a few recommendations were made in the report by Schermer et al. (1997). To achieve improvements, standards or guidelines are required such as those of the Dutch College of General Practitioners (NHG). These guidelines present state of the art health care management recommendations that are easily accessible for GPs. Some improvement will be achieved by simply applying these guidelines in a consistent manner. New guidelines for COPD/asthma have been published fairly recently (Geijer et al., 1997a; Geijer et al., 1997b; Geijer et al., 1997c).

Besides providing information for health care professionals and endeavouring to apply the NHG guidelines in a consistent manner, it is also necessary to provide further education for GPs and practice assistants. In particular, it is important that they refine their skills in giving advice, encouraging self-management and giving instructions about inhalation technique and medication use. From an organizational perspective, it should be possible to improve the ‘tuning’ of care within primary health care (GPs and home care organisations), and also between primary care (GPs) and secondary care (pulmonologists). Furthermore, lung function testing could be stimulated in general practice and the GP should have direct access to lung function laboratory facilities. In this way, better distinction can be made between COPD and asthma, which will also mean more adequate treatment targeting.

We recommend concentrating responsibilities and registration of data on patients who receive special treatments, such as the oxygen treatment at home and chronic intermittent respiratory support.

Owing to the lack of knowledge on the process of care and outcomes, we also recommend that relevant parameters are recorded in general practice registration systems so that evaluations can be made of these processes and outcomes. These parameters might include patient characteristics that predict the prognosis, or characteristics that form an indication for health care
intervention (such as symptoms, severity of the respiratory disorder, etc.), health care interventions that have already been applied and relevant outcomes (such as number of exacerbations and lung function test results). The value of this approach will increase further if the routine is incorporated into a quality improvement structure that can include audit and feedback.

In the future, it is expected that health benefit will be achieved in COPD patients by means of medication that affects the role played by free radicals in the pathophysiology and in asthma patients by means of medication that specifically influences the mechanism of the underlying inflammation process. In addition, it will become clear whether it is desirable to detect COPD and asthma at an early stage.

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Chapter 1

The value of spirometry for primary care: 
Asthma and COPD

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Schermer TR, Folgering HT, van den Boom G, Jacobs JE, van Weel C. 
The value of spirometry for primary care: Asthma and COPD

TRJ Schermer, HTM Folgering, BJAM Bottema, JE Jacobs, CP van Schayck and C van Weel

ABSTRACT
In this paper, the need for widespread use of spirometry in primary healthcare is appraised through a literature review. The added value of spirometry for and the quality of measurements made by general practitioners (GPs), and the economic consequences of greater use of spirometry in primary care are discussed.

Appropriate application of spirometry in general practice may lead to improved health status of patients with chronic obstructive pulmonary disease (COPD) or asthma, but consistent attention to quality assurance measures is vital. If good quality cannot be guaranteed in the general practice setting, the reliability and validity of the tests is uncertain. Pulmonary function laboratories, nurse-run asthma clinics, primary care group (PCG)-commissioned and mobile community-based spirometry services may be other choices, but it depends on local availability as to which choice is most suitable for organising primary care spirometry. It is concluded that spirometry is a potentially useful and feasible tool for GPs, provided that test results are easily integrated into the GP’s usual management of patients with obstructive lung disease. At this time, the health costs of widespread application of spirometry in primary care are unknown.

INTRODUCTION
The use of spirometry is a topic of discussion among general practitioners (GPs). At least one third of general practices in the UK either own a spirometer or have easy access to external spirometry services, and recent contributions to this journal have debated its value in primary care. In the 1997 COPD guidelines of the British Thoracic Society (BTS), spirometry was assigned a central role in diagnosing and monitoring COPD. Since management of patients with mild to moderate COPD usually takes place in primary care, these guidelines certainly apply to general practice.

The aim of this paper is to review the added value of spirometry for GPs, the quality of spirometric tests performed in general practice, and the economic consequences of large-scale application of spirometry in primary care. The evidence from the literature (collected by Medline search), recent dissertations and the three latest annual conference proceedings of the European Respiratory Society (ERS) and American Thoracic Society (ATS) annual conferences is summarised.

THE VALUE OF SPIROMETRY FOR GPS
Spirometry can benefit primary care in several ways (Table 1). Recent studies indicate that the number of undetected cases with asthma or COPD may be reduced significantly by spirometry screening in general practice. Based on FEV1/FVC ratio and reversibility after bronchodilatation, asthma can be differentiated from COPD and severity of airway obstruction assessed. Choice of reference equations appropriate for the local population is important, since different reference values may lead to dissimilar conclusions in terms of normal and abnormal values and therefore diagnosis.

When spirometry was introduced in one general practice, Spann demonstrated a significant reduction of the underdiagnosis of COPD in high-risk populations, as well as improved differentiation between reversible and irreversible airway obstruction. After bronchodilator treatment had been adjusted on the basis of spirometry results, 25% of patients reported a significant improvement in respiratory symptoms. More recently, Pinnock et al. found 56% of the cases referred to a primary care asthma clinic had the diagnosis modified after spirometry. However, GPs can be inconsistent in choosing to perform spirometry when chronic airway disease is suspected. Kesten et al. found that only 5% (4/75) of Canadian GPs requested a pulmonary function test when consulted by an individual with clear signs of COPD. Access to spirometry facilities was not a limiting factor, since the majority (2/3) of the GPs involved had access to such services. Although he did not consider COPD, Jones demonstrated that availability of spirometry facilities in itself does not guarantee integration of spirometry in the GPs’ management of asthma. Moreover, the author concluded that further consideration and clarification on a wider scale is required before limited resources, whether in terms of time or money, are committed to spirometry testing in asthma in primary care.

INTERPRETATION
Although the practice of expressing FEV1 values as a percentage of the predicted value is widely used, there is evidence that using 80% of the predicted FEV1 value as a consistent lower limit of normal is not the best method of assessment. This method could lead to more elderly and shorter individuals being classed as abnormal than the original regression equations would support. Although the use of standardised residual scores (SRS) would obviate this problem, this method is far more complicated and therefore impractical for use in general practice.

Assessment of exacerbation severity and recovery is another useful application of spirometry, especially in patients with COPD. Monitoring of annual FEV1 decline – a typical feature of COPD – may be a less
Table 1. Relevant indications for spirometry in general practice

Detection
- Screening of subjects ‘at risk’ for developing chronic airway diseases
  - Smokers
  - Occupational exposure to dust and/or irritants
  - Subjects with recurring respiratory infection
  - In routine physical examinations

Diagnosis
- Evaluation of
  - Respiratory symptoms (cough, dyspnoea, dyspnoea during exercise, wheezing or non-specific chest pain)
  - Physical signs (hyperinflation, cyanosis, chest deformation, crepitations during auscultation)
  - Abnormal laboratory findings (e.g. chest X-ray)
  - Nature and underlying mechanism of airway obstruction by reversibility testing
  - Determination of the influence of (worsening of) diseases on the lung function
  - Assessment of prognosis

Monitoring
- Determining the effect of therapeutic interventions
  - Bronchodilators
  - Inhaled and oral corticosteroids
- Providing information on the course of lung function decline

* Adopted and modified from reference 8

Useful indication for primary care spirometry. Although serial measurement of FEV1 provides valuable information on disease progression, changes over periods of less than a few years are difficult to detect because the annual rate of FEV1 decline is small relative to measurement variability. This problem cannot be overcome by increasing measurement frequency. Moreover, recent work by den Otter et al. suggests that annual FEV1 decline rates measured in general practice are not interchangeable with rates based on pulmonary function laboratory measurements, the latter tending to be higher.

**ACCURACY, LINEARITY AND REPRODUCIBILITY OF ELECTRONIC SPIROMETERS**

In recent years, spirometers have become more and more manageable and affordable, and therefore attractive, for use in primary care. The first question that emerges, however, is how these modern electronic spirometers perform compared to a ‘gold standard’ – a conventional spirometer or computer-driven calibration equipment. Linearity and reproducibility are also essential characteristics. Since the performance of different types of spirometers varies considerably, no general statements on these characteristics can be made, but they have have been evaluated for several spirometers. Correlations between parameters as measured by electronic spirometer and a gold-standard are generally high. Nonetheless, it has been shown that FEV1 and FVC values measured with rotary vane spirometers or pneumotachographs may be systematically lower than gold-standard values. This deviation seems to increase with higher values of the respective parameters (‘non-linearity’). Short-term reproducibility of electronic spirometers appears to be quite acceptable for both FEV1 and FVC, and there is some evidence that electronic spirometers keep producing valid measurements in the long term.

Quality control of spirometry needs to be checked regularly. Although manufacturers test each new type of spirometer to ATS-standards, individual spirometers of a particular brand may deviate substantially. As flow calibration or control requires sophisticated test equipment, this is not feasible in primary care. Calibration with a syringe provides information on volume accuracy, and does not guarantee accurate volume or flow readings during forced breathing manoeuvres. Frequent ‘biological calibration’ by a healthy test subject may be a valid alternative for primary care, but more studies on this matter are needed.

**TRAINING AND QUALITY ASSURANCE**

A prerequisite for sufficient test quality in primary care is training of the professionals responsible for the execution of spirometry. The consequences of inadequate expertise have recently been revealed in a New Zealand study by Eaton et al. In this study, experienced lung function technicians scored several quality aspects of spirometric tests performed by trained GPs. Sixty-seven percent (16/24) of the GPs scored above standard, compared to 16% (4/25) in a non-trained reference group. However, measurement quality dropped considerably after a few months, which stresses the importance of consistent attention to test procedures. In the same study, the practice nurses of the same general practices were also trained. Although the nurses’ performance scores were initially lower compared to the GPs, test performance became equal several months later. Work by our own research group showed that instruction and coaching of patients before and during forced expiratory manoeuvres were generally insufficient in general practice.

**RELIABILITY AND VALIDITY**

For valid spirometric test results, the measurements must be reliably performed. When measurement quality is insufficient, the error term and the ‘true’
lung function of the patient will each contribute to the test result, thus hindering good interpretation.\(^2\) Criteria are available for judging the reliability of spirometric tests in two aspects:

1. **Assessment of single breathing manoeuvres**
   (judged by full inspiration, rapid onset of forced expiration, smooth course of the forced expiration, and duration of expiration Ž6 s or to an adequate completion)

2. **Reproducibility after repetition of the manoeuvre**
   (i.e. FEV\(_1\) of the two highest acceptable manoeuvres differing by <5% or 100 ml [BTS] or 200 ml [ATS]).

In ideal circumstances, reliability of spirometry can be very high. Two large clinical trials performed in the USA showed that a high proportion of spirometry tests complying with ATS criteria can be achieved by pulmonary function laboratories (approximately 95%),\(^3\)\(^4\) but it is unclear whether this can be achieved in day-to-day situations. Eaton et al. investigated the reliability of spirometric tests in 15 New Zealand general practices.\(^2\) Four months after completion of a two-session training programme for GPs and practice nurses, one-third of the spirometric tests conducted were found to meet the ATS criteria. In the reference group of non-trained GPs and nurses, only 13% of all tests were reliable. So it may be difficult to guarantee sufficient reliability of spirometric tests when they are performed in general practices.

It is also important to know how spirometric tests in general practice compare to tests performed in pulmonary function laboratories. A group of 52 people with asthma, selected by 20 GPs who had previously attended a spirometry training session, were studied by van der Molen et al.\(^2\) FEV\(_1\), as well as FVC, values measured by the GPs were on average 280 ml lower than laboratory values. In a similar study, den Otter et al. evaluated spirometric tests of 68 subjects with respiratory symptoms.\(^2\) On average, FEV\(_1\) was 110 ml lower, to the disadvantage of the measurements obtained in general practice. In both studies, however, GPs and lung function technicians used different types of spirometers, which may explain an unknown part of the observed differences.

Recently, Woolhouse et al. reported results of a study in which two patients with severe, but stable, COPD visited 14 general practices for spirometry.\(^3\)\(^4\) Compared with measurements by a lung function technician, 86% of the GP-based FEV\(_1\) values measured were judged acceptable (i.e. <160 ml difference from the technician’s value). Of the FVC values, 54% were acceptable (FVC difference <330 ml). However, interpretation of these results is complicated by the fact that only two patients were involved, both with ample experience in undergoing spirometry.

**INTERPRETATION OF SPIROMETRY TEST RESULTS**

Interpretation of spirometry requires specific expertise, which can be expected from chest physicians, but not necessarily from GPs. Eaton et al. took a random sample from the spirometry records of the 15 trained New Zealand GPs to address this issue.\(^2\) The GPs had to label spirometric tests of some of their own patients out of seven pre-defined diagnoses (such as ‘normal’, ‘obstructive disorder’, ‘inadequate test performance’). Two chest physicians judged the interpretation of the GPs as correct in 53% of the cases, an almost similar percentage to that in a reference group of non-trained GPs.

These results need to be put in perspective. For instance, Hnatiuk et al. showed that internists in the US interpreted one out of every four screening spirometric tests incorrectly as normal, and one out of every three cases incorrectly as abnormal.\(^2\) Quadrelli et al. showed significant variation within a group of 15 Italian chest physicians in interpretation of spirometric tests.\(^6\) There was a substantial inter-observer variability between chest physicians (40% disagreement), particularly in the assessment of presence and severity of airway obstruction. However, it should be noted that Eaton’s GPs were provided with clinical data and indications for spirometry on their own patients, while Quadrelli’s chest physicians did not have such data, and were further required to agree on severity classifications as well as diagnosis.

**HEALTH ECONOMIC CONSEQUENCES**

Currently, little is known about the impact on healthcare cost of widespread application of spirometry in primary care. The only information available comes from Canada, where Chan et al. analysed trends in declared expenses for lung function testing by GPs.\(^7\) (In the Ontario area from which the data were derived, GPs could declare C$31.90 for a flow–volume curve examination and C$16.20 for a spirogram.) In this cost evaluation study, the possible health benefits were not included. When the total costs for spirometry by GPs for the periods 1989–90 and 1994–95 were compared, costs had increased by 37% (from C$10.3 to 14.1 million). A quarter of this increase could be explained by a rise in the total number of tests, attributable to the fact that in the 1994–95 period, 47% more GPs declared spirometric tests than in the earlier period, while the average number of declared tests per GP remained unchanged. Undoubtedly, the concurrent introduction of affordable electronic spirometers will have contributed to the increased costs.

**DISCUSSION**

From the evidence discussed above it is concluded that spirometry can be a valuable additional instrument to care for patients with obstructive airway disease in general practice. However, although the use of spirometry is disseminating fast among GPs, several aspects of primary care spirometry (especially GP surgery-based spirometry) deserve critical consideration. An important finding is that the reliability of modern electronic spirometers does not limit their use in general practice. Although these spirometers may produce systematically lower values than the conventional equipment used in pulmonary function laboratories, this is only a problem in the higher range of FEV\(_1\) and FVC values.
Table 2. Advantages and disadvantages of four different alternatives for organising spirometry in primary care

<table>
<thead>
<tr>
<th>Spirometry performed at:</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice surgery</td>
<td>Little access limitations</td>
<td>Reliability of measurements not always guaranteed</td>
</tr>
<tr>
<td></td>
<td>No extra healthcare costs</td>
<td>Extra workload for general practices</td>
</tr>
<tr>
<td></td>
<td>Small travelling distance for patients</td>
<td>General practice has to build up expertise</td>
</tr>
<tr>
<td></td>
<td>Enable GPs to acquire expertise</td>
<td>(Often) changes in practice organisation necessary</td>
</tr>
<tr>
<td>Nurse-run asthma clinic</td>
<td>Good reliability of measurements</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Little access limitations</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
<tr>
<td></td>
<td>No extra workload for general practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No high demands on spirometry expertise in general practices</td>
<td></td>
</tr>
<tr>
<td>PCG-commissioned spirometry service</td>
<td>Good reliability of measurements</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Little access limitations</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
<tr>
<td></td>
<td>No extra workload for general practices</td>
<td>Clear communication lines are indispensable</td>
</tr>
<tr>
<td></td>
<td>No high demands on spirometry expertise in general practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Centralisation of judgement and interpretation of spirometric tests</td>
<td></td>
</tr>
<tr>
<td>Hospital-based pulmonary function laboratory</td>
<td>Optimum reliability of measurements</td>
<td>Possible access limitations*</td>
</tr>
<tr>
<td></td>
<td>No extra workload for general practices</td>
<td>Limited capacity next to regular tasks</td>
</tr>
<tr>
<td></td>
<td>No high demands on expertise in general practice</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Easy consultation of chest physician*</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
</tbody>
</table>

* Depending on local cooperation with secondary care chest physician

As spirometry is only one of the many tasks demanding attention in the general practice setting, it is to be expected that practices will find it hard to fulfil the strict quality criteria that apply to laboratories. As a consequence, results of surgery-based spirometry should be handled differently to values obtained in pulmonary function laboratories. Spirometric indices obtained in a general practice generally turn out to be lower, but rarely higher. The problem of false positive diagnoses that might result from this is particularly relevant for general screening of subjects, much less so in selective screening of high-risk populations (i.e. smokers) or subjects with airway symptoms. In the case of low values or doubt about the reliability of a surgery-based spirometric test, GPs should seek confirmation by referring the patient to an experienced spirometry service.

In the light of the available evidence one could argue whether surgery-based spirometry is the best solution. There are several other good choices:

Pulmonary function laboratories may provide open access spirometry service directly to GPs or local nurse-run asthma clinics. Mobile community-based spirometry services or primary care group (PCG)-commissioned spirometry services could be initiated. Possible advantages and disadvantages of these alternatives are listed in Table 2.

It is obvious that GPs who consider implementing spirometry in their practice will have to invest sufficient time to develop expertise. A short training programme alone is not sufficient to acquire the specific knowledge, skills and insight necessary to judge quality and interpret results of spirometry adequately. This may result in false negative and positive diagnoses as well as misclassification of the severity of lung function impairment.

The health-economic implications of widespread spirometry in primary care are not clear from the literature. The results of the Canadian study reviewed are difficult to extrapolate to other countries, since declaration of spirometric tests by GPs is not possible in other countries.

As a result of intensified use of spirometry as a screening tool in primary care, more patients will be treated for respiratory diseases, which will generate additional expenses. An increase in the number of X-rays requested and referrals to secondary care is also conceivable. On the other hand, better focused care can save the costs of inappropriate treatment and is likely to improve health-status of patients with obstructive lung disease. Studies evaluating both costs and benefits are needed to establish the effectiveness of widespread use of spirometry in primary care.

References
6. den Otter JJ, van Dijk B, van Schayck CP et al. How to avoid underdiagnosed asthma/chronic obstructive pulmonary


Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD)

Published in: Thorax 2003;58:861–866

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Schermer TR, Folgering HT, Jacobs JE, Chavannes NH, Hartman J, van Weel C, Bottema BJAM.
Validity of spirometric testing in a general practice population of patients with chronic obstructive pulmonary disease (COPD)

T R Schermer, J E Jacobs, N H Chavannes, J Hartman, H T Folgering, B J Bottema, C van Weel

Objective: To investigate the validity of spirometric tests performed in general practice.

Method: A repeated within subject comparison of spirometric tests with a “gold standard” (spirometric tests performed in a pulmonary function laboratory) was performed in 388 subjects with chronic obstructive pulmonary disease (COPD) from 61 general practices and four laboratories. General practitioners and practice assistants undertook a spirometry training programme. Within subject differences in forced expiratory volume in 1 second and forced vital capacity (ΔFEV₁, and ΔFVC) between laboratory and general practice tests were measured (practice minus laboratory value). The proportion of tests with FEV₁ reproducibility <5% or <200 ml served as a quality marker.

Results: Mean ΔFEV₁ was 0.069 l (95% CI 0.054 to 0.084) and ΔFVC 0.081 l (95% CI 0.053 to 0.109) in the first year evaluation, indicating consistently higher values for general practice measurements. Second year results were similar. Laboratory and general practice FEV₁ values differed by up to 0.5 l, FVC values by up to 1.0 l. The proportion of non-reproducible tests was 16% for laboratory tests and 18% for general practice tests (p = 0.302) in the first year, and 18% for both in the second year evaluation (p = 1.000).

Conclusions: Relevant spirometric indices measured by trained general practice staff were marginally but statistically significantly higher than those measured in pulmonary function laboratories. Because of the limited agreement between laboratory and general practice values, use of these measurements interchangeably should probably be avoided. With sufficient training of practice staff the current practice of performing spirometric tests in the primary care setting seems justifiable.

In recent years the use of spirometric tests has rapidly increased in primary health care. Practice guidelines assign a central role to spirometry in the management of patients with chronic obstructive pulmonary disease (COPD).¹ ² As most of these patients are detected and treated in primary care, these guidelines are particularly relevant for general practice.³ ⁴ There is some evidence that application of spirometric testing in primary practice may reduce the number of undetected cases with chronic respiratory morbidity as well as diagnostic misclassification,⁵ ⁶ which may lead to overall improved respiratory health.⁷

The validity (or “reliability”) of spirometric tests is a prerequisite for their use as an instrument for diagnosis, monitoring, and management of respiratory disease.⁸ Despite their widespread use, little is known about the validity of spirometric tests in the primary care setting. It has been reported that at least one third of tests performed in general practice do not meet the quality criteria which apply to pulmonary function laboratories.⁹ Training of practitioners and nurses seems to enhance the quality of testing only temporarily.¹⁰ Four studies have shown that spirometric indices obtained in general practices may be considerably lower than those obtained in laboratories, suggesting insufficient test validity in general practice.¹¹ ¹² ¹³ ¹⁴ However, none of these reports has been peer reviewed and apparent methodological shortcomings justify further studies of this topic. The main objective of the current study was to assess the extent to which the results of spirometric tests performed in general practice correspond with the results of the same tests performed in a certified pulmonary function laboratory.

METHODS

Study design and participants

The study was a repeated cross sectional within subject comparison of spirometric testing in pulmonary function laboratories and general practices. Four pulmonary function laboratories (two in universities, two in general hospitals) and 61 general practices comprising 149 general practitioners (GPs) and 185 practice assistants were involved. (In Dutch general practice the practice assistant is a paramedical professional who has been trained for administrative and patient care related activities.) A priori, we considered the laboratory spirometric tests as “gold standard”¹⁵ measurements.

GPs selected subjects who met the following inclusion criteria: age 30–75 years; current or ex-smoker; diagnosis of COPD as assigned by a GP; meeting the clinical definition of COPD (“increased cough, sputum and dyspnoea on most days for a minimum of 3 months a year for at least the previous 2 years”);¹⁶ post-bronchodilator forced expiratory volume in 1 second (FEV₁) 40–90% of the predicted value and/or post-bronchodilator FEV₁/FVC (forced vital capacity) <88% of the predicted value for men and <89% for women. Subjects with severe co-morbidity and/or a history of asthma, allergic rhinitis, or atopic rash were excluded.

The study was approved by the medical ethics committee of the University Medical Centre Nijmegen and all subjects gave written informed consent.

Spirometry training programme

A spirometry training programme for GPs and practice assistants was developed and pretested before the study.
Training consisted of two 2.5 hour sessions separated by an interval of 1 month. The content of the training sessions is available online on the Thorax website (www.thorax.jnl.com/supplemental). The training programme specifically focused on elements that need improvement in general practice spirometric tests.\(^{16,17}\)

**Spirometric testing**

Data collection took place from December 1998 to January 2001. General practices and laboratories were all equipped with the same electronic spirometer (Microloop II; Medical Ltd, Rochester, UK) and spirometry software (Spirare; Diagnostica Ltd, Oslo, Norway). Durability of the Microloop turbine flow sensor has proved to be acceptable.\(^{18}\) The spirometry software displays real time flow-volume curves, patient instructions, and a time indicator to monitor duration of expiratory and inspiratory flow but does not contain “built in” quality assurance prompts.\(^{19}\)

In each study subject a pair of spirometric tests was performed. The first test always took place in one of the laboratories, the second in the subject’s general practice. Subjects with an interval of >30 days between the two tests were excluded from the analysis. In case of a recent exacerbation the measurement schedule was postponed until at least 6 weeks after clinical recovery. The test sequence was repeated one year later in the same subjects.

During laboratory and general practice visits subjects performed a full (pre-bronchodilator and post-bronchodilator) spirometric test. Subjects were instructed to abstain from short acting bronchodilators for 8 hours and long acting bronchodilators for 12 hours before testing. Post-bronchodilator tests were performed 15 minutes after administration of 400 μg aerosolised salbutamol by spacer. For each test at least three acceptable forced expiratory manoeuvres were required.\(^{20}\) The spirometric indices (including FEV\(_1\) and FVC) of the manoeuvre with the highest sum of FEV\(_1\)+FVC were stored and used for analysis. Spirometers were checked for errors in readings by a research nurse every 3 months using a 3 litre syringe and “biological control”—that is, a manoeuvre performed by the research nurse herself. In cases with a deviation of >3% in the volume reading or a divergent outcome of the biological control manoeuvre the spirometer was replaced.

**Outcomes and statistical analyses**

The primary outcomes were the within subject differences between laboratory and general practice spirometric tests in terms of FEV\(_1\) and FVC (ΔFEV\(_1\), and ΔFVC, respectively). Crude mean ΔFEV\(_1\) and ΔFVC were calculated by subtracting a subject’s laboratory value from the general practice value. Mean values for the primary outcomes with 95% confidence intervals (95% CIs) were calculated and difference versus mean plots and accompanying limits of agreement produced. The proportion of tests with a reproducibility of <5% and <200 ml (test variance) between the two highest FEV\(_1\) values from the three accepted forced manoeuvres was considered as a marker of the quality of the spirometric tests.\(^{21}\) Differences in the proportion of non-reproducible tests in laboratories and general practices were analysed using McNemar’s test. The Statistical Analysis System (SAS, Version 6.12 for UNIX) was used for analysis.

**RESULTS**

**Characteristics of general practices**

Of the 61 general practices involved, 21 (34%) were single handed practices, 35 (58%) were two handed or group practices, and five (8%) were multidisciplinary health care centres. Forty practices (65%) already possessed a spirometer before the study was initiated. Descriptive characteristics of the general practices are shown in table 1. Attendance rates in the spirometric training programme were 57% for GPs and 78% for practice assistants. In two practices GPs performed the spirometric tests, while in the remaining 59 practices the practice assistants undertook the testing.

**Study subjects and primary outcomes**

Matched pairs of laboratory and general practice spirometric tests were available for 388 subjects in the first year and 332

### Table 1  Baseline characteristics of general practices and study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practices (n=61)</td>
<td></td>
</tr>
<tr>
<td>No of GPs</td>
<td>2.5 (1.4)</td>
</tr>
<tr>
<td>GPs’ professional experience (years)</td>
<td>14.3 (8.2)</td>
</tr>
<tr>
<td>No of practice assistants</td>
<td>3.1 (1.4)</td>
</tr>
<tr>
<td>Practice assistants’ professional experience (years)</td>
<td>10.7 (7.4)</td>
</tr>
<tr>
<td>Practice population size (no of patients per GP)</td>
<td>1662 (771)</td>
</tr>
<tr>
<td>Time since introduction of spirometry (years)</td>
<td>4.3 (2.9)</td>
</tr>
<tr>
<td>No of spirometers present</td>
<td>1.8 (1.2)</td>
</tr>
<tr>
<td>Study subjects (n=388)</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>266/122</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.6 (9.7)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>228 (59)</td>
</tr>
<tr>
<td>Cumulative cigarette smoke exposure (pack years)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Use of inhaled corticosteroids, n (%)</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Use of bronchodilator, n (%)</td>
<td>285 (73)</td>
</tr>
<tr>
<td>FEV(_1)*</td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator (l)</td>
<td>1.80 (0.66)</td>
</tr>
<tr>
<td>% predicted</td>
<td>60.3 (18.2)</td>
</tr>
<tr>
<td>Post-bronchodilator (l)</td>
<td>2.00 (0.66)</td>
</tr>
<tr>
<td>% predicted</td>
<td>66.7 (17.4)</td>
</tr>
<tr>
<td>FVC*</td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator (l)</td>
<td>2.91 (0.92)</td>
</tr>
<tr>
<td>% predicted</td>
<td>78.2 (18.7)</td>
</tr>
<tr>
<td>Post-bronchodilator (l)</td>
<td>3.21 (0.94)</td>
</tr>
<tr>
<td>% predicted</td>
<td>85.9 (18.0)</td>
</tr>
<tr>
<td>FEV(_1)/FVC*</td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator (%)</td>
<td>61.9 (11.7)</td>
</tr>
<tr>
<td>% predicted</td>
<td>80.5 (14.8)</td>
</tr>
<tr>
<td>Post-bronchodilator (%)</td>
<td>62.6 (11.6)</td>
</tr>
<tr>
<td>% predicted</td>
<td>81.3 (14.8)</td>
</tr>
<tr>
<td>Reversibility of FEV(_1), % predicted</td>
<td>38.6 (2.2)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless stated otherwise.\(^*\)

Based on first year spirometric tests performed in the pulmonary function laboratories.\(^\dagger\)

Post-bronchodilator FEV\(_1\), % predicted minus pre-bronchodilator FEV\(_1\), % predicted.
The results of the current study indicate that, on average, the validity and quality of spirometric tests in Dutch general practices is satisfactory in comparison with the "gold standard" procedure, a spirometric test performed in a pulmonary function laboratory. We observed mean differences in the primary outcomes consistently in favour of general practice spirometric testing in the first as well as the second year evaluation. The overall proportion of non-reproducible spirometric tests was similar for laboratories and general practices. However, the agreement between laboratory and general practice measurements seems limited. This means that using laboratory and general practice

subjects in the second year evaluation (table 1). The mean (SD) number of days between laboratory and general practice tests was 7.2 (7.8) for the first year evaluation and 11.2 (8.1) for the second year evaluation. There was no significant correlation between the number of days between measurements and the primary outcomes (ΔFEV₁: r = 0.11; ΔFVC: r = 0.13). In 24% of the spirometric test pairs the laboratory test was favoured by the circadian variation, in 21% of the tests the general practice test was favoured, and in 55% neither test was favoured.

Adjusted estimates of the primary outcomes were consistently (but only marginally) higher than crude estimates (table 2). First year and second year mean ΔFEV₁ and ΔFVC values were all higher for the general practice measurements. These findings were consistent for each of the laboratories involved (table 3). The scatter of the ΔFEV₁ and ΔFVC values did not vary in a systematic way over the range of measurements (fig 1 and 2). The interval between the limits of agreements was wide in both study years for ΔFEV₁, as well as for ΔFVC, which indicates considerable discrepancies between the two measurements.

**Quality of spirometric test performance**

Because of occasional imperfections in the data transfer between the spirometer and spirometric software, information on the number of forced manoeuvres performed and FEV₁ reproducibility was missing for 12 (1%) laboratory and 89 (3%) general practice tests. Within the set of tests with complete information there were no tests with fewer than two forced manoeuvres in either the laboratories or practices. Table 4 shows that the proportion of non-reproducible tests—that is, FEV₁ reproducibility >5% or >200 ml—in the first year evaluation was 16% for the laboratories and 18% for the general practices (p = 0.302). The corresponding figures for the second year were 18% and 18%, respectively (p = 1.000). The proportion of non-reproducible tests in the general practices ranged from 4% in the best to 35% in the worst performing practice for the pooled first and second year data. For the four pulmonary function laboratories the corresponding range was 13–20%.

**DISCUSSION**

The results of the current study indicate that, on average, the validity and quality of spirometric tests in Dutch general practices is satisfactory in comparison with the "gold standard" procedure, a spirometric test performed in a pulmonary function laboratory. We observed mean differences in the primary outcomes consistently in favour of general practice spirometric testing in the first as well as the second year evaluation. The overall proportion of non-reproducible spirometric tests was similar for laboratories and general practices. However, the agreement between laboratory and general practice measurements seems limited. This means that using laboratory and general practice

### Table 2

Mean (95% CI) and trimmed mean for crude and adjusted estimates of the primary outcomes

<table>
<thead>
<tr>
<th></th>
<th>First year (n = 388)</th>
<th></th>
<th>Second year (n = 335)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Crude estimate</td>
<td>Adjusted estimate</td>
<td>Crude estimate</td>
<td>Adjusted estimate</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Trimmed† mean</td>
<td>Mean (SD)</td>
<td>Trimmed† mean</td>
</tr>
<tr>
<td>ΔFEV₁ (l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator</td>
<td>0.079 (0.057 to 0.101)</td>
<td>0.077 (0.063 to 0.107)</td>
<td>0.076 (0.043 to 0.085)</td>
<td>0.075 (0.061 to 0.091)</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td>0.069 (0.053 to 0.084)</td>
<td>0.069 (0.061)</td>
<td>0.067 (0.058)</td>
<td>0.065 (0.043 to 0.073)</td>
</tr>
<tr>
<td>Pooled†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-bronchodilator</td>
<td>0.103 (0.062 to 0.143)</td>
<td>0.104 (0.064 to 0.144)</td>
<td>0.104 (0.022 to 0.100)</td>
<td>0.097 (0.035 to 0.108)</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td>0.062 (0.017 to 0.095)</td>
<td>0.061 (0.022 to 0.100)</td>
<td>0.068 (0.028 to 0.107)</td>
<td>0.063 (0.051 to 0.108)</td>
</tr>
<tr>
<td>Pooled†</td>
<td>0.081 (0.033 to 0.109)</td>
<td>0.084 (0.035 to 0.112)</td>
<td>0.086 (0.056 to 0.112)</td>
<td>0.086 (0.056 to 0.112)</td>
</tr>
</tbody>
</table>

A minus sign indicates higher mean laboratory values, absence of a minus sign indicates higher general practice values.

*Adjusted for the influence of differential timing between measurements performed in pulmonary function laboratory and general practice.

†Arithmetic mean calculated with exclusion of the largest 5% and the smallest 5% of the values.

‡Combined results of pre-bronchodilator and post-bronchodilator values.

### Table 3

Mean (SD) crude estimates of the primary outcomes by pulmonary function laboratory

<table>
<thead>
<tr>
<th></th>
<th>Laboratory 1 (n = 218)</th>
<th>Laboratory 2 (n = 131)</th>
<th>Laboratory 3/4† (n = 39)</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFEV₁ (l)</td>
<td>0.078 (0.20)</td>
<td>0.053 (0.21)</td>
<td>0.078 (0.22)</td>
<td>0.286</td>
</tr>
<tr>
<td>ΔFVC (l)</td>
<td>0.079 (0.36)</td>
<td>0.095 (0.44)</td>
<td>0.046 (0.39)</td>
<td>0.636</td>
</tr>
<tr>
<td>ΔFEV₁ (l)</td>
<td>0.082 (0.21)</td>
<td>0.016 (0.19)</td>
<td>0.036 (0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ΔFVC (l)</td>
<td>0.086 (0.36)</td>
<td>0.095 (0.42)</td>
<td>-0.016 (0.25)</td>
<td>0.115</td>
</tr>
</tbody>
</table>

A minus sign indicates higher mean laboratory values, absence of a minus sign indicates higher general practice values.

*Combined results of pre-bronchodilator and post-bronchodilator values

†Because of the small number of study subjects (n = 7) the results of laboratory 4 have been added to the results of laboratory 3, the laboratory with the next smallest number of subjects.

‡ANOVA test for difference between laboratories.
measurements interchangeably should probably be avoided in practice.

**Strengths and limitations of the study**

We aimed to compare, as strictly as possible, the spirometric performance of general practice and laboratory staffs. Performance depends on a number of factors related to the executor of the test—quality of subject instruction, intensity of coaching during forced manoeuvres, critical assessment of acceptability of separate manoeuvres, and test reproducibility. As we wished to minimise any potential bias in the comparison, we chose to equip practices and laboratories with the same type of spirometer and to check spirometer readings at the same 3 monthly intervals at both locations. Although portable turbine spirometers like the one used in our study cannot easily be calibrated on the spot and are not commonly used in laboratories, we believe that ruling out the “equipment factor” makes the comparison fairer, as turbine spirometers may produce FEV₁ and FVC values which diverge "equipment factor" makes the comparison fairer, as turbine spirometers may produce FEV₁ and FVC values which diverge

From a methodological point of view, randomisation of the order in which laboratory and general practice tests took place would have been the preferred approach. However, because most of our study subjects (67%) were participating in an ongoing randomised controlled clinical trial, the order of the tests was dictated by the trial protocol. We cannot therefore rule out the possibility of a systematic “one sided” bias in favour of either general practice or laboratory spirometric testing due to natural variability in lung function. Sources of short term intra-individual variability such as airway reactivity\(^{11}\) and diurnal variation in lung function\(^{20}\) may have influenced our findings. Although we used a rather approximate method to adjust for the latter variable, this factor did not seem to bias the results significantly. We consider it implausible that other intra-individual factors may have systematically put the laboratory tests at a disadvantage.

Although we cannot rule out a possible “learning effect” in study subjects due to repetition of spirometric testing within a short time span,\(^{14}\) we believe that the order of tests alone cannot fully explain our results. Three arguments support this view: (1) Most subjects had been diagnosed as having COPD several years earlier, which makes it quite likely that most of them already had a “history” of spirometric testing before entering the study, especially since most practices had been using spirometric tests for some time. (2) All subjects performed a full spirometric test in their general practice several weeks before the first visit to the laboratory to assess study eligibility. In other words, they could not be entirely “naïve” with regard to spirometric testing before the tests for the actual evaluation study were performed. (3) The differences in favour of general practice spirometric testing persisted after a year of regular monitoring of lung function.
FEV1 cannot be calculated on the basis of a single FEV1 value. Data, we can be sure that at least two manoeuvres were from the relatively small proportion of tests with missing symptoms,13 adult patients with limited airflow, 14 those with 280 ml for FEV1 previously reported that real time feedback of information spirometers which display flow-volume curves. We have from the published reports, other studies did not use and GPs better for their task. Also, as far as can be extracted tailored programme may have prepared practice assistants severe COPD, 12 and a heterogeneous group of patients with consistently reported lower mean FEV1 and FVC values for discrepancies between the studies, as may the diverging study lung function variability, as discussed above, may explain the absence of factors responsible for short term intra-individual reproducibility in FEV1, in spirometric tests for the first year data (n = 693)*

<table>
<thead>
<tr>
<th>Pulmonary function laboratory</th>
<th>General practice</th>
<th>FEV1 reproducibility &lt;5% and &lt;200 ml</th>
<th>FEV1 reproducibility &gt;5% and ≥200 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 reproducibility &lt;5% and &lt;200 ml</td>
<td>484 (70)†</td>
<td>85 (12)</td>
<td>569 (82)</td>
</tr>
<tr>
<td>FEV1 reproducibility &gt;5% and ≥200 ml</td>
<td>99 (14)</td>
<td>25 (4)</td>
<td>124 (18)</td>
</tr>
<tr>
<td>Values are numbers (%) of tests. *Pre-bronchodilator and post-bronchodilator tests are pooled. †Concordance between laboratory and general practice test reproducibility within the same subject.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Comparison with previous studies

Our findings contradict previous reports on the validity of general practice spirometric testing.11–14 These studies consistently reported lower mean FEV1 and FVC values for general practice spirometric tests with differences of 70–280 ml for FEV1,11,13 and 360 ml for FVC.11 The presence or absence of factors responsible for short term intra-individual lung function variability, as discussed above, may explain the discrepancy between the studies, as may the diverging study populations involved (asthmatics,11 subjects with respiratory symptoms,12 adult patients with limited airflow,13 those with severe COPD,14 and a heterogeneous group of patients with COPD in our study).

There are several reasons why we believe that our study reflects the actual validity of general practice spirometric testing. Firstly, our training programme was probably more elaborate than those in other studies because we specifically emphasised elements of test performance which are now known often to be insufficient in general practice.10 17 This tailored programme may have prepared practice assistants and GPs better for their task. Also, as far as can be extracted from the published reports, other studies did not use spirometers which display flow-volume curves. We have previously reported that real time feedback of information from flow-volume curves may lead to improved performance in spirometric testing.26 A final alternative explanation may be that in our study, unlike in some of the earlier studies,11 14 most of the spirometric tests were performed by practice assistants instead of practitioners. As practice assistants will generally have more time available, they might take more time to attain a satisfactory test result. In our view, similar results could be achieved in other countries or healthcare settings as long as training of the professionals who perform the spirometric tests is of sufficient quality and intensity.

Conclusions

We conclude that spirometric indices relevant for the management of COPD obtained in trained general practices were marginally but statistically significant higher than those measured in certified pulmonary function laboratories. The quality of spirometric tests in laboratories and general practices in terms of test reproducibility seemed equivalent. However, as the agreement between spirometric tests performed in the laboratory and in general practice was limited, using these measurements interchangeably should probably be avoided in practice. The results of this study seem to support the already widespread practice of performing spirometric tests in primary care settings. Further encouragement of primary care physicians to implement spirometric tests therefore seems justifiable, providing the training of practice staff is sufficient.

Authors’ affiliations

T R Schermer, J E Jacobs, N H Chavannes, J Hartman, H T Folgering, B J Bottema, C van Weel, Department of General Practice, University Medical Centre Nijmegen; Centre for Quality of Care Research, University Medical Centre Nijmegen and University of Maastricht; Department of General Practice, University of Maastricht, Department of Pulmonology Dekkerswald, University Medical Centre Nijmegen, The Netherlands

Table 4 Differences between general practices and pulmonary function laboratories in reproducibility in FEV1 in spirometric tests for the first year data (n = 693)*

REFERENCES


Supplement. Contents of the training sessions for general practitioners and practice assistants

<table>
<thead>
<tr>
<th>First training session</th>
<th>Time</th>
<th>Second training session</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General practitioners</strong></td>
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<td><strong>Practice assistants</strong></td>
<td></td>
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<td>• General aspects of COPD and asthma (e.g., basic pathophysiology, treatment)</td>
<td>30’</td>
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<tr>
<td>• Indications for spirometry in general practice</td>
<td>15’</td>
<td>• Basics of respiratory physiology, spirometric indices, flow/volume-curve</td>
<td>20’</td>
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<tr>
<td>• Physiology of the respiratory system, spirometric indices, flow/volume-curve</td>
<td>40’</td>
<td>• Basic aspects of spirometry test performance (measurement technique)†</td>
<td>30’</td>
</tr>
<tr>
<td>• Basic aspects of spirometry test performance (measurement technique)‡</td>
<td>20’</td>
<td>• Demonstration of Microloop® spirometer and Spirare® software</td>
<td>15’</td>
</tr>
<tr>
<td>• Demonstration of Microloop® spirometer and Spirare® software</td>
<td>15’</td>
<td>• Practising pre-bronchodilator spirometry in small groups</td>
<td>55’</td>
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<tr>
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<td>+</td>
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<tr>
<td></td>
<td>150’</td>
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<td>150’</td>
</tr>
<tr>
<td><strong>Second training session</strong></td>
<td></td>
<td><strong>References</strong></td>
<td></td>
</tr>
<tr>
<td>• Implementation and organisation of spirometry</td>
<td>20’</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150’</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* Instructors in GP course: pulmonologist, pulmonary physiologist, general practitioner, lung function technician; instructors in practice assistant course: pulmonary physiologist, general practitioner, lung function technician
† Special attention for errors commonly made during spirometry in general practice\(^1\) and markers of acceptability and reproducibility of maneuvers\(^3\)
‡ A videotape with examples of both good and bad subject instruction and execution of spirometry tests was used
§ Special attention for judging the flow-volume curve with respect to acceptability of maneuvers

pMDI = pressurized Metered Dose Inhaler
Chapter 3

Effect of educational outreach visits by lung function technicians on the validity of spirometric tests in general practice

submitted
Effect of educational outreach visits by lung function technicians on the validity of spirometric tests in general practice

TRJ Schermer, JE Jacobs, AV Thuyns, J Hartman, HTM Folgering, C van Weel, BJAM Bottema

Abstract

Objective - To assess the effect of periodic educational outreach visits by lung function technicians on the validity of general practice spirometry.

Methods – 1-yr prospective study involving 4 pulmonary function laboratories, 45 outreach visit group (‘intervention’, n=262 subjects with COPD) and 16 reference group (n=126 subjects) general practices. The same baseline spirometry training was offered to both groups of practices. Subsequently, intervention group practices were periodically visited by lung function technicians, who focussed on optimization of spirometric test performance. Outcomes were the within subject differences in forced expiratory volume in 1 second (ΔFEV₁) and forced vital capacity (ΔFVC) between laboratory and general practice tests (practice minus laboratory value).

Results – Intervention and reference group practices differed in number and age of practice assistants and GPs’ attendance at the baseline spirometry workshops. In the first year evaluation the mean ΔFEV₁ and ΔFVC favored the general practice tests (i.e., were >0) in both groups. A year later ΔFEV₁ was higher in intervention group compared to reference group subjects (0.068 L [95%CI 0.048; 0.088] versus 0.035 L [0.013; 0.058]). ΔFVC was also higher in intervention (0.126 L [0.088; 0.163]) compared to reference group subjects (-0.021 L [-0.060; 0.017]).

Conclusion – Although initially the validity of spirometric tests was sufficient in intervention as well as reference group practices, periodic educational outreach visits by lung function technicians seemed to prevent regression of test validity over time, especially in terms of FVC values. Less labor-intensive options to maintain spirometric test validity in general practice may be more attractive.
Introduction

Spirometry provides important indices to assess the severity and reversibility of airflow obstruction. Therefore, spirometry is assigned an important role in diagnosing and monitoring of patients with chronic respiratory diseases(1). In developed countries, convenient electronic spirometers have rapidly disseminated in primary care during the past few years. Advantages of using spirometry in primary care settings are, among others, early detection of, and improved differentiation between chronic obstructive pulmonary disease (COPD), asthma, and other chronic respiratory conditions(2). Moreover, primary care spirometry provides the opportunity to monitor disease progression as well as effects of smoking cessation interventions and bronchodilator and anti-inflammatory treatment.

Regardless of the setting, validity of tests is a prerequisite for using spirometry. Several professional organizations have emphasized the importance of training and assign a central role to education before implementing spirometry in practice(3-5). A randomised controlled study showed that general practitioners (GPs) and practice nurses who had participated in a spirometry training program achieved better test results compared with GPs and nurses who had not been trained, although the training effect appeared to be transient(6). In epidemiological studies and clinical trials the institution of site visits and technician performance monitoring have been shown to improve quality of tests and maintenance of high quality grades thereafter(7;8). For primary care settings, however, such research data are non-existing.

In healthcare research, several other interventions to improve the quality of primary care have been investigated: performance-linked feedback (e.g., reminders), learning through social influence (e.g., peer review groups), and management support (e.g., rules or obligations)(9). Outreach visits by consultants who meet with healthcare providers in their own practice setting to provide oriented information and ‘on the spot’ feedback seem to be effective(9;10). It has been reported that this approach may optimize drug prescription routines(11-13), enhance smoking cessation interventions(14) and other preventive activities in general practice (i.e., screening for cardiovascular disease(15) and cervical cancer(16)). The objective of the current study was to assess the effect of periodic educational outreach visits by lung function technicians as an addition to a baseline spirometry training program with regard to the long-term validity of spirometric testing as performed in Dutch general practices.

Methods

Study design and participants

We report a subgroup analysis of a 1-year prospectively controlled spirometry evaluation study which has previously been reported in full(17). Patients with COPD served as study subjects. GPs recruited subjects who met the following inclusion criteria: age 30–75 years;
current or ex-smoker; diagnosis of COPD as assigned by a GP; meeting the clinical definition of COPD (“increased cough, sputum and dyspnoea on most days for a minimum of 3 months a year for at least the previous 2 years”)(18); post-bronchodilator forced expiratory volume in 1 second (FEV$_1$) 40–90% of the predicted value and/or post-bronchodilator FEV$_1$/FVC (forced vital capacity), 88% of the predicted value for men and 89% for women. Subjects with severe co-morbidity and/or a history of asthma, allergic rhinitis, or atopic rash were excluded. The study was approved by the medical ethics review board of the University Medical Centre Nijmegen and all study subjects gave written informed consent.

Intervention and reference group practices
Forty-five (45) general practices comprising 262 study subjects served as intervention group (‘outreach visit’) practices. These practices all participated in a clinical trial in which spirometry was used to measure annual lung function decline(19). Another 16 practices comprising 126 study subjects were specifically recruited to serve as a reference group. A postgraduate spirometry training program was developed and offered to all GPs and practice assistants of the intervention as well as the reference group practices. In Dutch general practice, practice assistants are paramedical professionals who have been trained for administrative and patient care related activities. Spirometry training consisted of two 2.5 h sessions scheduled with an interval of one month. Training for practice assistants specifically focussed on elements of spirometry performance that need improvement in general practice(6;20). (Details on the contents of the training program can be found at www.thoraxjnl.com/supplemental.) All practices received a written protocol describing spirometry test procedures, which was based on existing guidelines(3).

After the baseline spirometry training program the intervention group practices were periodically visited by one of the three lung function technicians involved in the study in order to optimize spirometry test performance. Lung function technicians are professionals who have completed a three year higher vocational training and are engaged in performing self-employed lung function tests. The frequency of visits depended not only on the needs and wishes of the practice assistants, but was also determined at the discretion of the technicians. On average, the practices were visited once every 3 to 4 months. Several methods were used by the technicians to maintain or improve spirometric test quality (figure 1). Practice assistants and GPs were encouraged to contact the visiting technician whenever they experienced difficulties, or with questions regarding spirometry. Apart from the same baseline spirometry program as in the intervention group, no subsequent quality-promoting activities aiming at spirometry were offered to the reference group practices.
Figure 1. Methods used by lung function technicians to optimize the quality of spirometric test performance during the outreach visits in general practices

A. Make an inventory of, and discuss problems encountered, and answer questions regarding the execution of spirometric tests with practice assistants and GPs

B. Judging of F/V-curves already present in the practice database:
   • Selection of manoeuvre (highest sum of FEV₁ and FVC)
   • Reproducibility (difference between two highest FEV₁ values <5%)
   • Relevant aspects of selected manoeuvre (PEF, exhalation ≥6”, etc.)

C. Real time supervision of the execution of a spirometric test:
   Preparation
   • Correct demographic data are entered (e.g., height)
   • Correct administration of bronchodilator in post-BD tests
   Execution
   • Adequate body position
   • Correct positioning of mouthpiece
   • Encouragement to attain maximum effort
   • Number of manoeuvres performed in a test (min. 3, max. 8)
   plus the points mentioned at B

*derived from the criteria of the American Thoracic Society for performance of maneuver, acceptability and reproducibility of spirometric tests with special attention for errors commonly made during spirometry in general practice [10,26]

Data collection, equipment and spirometric testing

Data collection took place from December 1998 through January 2001. Each study subject performed a pair of spirometry tests at baseline and after one year. The first test always took place in one of the four certified pulmonary laboratories involved, the second test in the subjects’ general practice.

In the intervention group practices the inclusion of study subjects started before the first outreach visit had taken place, but lasted until weeks after this first visit in most practices. The investigators encouraged the spirometric tests in general practices to be performed by practice assistants. A priori, we considered the tests performed in the pulmonary function laboratories as “gold standard” measurements [21].

General practices and laboratories were all equipped with an electronic turbine spirometer (Microloop II® , Micro Medical Ltd, Rochester, Kent, UK) and compatible spirometry software (Spirare® for DOS, Diagnostica Ltd, Oslo, Norway). Spirare® software displays real-time flow-volume and volume-time curves, a reminder message for patient instruction and a time indicator to monitor duration of expiratory and inspiratory flow, but does not provide built-in quality assurance prompts [22]. During the intermediary year subjects returned to their general practice for a spirometry test every three months. When the time interval between the
‘paired’ laboratory and general practice tests exceeded 30 days, subjects were excluded from the analysis. In case of an acute exacerbation within two months before the laboratory measurement, the whole measurement schedule was postponed until at least six weeks after clinical recovery.

During each visit to the laboratory or general practice, subjects performed a full (pre-bronchodilator and post-bronchodilator) spirometric test. Subjects were instructed not to use short-acting bronchodilators 8 h, or long-acting bronchodilators 12 h prior to testing. Post-bronchodilator tests were performed 15 minutes after administration of 400 micrograms aerosolized salbutamol by spacer. For each test at least three acceptable forced blows were required(3;4). Spirometric indices, flow-volume, and volume-time curves of the manoeuvre with the highest sum of FEV$_1$ and FVC were stored and used for analysis. In the intervention and reference group practices as well as in the laboratories the spirometers were checked for errors in volume readings every three months using a 3 litre calibration syringe(3;4). In case of a $\geq$3% deviation of the volume reading, the spirometer was replaced.

Baseline data of general practices and practice staffs were collected by questionnaires that comprised questions within the following domains: practice characteristics and professional experience; practice organisation and infrastructure; existing quality enhancing activities; application and appreciation of spirometry. Using the questionnaire data a general practice delegation index was calculated for each practice assistant: a validated index that expresses the autonomy of practice assistants with regard to five patient care related activities: removing stitches; performing vena punctures; checking patients with hypertension; freezing warts; and removing ear wax(23).

Outcomes and statistical analysis
In order to analyze differences in baseline characteristics between intervention and reference practices, p-values were calculated using appropriate univariate statistical tests. Mean values of the primary outcomes for both groups and accompanying t test based ninety five percent confidence intervals (95% CIs) were calculated. Within and between group differences were analyzed using paired and unpaired t tests, respectively.

Primary outcomes were the within-subject differences between the laboratory and general practice spirometric tests (laboratory minus general practice value) in terms of FEV$_1$ and FVC, further referred to as $\Delta$FEV$_1$ and $\Delta$FVC, respectively. The higher the $\Delta$FEV$_1$ or $\Delta$FVC the better the general practice spirometric test had been performed relative to the laboratory test. The proportion of tests with a reproducibility (‘test variance’) of $<5\%$ and $<200$ ml between the two highest FEV$_1$ values from the three accepted forced manoeuvres was considered as a quality marker of the spirometric tests(3;6). Differences in the proportion of non-reproducible tests in laboratories and general practices were analysed using McNemar’s test. SPSS 9.0 for Windows® was used for the analyses.
Results

Baseline characteristics

Descriptive characteristics of the general practices, GPs, practice assistants, and study subjects are given in table 1. Several practice and professional characteristics differed statistically significant between the intervention and reference group practices: number of practice assistants employed; proportion of GPs ever having attended spirometry training; proportion of GPs taking part in the spirometry refresher training at the start of the study; age of practice assistants. Study subjects from the reference group practices were more often female and tended to have somewhat lower lung function values. Of the 61 general practices involved, spirometry was performed by practice assistants in 58 (96%) practices and by GPs in 3 (4%) practices. In the year following the baseline spirometry training program 41% of the intervention group and 39% of the reference group GPs attended additional external spirometry training courses (p=0.768). Corresponding figures among the practice assistants were 48% for the intervention group and 31% for the reference group, respectively (p=0.061).
<table>
<thead>
<tr>
<th>General practices*</th>
<th>Intervention group</th>
<th>Reference group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>45</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Type of practice (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single handed</td>
<td>14 (30)</td>
<td>7 (44)</td>
<td></td>
</tr>
<tr>
<td>Two handed</td>
<td>10 (23)</td>
<td>5 (31)</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>16 (35)</td>
<td>4 (25)</td>
<td></td>
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<tr>
<td>Multidisciplinary healthcare centres</td>
<td>5 (12)</td>
<td>0 (0)</td>
<td>0.342</td>
</tr>
<tr>
<td>Number of GPs</td>
<td>2.8 (1.5)</td>
<td>2.1 (1.0)</td>
<td>0.091</td>
</tr>
<tr>
<td>Number of practice assistants</td>
<td>3.4 (1.6)</td>
<td>2.6 (1.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Time since introduction of spirometry, years</td>
<td>4.7 (3.1)</td>
<td>3.9 (2.5)</td>
<td>0.384</td>
</tr>
</tbody>
</table>

| General practitioners | | | |
| N                  | 109                | 31              |         |
| Age, years         | 44.4 (6.9)         | 46.2 (6.9)      | 0.196   |
| Professional experience, years | 14.1 (8.2)      | 15.0 (8.6)      | 0.675   |
| Number of patients per GP | 1860 (773)    | 1849 (758)      | 0.941   |
| Working hours per week | 39.8 (14.1)     | 38.9 (14.4)     | 0.778   |
| Attended spirometry training (%) | 73 (67)         | 27 (87)         | 0.033   |

| Practice assistants | | | |
| N                  | 132                | 41              |         |
| Age, years         | 34.3 (9.0)         | 38.7 (9.6)      | 0.011   |
| Professional experience, years | 10.6 (7.2)    | 11.4 (8.0)      | 0.570   |
| Working hours per week | 26.1 (10.8)     | 22.5 (9.7)      | 0.069   |
| Attended spirometry training (%) | 67 (50.8)      | 25 (61.0)       | 0.252   |
| Number of spirometric tests per month (median, IQR) | 3 (0-8)        | 2 (0-6)         | 0.483   |
| High delegation index* (%) | 121 (91)       | 28 (89)         | 0.715   |

| Study subjects* & | | | |
| N                  | 262                | 126             |         |
| Age, years         | 59.2 (9.7)         | 60.6 (9.7)      | 0.152   |
| Male/female        | 193/69             | 73/53           | 0.002   |

**FEV₁**

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Pre-bronchodilator (l)</td>
<td>1.85 (0.68)</td>
<td>1.69 (0.60)</td>
<td>0.025</td>
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<tr>
<td>% predicted</td>
<td>60.3 (17.9)</td>
<td>60.1 (18.7)</td>
<td>0.913</td>
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<tr>
<td>Post-bronchodilator (l)</td>
<td>2.08 (0.67)</td>
<td>1.84 (0.60)</td>
<td>0.001</td>
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<tr>
<td>% predicted</td>
<td>67.3 (16.4)</td>
<td>65.4 (18.8)</td>
<td>0.312</td>
</tr>
</tbody>
</table>

<table>
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<th>Reference group</th>
<th>p value</th>
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<tr>
<td>Pre-bronchodilator (l)</td>
<td>3.02 (0.96)</td>
<td>2.67 (0.76)</td>
<td>&lt;0.001</td>
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<tr>
<td>% predicted</td>
<td>78.9 (19.0)</td>
<td>76.4 (17.9)</td>
<td>0.217</td>
</tr>
<tr>
<td>Post-bronchodilator (l)</td>
<td>3.40 (0.98)</td>
<td>2.86 (0.75)</td>
<td>&lt;0.001</td>
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<tr>
<td>% predicted</td>
<td>88.0 (17.9)</td>
<td>81.9 (17.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**FVC**

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Reference group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-bronchodilator (%)</td>
<td>61.9 (12.3)</td>
<td>63.8 (10.2)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

* data on characteristics of practices, general practitioners and practice assistants were missing for 2 intervention group practices
* score of ≥3 patient care related activities defined as high delegation index
* lung function indices measured in pulmonary function laboratories at first year evaluation

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = inter quartile range; BD = bronchodilator
Validity and quality of spirometric tests

In the first year evaluation the mean ΔFVC was higher for the intervention group subjects compared to the reference group subjects (p<0.001), whereas the mean ΔFEV₁ was not (p=0.126, table 2). In the second year evaluation, approximately a year after the outreach visits had been first implemented, the mean ΔFEV₁ and ΔFVC were higher in the intervention group compared to the reference group (p=0.049 and p<0.001, respectively). Compared to the first year evaluation, the mean ΔFVC had slightly improved in the intervention group whereas in the reference group this outcome had turned to a negative value (i.e., general practice FVC values were now, on average, lower than laboratory FVC values). The changes in ΔFEV₁ and ΔFVC from the first to the second year were not statistically significant different between the two study groups (table 2).

Table 2. Mean (95% CI) values of primary outcomes* in the intervention and reference group study subjects for the first and second year evaluation

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
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<th>p value of between group difference</th>
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<td><strong>First year evaluation</strong></td>
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</tr>
<tr>
<td>N</td>
<td>262</td>
<td>126</td>
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<tr>
<td>ΔFEV₁ (l)</td>
<td>0.078</td>
<td>0.053</td>
<td>0.126</td>
</tr>
<tr>
<td>(0.059; 0.097)</td>
<td>(0.029; 0.077)</td>
<td></td>
<td></td>
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<tr>
<td>ΔFVC (l)</td>
<td>0.119</td>
<td>0.008</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(0.083; 0.155)</td>
<td>(-0.037; 0.052)</td>
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<tr>
<td><strong>Second year evaluation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>230</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁ (l)</td>
<td>0.068</td>
<td>0.035</td>
<td>0.049</td>
</tr>
<tr>
<td>(0.048; 0.088)</td>
<td>(0.013; 0.058)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFVC (l)</td>
<td>0.126</td>
<td>-0.021</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(0.088; 0.163)</td>
<td>(-0.060; 0.017)</td>
<td></td>
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<tr>
<td><strong>Difference between first and second year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>230</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁ (l)</td>
<td>0</td>
<td>0.012</td>
<td>0.598</td>
</tr>
<tr>
<td>(-0.027; 0.027)</td>
<td>(-0.046; 0.022)</td>
<td></td>
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</tr>
<tr>
<td>ΔFVC (l)</td>
<td>0.015</td>
<td>-0.040</td>
<td>0.173</td>
</tr>
<tr>
<td>(-0.038; 0.068)</td>
<td>(-0.098; 0.019)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* combined results of pre-bronchodilator and post-bronchodilator values
& a minus sign indicates higher mean laboratory values, absence of a minus sign indicates higher general practice values
# difference of matched primary outcomes in the second year minus the value in the first year
$ a minus sign indicates a higher primary outcome in the first year compared to the second year evaluation
Discussion

The results of this study suggest that a structure of educational outreach visits by lung function technicians on top of a basic spirometry training program has added value in maintaining the validity of spirometric testing in general practice. In the first year evaluation, the primary outcomes (i.e., $\Delta FEV_1$, $\Delta FVC$) were already statistically significant higher in the intervention group compared to the reference group practices. Because the two groups were rather comparable with regard to the practice and professional characteristics and because all practices received the same baseline intervention (i.e., the spirometry training program) we explain this first year difference in favor of the intervention group from the fact that in most intervention group practices the inclusion of study subjects went on until well after the first outreach visit had taken place. Nonetheless, the effect in the intervention group still existed a year later, whereas in the reference group the already lower initial outcome values had further regressed.

As we anticipated beforehand based on the studies by Eaton et al.(6) and den Otter et al.(20), the reference group showed the most pronounced regression in the $\Delta FVC$, whereas the $\Delta FEV_1$ hardly declined after the first year evaluation. This is an important observation, because too low FVC values caused by inadequate testing are likely to cause higher $FEV_1/FVC$ ratios. As this ratio is a crucial index in the diagnosis of COPD(1;24), false-negative diagnoses may be the undesirable consequence of inadequate spirometric tests in general practice(25). Periodic outreach visits by lung function technicians seem to prevent this from happening.

Strengths and limitations of the study

A particular strength of the current study was the fact that we had the opportunity to implement the same baseline spirometry training program and could standardize other factors that may influence the long-term validity of spirometric testing in the intervention as well as in the reference group practices. For instance, the frequency of monitoring of study subjects was set on once every three months for both groups of practices; all practices were equipped with the same type of spirometer and spirometry software; and the spirometers were checked every three months for errors at all locations. Thus, we were able to create identical conditions which, in our view, minimizes the possibility of systematic bias in favor of one of the study groups.
From a methodological point of view random allocation of practices to the intervention and reference group conditions would have been the preferred approach. However, intervention group practices had to commit themselves to participate in a three year randomised controlled clinical trial and -by protocol- received maximal supervision of spirometric test performance. In contrast, reference group practices were specifically recruited to serve as controls for the comparison reported in this paper. Although the two groups of practices did not seem to differ on most baseline characteristics, we may have recruited particularly motivated reference group practices. The observed higher attendance rates at the baseline spirometry training (table 1) agrees with this presumption. This could mean that in real life, where general practice staffs may prepare less intensively before taking up spirometry in their practice, the regression of the primary outcomes might be larger. Thus, we may have underestimated the actual effect of outreach visits on the long-term validity of spirometric testing in the current study.

Effectiveness of educational outreach visits in general practice
To our knowledge, no previous studies have been performed to evaluate the effect of educational outreach visits on the validity of spirometric testing in general practice. Although at baseline ∆FVC was significantly different between the intervention and reference group subjects, the changes following the year in which the intervention took place were -as expected- in favor of the intervention group. There are several arguments that support the plausibility of this finding. Firstly, it is well established that outreach visits in which experts provide face to face education tailored to the unique attributes and needs of the professionals involved are an effective multifaceted method to improve quality of care(10). In the current study the outreach visits also involved interventions like feedback and audit, and emphasis was put on the improvement of skills necessary to conduct spirometry adequately. Secondly, our observations are consistent with the study performed by Eaton et al.(6), in which a significant training effect on the quality of spirometric tests performed in general practice was observed. In our study the effects of the baseline spirometry training also appeared to have diminished in the reference group in the second year evaluation, which points to the ineffectiveness of a one-off training intervention in the long term(6). Thirdly, the results of the current study seem to confirm observations from studies conducted in other research domains, in which educational outreach visits have been shown effective in improving various elements of healthcare provision in primary care(10).

In this paper we did not include an evaluation of the costs of the outreach visits made by the lung function technicians. Because site visits by these professionals with higher vocational training are rather expensive, other options for maintaining spirometric test quality in general practice should be considered. Build-in quality prompts in spirometry software and equipment which can guide the operator to the best attainable test result may be a cheap and realistic option(8). Periodic feedback based on spirometric tests that are send to a local lung function
laboratory for appreciation might be another option. The actual impact of these alternative options on the validity of general practice spirometry should be further investigated. We conclude that the overall performance with regard to spirometric testing in Dutch general practices was quite acceptable compared with the performance of lung function laboratories, even without additional quality assurance measures. Nonetheless, periodic educational outreach visits by lung function technicians may contribute to maintaining -or even further improving- the validity of spirometric tests in general practice. Because of the labor-intensive nature of the educational outreach visits, other options to maintain spirometric test validity in general practice might be more attractive.

References


Chapter 4

Feedback information from flow volume curves to the practice assistant improves spirometry test quality in general practice

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Feedback information from flow volume curves to the practice assistant improves spirometry test quality in general practice
T Schermer, J Hartman, C Lauwers, H Folgering, A Jacobs, B Bottema, C van Weel

ABSTRACT
Objective: To investigate whether the use of feedback information provided by viewing flow volume (F/V) curves during spirometry performed by practice assistants improves spirometry test quality.
Methods: Randomised controlled single session crossover study. Eight practice assistants performed spirometry in healthy subjects (n=47). Two measurement conditions were applied, one allowing viewing of F/V curves during the tests (‘unblinded’) the other not (‘blinded’). Outcomes were differences in FEV1, FVC, FEV1/FVC ratio, PEF, FEV1, repeatability and number of manoeuvres per test. Two lung function technicians indicated their preference for either the blinded or unblinded F/V curve.
Results: Higher PEF values were observed for the unblinded condition (0.43 L/s, 95% CI 0.08, 0.77). The other outcomes showed no differences. One lung function technician judged that in 62% (p=0.012) of the pairs the F/V curve from the unblinded condition was better, the other technician judged so in 51% (p=0.349).
Conclusion: This study in healthy subjects showed that the use of information from F/V curves leads to a modest quality improvement of spirometric tests performed by practice assistants and can therefore be recommended for use in general practice.

INTRODUCTION
The use of spirometry is rapidly increasing within primary health care in many developed countries. International practice guidelines on lung function measurement stress the importance of standardisation of measurement conditions during spirometry.1,2 These guidelines underline the value flow volume (F/V) curves may have in optimising spirometry test quality. Most modern spirometers display real-time F/V or volume-time curves during forced breathing manoeuvres. However, apart from one single observational study3 we could find no evidence for the assumption that providing technicians with feedback information from F/V curves contributes to the overall quality of forced breathing manoeuvres including spirometry testing.

If information from the F/V curve does indeed optimise quality of spirometry, ample attention on how to judge curves is appropriate for primary care professionals, since sufficient test quality is not always guaranteed there.4 The objective of the study reported in this paper was to investigate the added value of information obtained from viewing F/V curves on the quality of spirometric tests performed by sufficiently trained practice assistants. The study focused on the performance of the practice assistant. In Dutch general practice this is the paramedical discipline that has been trained for administrative and patient care related activities.

METHODS
Design
The study was designed as a randomised controlled single session crossover study. In order to assess the feedback value of F/V curves during spirometry performance by practice assistants, two measurement conditions were created, one with and one without feedback information to the practice assistant. Of each study subject a pair of F/V curves – consisting of the ‘best’ manoeuvre of both conditions - was judged by two experienced lung function technicians with special
attention on quality criteria for F/V curves. The technicians indicated whether they preferred one curve over the other, or if both curves were of equal quality being unaware of the condition in which each curve was obtained (blinded or unblinded).

Before they performed any spirometric tests in study subjects, the practice assistants received a short, standardised oral reminder on how to perform spirometry and how to assess the ‘quality’ of forced breathing manoeuvres (table 1).

**Measurements**
All spirometric tests were performed using one single turbine spirometer (Microloop II, Micro Medical Ltd, Rochester, UK) connected to a laptop computer on which Spirare® spirometry software (Version 2.11, Diagnostica, Oslo, Norway) was installed. Volume readings of the spirometer were checked with a 3-L calibration syringe after each subject had completed the measurements.

A full spirometry test consisted of at least three forced breathing manoeuvres. After completing a full test the practice assistant saved the F/V curve and matching indices of the - in her opinion - ‘best’ manoeuvre. Thus, a pair of single ‘best’ F/V curves was obtained for each study subject, one from the blinded and one from the unblinded measurement condition.

The two measurement conditions were created as follows: **Blinded condition**: The computer screen was covered to hide the F/V curves. Only a table showing relevant spirometric indices (FEV₁, FVC, PEF) and the percentage FEV₁ repeatability between the various performances in one full test was displayed on the screen. **Unblinded condition**: spirometric indices as well as F/V curves were visible throughout measurements. The order in which blinded and unblinded measurement conditions were applied was randomised for each subject. A time interval of at least 5 minutes was kept between consecutive series of manoeuvres. In neither measurement condition the test subjects could look on the computer screen.

Prior to the measurements, the practice assistant instructed each test subject according to the standardised instructions (table 1). Each subject performed one single forced expiration and inspiration.

**Practice assistants and test subjects**
Eight female practice assistants from 4 general practices in the eastern part of The Netherlands participated. All assistants had attended a two-session spirometry training course 6 to 12 month earlier and all regularly performed spirometry within their practice setting.

Test subjects were recruited from the general practitioners’ waiting room. Eligible subjects had to meet the following criteria: age 25 – 80 years, no medical history of respiratory diseases, no use of airway medication and no previous spirometry tests.

**Outcomes**
Differences between blinded and unblinded conditions in FEV₁ (Forced Expiratory Volume in One Second), FVC (Forced Vital Capacity), FEV₁/FVC ratio, PEF (Peak Expiratory Flow), FEV₁ repeatability and the number of manoeuvres per full spirometry test served
as outcomes. FEV₁ repeatability is the relative difference between the two highest FEV₁ values from three manoeuvres. A spirometry test was considered adequate when FEV₁ repeatability was less than 5% or 200 ml. The rating of the two lung function technicians regarding the quality of blinded and the unblinded measurements was also considered as an outcome.

Statistics

A power calculation showed that 46 subjects were needed to detect a difference of 3% in FEV₁ repeatability. The intra-cluster correlation introduced by the fact that each practice assistant contributed measurements from several (5 to 7) subjects was accounted for in this calculation. Predicted FEV₁ and FVC values were calculated using ERS reference equations. Student-t and Wilcoxon tests for matched pairs were used to analyse differences between unblinded and blinded conditions. Student-t test for independent samples to analyse carry-over and order-effects between consecutive test series. Bland-Altman plots were generated to graphically express relative differences in outcomes between conditions.

Distribution of the lung function technicians’ judgements of the pairs of F/V curves was analysed for technician A and B separately by sign-test. Cohen’s kappa was calculated to determine the degree of mutual agreement between the technicians. This statistic takes the difference between the proportion of cases agreed between two observers and the proportion expected by chance and standardises this by 1 minus the proportion expected by chance. In biological systems a value of 0.40 to 0.60 is generally considered as moderate agreement. Alpha was set on 0.05 and 95% Confidence Intervals (95% CI) were calculated if applicable. SPSS for Windows (Release 9.0.1, 24 February 1999) was used for data analysis.

RESULTS

Test subjects and practice assistants:

Descriptive characteristics of the test subjects – all Caucasian - are shown in Table 2. Although we aimed to include equal numbers of males and females, this turned out to be difficult because more females than males visited their GP on the chosen study days. Mean age of the practice assistants was 34.7 (SD 8.0) years, mean experience with spirometry 4 years (range 0.5-8).

Differences between measurement conditions:

Mean PEF was 0.43 L/s or 6.1% higher (95% CI 0.08, 0.77) when practice assistants used the F/V curves as visual feedback. No statistical significant differences were observed for the FVC, FEV₁, FVC/FEV₁ or FEV₁ repeatability (Table 3). While blinded for the F/V curve, practice assistants used an average of 3.8 manoeuvres, 4.0 manoeuvres when unblinded (p=0.375).

The relationship between the average value of each subject and the difference between blinded and unblinded measurements is shown in Bland-Altman plots for the FVC and PEF (Figure 1a and 1b). Both plots show two outliers but no clear systematic deviations. Excluding the two outliers (n=45) resulted in a reduction of the mean PEF difference to 0.22 L/s (95% CI 0.02, 0.43). No carry-over effects in favour of the second measurement condition were observed.

Judgement of lung function technicians:

Lung function technician A judged F/V curves from unblinded conditions superior to blinded curves in 24 (51%) pairs and inferior to 17 (36%) pairs. Technician B judged 29 (62%) of the unblinded curves as superior, 12 (26%) as inferior compared to the blinded curves. For the remaining 6 pairs, the technicians could not decide in favour of either curve. The distribution of the judgements (“unblinded measurement preferred above blinded” versus “blinded measurement preferred above unblinded”) was statistically significant (p=0.013) for technician B, not for technician A. Agreement between lung function technicians was acceptable (Kappa=0.44).
The objective of this study was to investigate the value of feedback information obtained from F/V curves on the quality of spirometry performed by trained practice assistants. International guidelines recommend the use of F/V curves to improve test quality, but this is not firmly supported by empirical data. We only found one study addressing this issue: Banks et al.3 investigated changes in lung function indices after the spirometer of an occupational health service had been replaced by equipment that automatically gave feedback on test quality by assessing the F/V curve. The authors observed an increased number of tests fulfilling ATS acceptability criteria as well as increased FVC and PEF values. FEV1 values did not change after implementation of the advanced spirometry system. Our finding that PEF values increased and FEV1 values remained unaltered when trained practice assistants used F/V curves is in line with these findings. Because we did not observe increased FVC values, the two studies are contradictory with regard to the effect of feedback on this outcome. One explanation for this inconsistency may be the fact that in Banks’ study nurses with ample experience performed the spirometry tests, whereas in our study less seasoned practice assistants were engaged. Indeed, previous work from our department showed that practice assistants are particularly uncritical in stimulating subjects to exhale maximally6, which will inevitably result in lower FVCs. A recent study by Eaton et al.4 confirms that most spirometry failures seen in general practice are end-of-test related. Although F/V curves typically provide information to critically assess FVC adequacy, our data suggest that practice assistants do not utilise this information optimally.

However, it is important to realise that we used healthy individuals (test subjects) as study subjects. Patients suffering from chronic airway disease (especially COPD) may need more time to reach their FVC plateau, enabling practice assistants to profit more from the information the F/V curve provide.

In conclusion, in this study among healthy subjects feedback information to the practice assistants from F/V curves led to a modest quality improvement of spirometric tests and can therefore be recommended for use in general practice. In spirometry training programs, special attention should be given on how to critically assess F/V curves. Finally, if a GP considers purchasing a spirometer, the device chosen should preferably display a real-time F/V curve.

References
Impact of spirometry on GPs’ diagnostic differentiation and decision-making

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Impact of spirometry on GPs’ diagnostic differentiation and decision-making

Niels Chavannes, Tjard Schermer, Reinier Akkerman, J.E. Jacobs, Gabrielle van de Graaf, Ralf Bollen, Onno van Schayck, Ben Bottema

Summary  Background: Spirometry is increasingly implemented in general practice, while the ability of general practitioners (GPs) to interpret flow-volume curves (F–V curves) has been questioned. Furthermore, the role of spirometry in the GPs decision-making process has barely been studied.

Aim: To compare the achievements of trained GPs in spirometric diagnosis with an expert consensus panel (1) and to assess the influence of spirometry on the GPs decision-making (2).

Method: Twelve cases including a wide range of F–V curves were interpreted by 39 GPs as well as the expert panel. Diagnostic test characteristics were calculated using multi-level analysis and summarised by diagnostic odds ratios (DOR). Differences in decision-making indicators were expressed as odds ratios and 95% confidence intervals.

Results: Normal F–V curves (DOR 65.0) and obstructive F–V curves (DOR 48.9) were reasonably well diagnosed, while rare and mixed pathological patterns achieved considerably lower scores (DOR 3.8). Intermediate scores were obtained in the recognition of incorrect test manoeuvres (DOR 24.4). Spirometry influenced the GPs decision-making in reducing the number of alternative diagnoses (OR 0.266 [0.200, 0.353]), but also increased referral rates (7.26 [4.71, 11.2]) and the use of diagnostic prednisolone courses (4.55 [3.12, 6.64]) substantially.

Conclusion: Trained GPs were able to differentiate between normal and obstructive disease patterns, while F–V curves suggestive of rare and mixed pathology were often missed. Spirometry seems to influence the decision-making process of the GP; whether this represents an initial or a more sustained effect remains to be evaluated in studies of daily primary care practice.
Introduction

In general practice, medical history taking and physical examination are the most important instruments to establish diagnosis and initiate treatment. Diagnostic tools originating from secondary care settings such as electrocardiography\(^1,2\) and spirometry\(^3,4\) are increasingly used in primary care and the results are being interpreted by general practitioners (GPs). Access to spirometry in primary care has increased rapidly in the past years, surveys ranging from 21\(^6\) (1998) to 77\(^7\) (2001) in the UK.\(^7\) By contrast, spirometer utilisation is hampered by insufficient training: less than half are used to diagnose COPD.\(^7\) Several national and international guidelines consider formal spirometric testing essential to establish a diagnosis of COPD,\(^4,8,9\) while education in its use has been identified as a major goal for primary care physicians.\(^4,10,11\)

However, the value of spirometry in differentiating between specific respiratory disease patterns still needs to be assessed in general practice. Most authors focus on the quality of spirometry test performance,\(^5,12,13\) while studies investigating the interpretative skills of physicians report rather disappointing results, both in primary\(^2\) and secondary care\(^14,15\) setting.

A number of studies in COPD and asthma suggest that spirometry could reduce both under- and overdiagnosis of obstructive airway disease in general practice,\(^16–18\) which might influence disease management. Adjustment of treatment after spirometry has been reported in 4–25\(^%\) of patients with mostly asthmatic complaints.\(^19,20\) However, the direct influence of spirometry on the decision-making process of GPs has not been assessed. Therefore, the aim of the current study was to determine the achievements of GPs in differentiating between various chronic respiratory diseases when spirometry is provided as a supplementary diagnostic tool. In addition, we investigated the impact of the flow-volume curve on the GPs decision-making process.

Methods

Participants and spirometry training

GPs with an interest in spirometry were recruited from the general practice networks of the Nijmegen and Maastricht Universities in the Netherlands. Most of these GPs already used spirometry in daily practice, had received previous training and were motivated to assess their skills. Additionally, GPs involved in the vocational training in the Nijmegen and Maastricht regions were invited by postal mailing to participate in the study.

Participating GPs received a standardised postgraduate spirometry training course (two three-hours sessions with an interval of one month), and could bring their newly acquired spirometric knowledge and skills into practice for a period of six to nine months before the study started. The spirometry course was based on a format widely used in the Netherlands. During the first session the focus was mainly on the pathogenesis and clinical characteristics of asthma, COPD and other chronic respiratory diseases; theoretical concepts of lung function testing; execution of spirometry tests; and practical guidelines and strategies for spirometry interpretation. The second session was mainly used to discuss actual case descriptions submitted by either the participants or course leaders. Training was provided by a pulmonologist and an experienced lung function technician. Interactive education and feedback on the spot were emphasized throughout the course.

Standardised case descriptions

A set of 12 standardised case descriptions was constructed, based on actual patients from two general practices from our academic networks. The cases were designed in cooperation with a pulmonologist and a GP with ample experience in the field of chronic respiratory diseases. The case set included a range of typical flow-volume curves suggesting mild obstruction (n = 1); moderate obstruction (n = 1); severe obstruction (n = 2); rare pattern of restriction (n = 1); fixed upper airways obstruction (n = 1); mixed pattern of both obstruction and restriction (n = 1); incorrect test manoeuvres (n = 2); and normal curves (n = 3). The participating GPs worked through two sets of six cases each, which were assessed in random order within a period of one year. Randomisation codes were prepared by a fellow-researcher who was not involved in the study and stored in sealed envelopes until use. Data were collected in the period July 1999 through April 2001.

A research assistant visited the GPs in their practice. For each case, a concise medical history and results of the physical examination were presented to the GP first. Subsequently, absolute and predicted postbronchodilator spirometry test results (including FEV\(_1\), FEV\(_1\)/FVC and flow-volume curves) were provided. After having assessed a case, GPs had to select one spirometric diagnosis
from a preformulated list. An example of the case structure is depicted in Fig. 1.

Before the study, the 12 paper cases had been judged by an independent expert panel consisting of two pulmonologists, a pulmonary physiologist and a GP with specific expertise in the pulmonary field. The panel reached consensus on the spirometric and clinical diagnoses of the paper cases during a panel discussion meeting, while no cases were excluded. The panel meeting was audiotaped and independently scored by two of the authors (NC and TS) in order to establish the panel's final diagnosis and alternative diagnoses for each case. There was 100% agreement between the two observers with respect to the panel's final and alternative diagnoses. The panel consensus diagnoses served as 'the gold standard' in the subsequent evaluation of the GPs' diagnostic achievements.

Outcome measures

To assess the diagnostic achievements of GPs with regard to interpretation of spirometry, the following four outcome categories were considered most relevant and contrasting from a clinical point of view: (1) bronchial obstruction (from mild to severe); (2) rare respiratory pathology (i.e., restriction, fixed upper airways obstruction, mixed pattern); (3) normal lung function; and (4) incorrect test manoeuvre.

In addition, the impact of spirometry on the GPs decision-making process was assessed using four indicators: (1) diagnostic uncertainty (size of differential diagnosis, i.e. the number of alternative diagnoses considered by the GPs while assessing a case); (2) probability of prescribing respiratory medication; (3) probability of initiating a diagnostic prednisolone course, a commonly used test (albeit its' value is uncertain); and (4) probability of referral to a pulmonologist and/or cardiologist. These process indicators of GP decision-making were assessed before and after the results of spirometry were shown to the GPs (Fig. 1).

Statistical analyses

First, the agreement between the GPs' interpretations and the expert panel's 'gold standard' diagnoses was investigated univariately using the SPSS® software package (Version 9.0 for Windows). Subsequently, multi-level linear and logistic modelling was used to account for the intra-cluster correlation induced by the fact that each GP
assessed more than one case. SAS software (Release 6.12 for Windows) was used for these multi-level analyses.

The following diagnostic test characteristics were calculated for each outcome measure: positive and negative predictive values (further referred to as PPV and NPV, respectively), positive and negative likelihood ratios (LR+ and LR-, respectively) and the diagnostic odds ratio (DOR). PPV expresses the probability of disease in subjects with a positive test result, NPV the probability of absence of disease in subjects with a negative test result. LR+ is the ratio of the probability of a positive test in subjects with disease and the probability of a positive test in subjects without disease. Conversely, LR- is the ratio of the probability of a negative test in subjects with disease and the probability of a negative test in subjects without disease. A diagnostic test is better the more LR differs from 1, that is, greater than 1 for LR+ and lower than 1 for LR-. Finally, the DOR summarises the overall discrimination of a diagnostic test with a dichotomous outcome. In fact, it is the ratio of LR+ and LR-. Therefore, a diagnostic test is useless if DOR = 1.

After the four indicators of decision-making were dichotomised (1 vs. >1 diagnosis; 0 vs. 1 diagnostic prednisolone course; 0 vs. 1 or more referrals; 0 vs. 1 or more prescriptions), the before-after spirometry measurements were compared using multi-level logistic regression analysis and expressed as odds ratios with 95% confidence intervals (95% CI).

Results

General practitioners

Thirty-nine (39) GPs participated in the study. Three GPs dropped out during the study, one because of early retirement, the others due to loss of interest. These three GPs completed one set of six cases, instead of both sets. Table 1 shows that the study population consisted predominantly of middle-aged male doctors who had been using spirometry in their daily practice for a mean of 4.3 (SD 3.7) years, having received 4.2 (SD 4.9) hours of spirometry training in the year preceding the experiment.

Diagnostic achievements by GPs

Altogether, the GPs assessed 444 cases. Table 2 shows the agreement between GP judgements and expert panel for each of the diagnostic outcome categories. Concordance with the expert panel regarding obstruction was present in 91.3% [95% CI 86.8, 95.8] of cases, followed by normal spirometry obtaining 77.9% [95% CI 70.2, 85.6] correct answers, while incorrect manoeuvres reached a score of 64.9% [95% CI 54.0, 75.8], and rare pathological curves were recognised in 41.3% [95% CI 32.1, 50.5] of cases.

Table 3 shows that normal and obstructive curves were characterised by high DORs: 65.0 and 48.9, respectively. By contrast, rare pathological curves obtained a low DOR of 3.8. Scoring of an incorrect test manoeuvre generated an intermediate DOR of 24.4. The negative predictive values (probability of righteously ruling out disease) varied between 0.93 and 0.96, except for rare pathology, which reached 0.82. Positive predictive values (probability of righteously labelling disease) however, revealed a range of values between 0.87 (normal curves) and 0.49 (rare pathology).

Indicators of GPs decision-making

Before spirometry, GPs considered an average of 2.05 diagnoses per case, with a maximum of eight, while after spirometry this was reduced to a mean of 1.35, with a maximum of six. Table 4 quantifies this significant reduction of diagnostic uncertainty: >1 diagnosis is considered in 59.6% [55.1, 64.1] of cases before spirometry, while after spirometry >1 diagnosis is considered in 31.2% [26.9, 35.5] of cases (OR 0.266 [0.200, 0.353]). Conversely, spirometry significantly increases the number of diagnostic prednisolon courses and the referral rate, while the proportion of cases where medication is prescribed increases, but not significantly. The probability of diagnostic prednisolon testing rises three-fold, from 8.0% [5.5, 10.5] to 27.6% [23.5, 31.7] per case (OR 4.55 [3.12, 6.64]) as a result of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of participating general practitioners (n = 36a).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>33/3</td>
</tr>
<tr>
<td>Age, years</td>
<td>48 (5.1)</td>
</tr>
<tr>
<td>Patients enlisted per GP, number</td>
<td>2086 (712)</td>
</tr>
<tr>
<td>Surgery hours per week, hours</td>
<td>43.6 (12.7)</td>
</tr>
<tr>
<td>Use of spirometer in daily patient care, yes/no</td>
<td>35/1</td>
</tr>
<tr>
<td>Duration of spirometry utilisation, years</td>
<td>4.3 (3.7)</td>
</tr>
<tr>
<td>Spirometry training in previous year, hours</td>
<td>4.2 (4.9)</td>
</tr>
<tr>
<td>Values are means (standard deviation) unless stated otherwise.</td>
<td></td>
</tr>
<tr>
<td>aData missing on 3 GPs who dropped out during the study.</td>
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</tbody>
</table>
### Table 2: Agreement between expert panel and GP judgement for the presence (or absence) of obstructive disease (A), rare pathology (B), normal spirometry (C), and incorrect manoeuvre (D).

<table>
<thead>
<tr>
<th>Expert panel judgement</th>
<th>Obstruction</th>
<th>No obstruction⁴a</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) GP judgement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>136 (31)</td>
<td>52 (12)</td>
</tr>
<tr>
<td>No obstruction³</td>
<td>13 (3)</td>
<td>243 (55)</td>
</tr>
<tr>
<td></td>
<td>149 (34)</td>
<td>295 (66)</td>
</tr>
<tr>
<td>(B) GP judgement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rare pathology</td>
<td>45 (10)</td>
<td>52 (12)</td>
</tr>
<tr>
<td>No rare pathology⁵</td>
<td>64 (14)</td>
<td>283 (64)</td>
</tr>
<tr>
<td></td>
<td>109 (25)</td>
<td>335 (75)</td>
</tr>
<tr>
<td>(C) GP judgement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal spirometry</td>
<td>88 (20)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Not normal spirometry⁶</td>
<td>25 (6)</td>
<td>314 (71)</td>
</tr>
<tr>
<td></td>
<td>113 (25)</td>
<td>331 (75)</td>
</tr>
<tr>
<td>(D) GP judgement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorrect manoeuvre</td>
<td>48 (11)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Not incorrect manoeuvre</td>
<td>26 (6)</td>
<td>344 (77)</td>
</tr>
<tr>
<td></td>
<td>74 (17)</td>
<td>370 (83)</td>
</tr>
</tbody>
</table>

Percentages of total number of cases within parenthesis.

⁴aEither rare pathology, normal spirometry, or incorrect manoeuvre.
⁵Either obstruction, normal spirometry, or incorrect manoeuvre.
⁶Either obstruction, rare pathology, or incorrect manoeuvre.

### Table 3: Predictive values, likelihood ratios and diagnostic odds ratios for general practitioners diagnoses.

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
<th>LR⁺</th>
<th>LR⁻</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal spirometry</td>
<td>0.87</td>
<td>0.93</td>
<td>15.16</td>
<td>0.23</td>
<td>65.0</td>
</tr>
<tr>
<td>Obstructive disease</td>
<td>0.75</td>
<td>0.96</td>
<td>5.18</td>
<td>0.11</td>
<td>48.9</td>
</tr>
<tr>
<td>Incorrect manoeuvre</td>
<td>0.68</td>
<td>0.93</td>
<td>9.23</td>
<td>0.38</td>
<td>24.4</td>
</tr>
<tr>
<td>Rare pathology</td>
<td>0.49</td>
<td>0.82</td>
<td>2.66</td>
<td>0.70</td>
<td>3.8</td>
</tr>
</tbody>
</table>

PPV: positive predictive value; NPV: negative predictive value; LR⁺: positive likelihood ratio; LR⁻: negative likelihood ratio; DOR: diagnostic odds ratio.

### Table 4: Impact of flow-volume curve on indicators of the decision-making process in general practitioners.

<table>
<thead>
<tr>
<th>Process indicators</th>
<th>Before F /V-curve</th>
<th>After F /V-curve</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic uncertainty³</td>
<td>59.6% (55.1, 64.1)</td>
<td>31.2% (26.9, 35.5)</td>
<td>0.266 (0.200, 0.353)</td>
</tr>
<tr>
<td>Prednisolon course</td>
<td>8.0% (5.5, 10.5)</td>
<td>27.6% (23.5, 31.7)</td>
<td>4.55 (3.12, 6.64)</td>
</tr>
<tr>
<td>Referral rate</td>
<td>6.0% (3.8, 8.2)</td>
<td>31.7% (27.4, 36.0)</td>
<td>7.26 (4.71, 11.2)</td>
</tr>
<tr>
<td>Medication prescription</td>
<td>36.5% (32.0, 41.0)</td>
<td>39.4% (34.9, 43.9)</td>
<td>1.14 (0.87, 1.50)</td>
</tr>
</tbody>
</table>

Numbers are percentages with 95% confidence intervals.
³Proportion of >1 diagnoses in the differential diagnosis.
 Spirometry. The probability of referral changes from 6.0% [3.8, 8.2] to 31.7% [27.4, 36.0] as a result of spirometry (OR 7.26 [4.71, 11.2]).

Discussion

The present study demonstrates for the first time the reasonable diagnostic achievements of trained GPs with regard to commonly encountered spirometric patterns. Curves of obstructive airways disease as well as the physiological can be considered the more prevalent conditions, as opposed to patterns suggestive of restriction or fixed upper airways obstruction, which GPs can be expected to be less familiar with. On the whole, the positive predictive values are lower than the negative predictive values. This reflects the fact that in primary care it remains more difficult to label a disease than to exclude it, due to the lower a priori probability. The relatively low positive predictive value of an incorrect test manoeuvre illustrates the need to emphasise the importance of quality assessment of the flow-volume curve, which should precede interpretation. The low diagnostic achievements in the less prevalent categories points out the paradoxical necessity of recognising patterns one does not understand. Another explanation might be that dynamic spirometry is of limited use in differentiating between normal and restrictive disease, thus contributing to the low diagnostic yield. These elements should receive considerable attention in future spirometry courses, professional supervision or automated supportive software.

The significant influence of the flow-volume curve on the trained GPs’ decision-making is expressed in a reduction of the number of alternative diagnoses but an increase in referral rates and diagnostic prednisolone courses. Thus, the flow-volume curve seems to support establishing a diagnosis in patients with respiratory morbidity, but probably leads to an increased use of additional diagnostic procedures or specialist care, at least initially. This could partially reflect the relatively high prevalence of pathology in this specific case-set, warranting further work-up. Another explanation could be that the number of options was limited; for example, an option to repeat spirometry to verify correctness of the manoeuvre was missing, possibly leading to increased prednisolone testing or referral instead. The current design does not allow us to deduct if this initial increase would be sustained in time, nor does it predict the exact effect size in daily practice.

Spirometers are increasingly available but seem underused,7 while doctors have been observed to overestimate their actual interpretative skills in spirometry,22 as well as in ECGs.23 This underlines that training is a prerequisite for meaningful implementation of advanced diagnostic tools in primary care. Both quality assessment and pattern recognition have been part of our standardised spirometry training course, which took place 6–9 months preceding the measurements, allowing the primary care physicians to integrate skills in daily practice. The format and duration of the training were directly derived from a common postgraduate spirometry course, which has been attended by large numbers of Dutch primary care physicians in the past few years.

The results of the present study reflect the ability of trained GPs to diagnose this specific case-set. Therefore, we do not pretend to reflect actual prevalences of the disease patterns within the constitution of the cases. By analysing spirometric patterns separately this over-representation is corrected for. Consequently, the multi-level analysis was performed to account for intra-cluster correlation within the GPs. However, it remains to be investigated what the results will be in a real-life setting, with actual patients and less or even untrained GPs. The case-set structure allowed us to compare the level of pattern recognition quite precisely with an expert panel, which was confronted with the identical set of cases. Moreover, the expert panel scored cases preceding the study, independent of the results of the primary care physicians, thereby eliminating a potential bias which might have been overlooked in previous studies.5,14,15

In this study we demonstrated that the novel method of combining standardised case material with techniques of multi-level analysis may be useful to evaluate complex diagnostic tools, like spirometry. We conclude that trained GPs were able to differentiate between normal and obstructive disease patterns, while F–V curves suggestive of rare and mixed pathology were often missed. Spirometry seems to influence the decision-making process of the GP by reducing diagnostic uncertainty but increasing use of additional diagnostics and referral to specialist care. Whether this represents an initial or a more sustained effect remains to be evaluated in studies of daily primary care practice.

Acknowledgements

The authors are grateful to Dr. JWM Muris, GP, and Dr. GJ Wesseling, pulmonologist, who kindly assisted the preparation of the cases used in this
study. We also wish to thank all participating GPs for their interpretative efforts.

References


Spirometry in primary care: is it good enough to face demands like World COPD Day?

Published in: Eur Respir J 2003;22(5):725-7
On November 19th this year, World Chronic Obstructive Pulmonary Disease (COPD) Day 2003, people worldwide will be encouraged to review their respiratory health status and consult a doctor in case of certain symptoms [1]. Spirometry would be regarded as an integral component of this consultation. Additionally, asymptomatic smokers >40 yrs will be advised to have their lung function checked [1]. Thus, a likely and desirable outcome of World COPD Day could be a considerable and perhaps dramatic increase in demand for spirometry. This is a potentially daunting prospect with important implications in terms of the availability and utilisation of healthcare resources. It is therefore not only timely but essential to reflect on the current status of spirometry in primary care.

Thus far, a New Zealand study which was reported in 1999 presents the only, but extremely welcome, randomised prospective evaluation of the implementation of spirometry in primary care practice formally assessing both the impact of training and quality assurance [2]. The results of this study should be placed in the context of the growing prevalence of COPD which presents an increasing burden on healthcare resources globally [3]. An essential requirement would seem to be the development of high quality spirometry by family physicians on a large scale. The implications are sobering. Family physicians already diagnose 5–10 new cases annually [4], a figure expected to increase in the coming decades. This figure, albeit dramatic, still underestimates the true challenge of COPD. The burden of the disease in the community is much higher and for a substantial number of patients COPD remains undiagnosed and consequently untreated [5]. Cigarette smoking remains the leading cause of COPD and despite heightened public awareness and smoking cessation initiatives, a significant impact on global COPD numbers is not expected in the short or medium term. World COPD Day aims to promote public awareness of COPD. It is to be hoped that early diagnosis of COPD will facilitate the prevention of further damage to the airways and lungs, predominantly by focusing on smoking cessation.

Interface between primary and secondary care

A crucial initial success of the Global Initiative for Obstructive Lung Disease (GOLD) has been the establishment of a working relationship with primary care, with the involvement of the World Organization of Family Doctors (WONCA) [6] and the International Primary Care Respiratory Group (IPCRG) [7]. Early next year the first global primary care guidelines for COPD, based on GOLD, will be published: the International Primary Care Airways Guidelines (IPAG) project [8], developed in cooperation with the World Health Organization (WHO). The introduction of these guidelines will substantially coordinate diagnosis and treatment of COPD in primary care. Although a welcome and valuable initiative, the guidelines do not by themselves address the critically important issue of ensuring that family physicians and other primary care professionals have ready access, not just to spirometry but to quality spirometry.

Spirometry quality assurance

The impact of World COPD Day is expected to be considerably diminished if spirometry is not widely available and accessible. However, more importantly, poorly performed spirometry may lead to “misdiagnosis” with consequent misdirection of precious healthcare resources and giving rise to unnecessary patient concern. The pivotal role of family physicians dictates that ideally spirometry should be directly available in “every” practice. However, spirometry on this scale does present considerable logistic challenges. Resource and training constraints have for a long time hampered the large-scale introduction of spirometry to primary care. Research and development projects have emphasised rigorous training and performance standards as essential prerequisites of a successful spirometry programme [2, 9]. Furthermore, longer term “maintenance of standards” is crucial. It is salutary that even under the strict conditions of the Lung Health Study it was observed that the performance of certified technicians with regard to spirometry fell over time [9]. In primary care, spirometry is often, wrongly, regarded as a noninvasive simple screening test. However, it is apparent that careful consideration needs to be given to a number of aspects including selection and maintenance of equipment, optimal performance of the test by both patient and operator, adherence to standard criteria for acceptability and repeatability, appropriate selection of normal predicted values, and careful and informed interpretation of the results [10]. The newer generation electronic spirometers facilitate the adoption of acceptability and reproducibility criteria in primary care, but this should not engender complacency.

While well-established criteria for acceptability and reproducibility have been widely disseminated, it is by no means certain that these are adhered to in clinical practice. The aforementioned New Zealand study of spirometry by family physicians highlights some of these issues and possible solutions [2]. Although a significant training effect was demonstrated, the quality of the spirometry performed by family physicians did not generally satisfy full American Thoracic Society (ATS) criteria for acceptability and reproducibility.

Spirometry in primary care: is it good enough to face demands like World COPD Day?

T. Schermer, T. Eaton, R. Pauwels, C. van Weel
Organising spirometry in primary care

The British Thoracic Society guidelines for COPD [13] acknowledge that healthcare planners may need to consider options for the provision of primary care spirometry other than having the appropriate equipment on-site. Alternatively, could include utilising primary care diagnostic services or hospital-based laboratories, although there may be certain disadvantages, including barriers to access (table 1) [10]. Furthermore, relevant spirometric indices measured by trained family physicians or their staff may be marginally higher compared with pulmonary function laboratories [14]. In view of the limited agreement between laboratory and primary care practice FEV1 and forced vital capacity values, these measurements should not be used interchangeably [14].

The bottom line is that with sufficient training of family physicians and their staff, the current practice of performing spirometry in primary care seems justifiable. However the experience serves as a valuable insight into the clinical reality of performing spirometry on a larger scale in primary care practice. It is envisaged that the optimal method of ensuring quality spirometry will entail a close partnership between primary healthcare providers and specialised respiratory care. This integrated approach with specialist respiratory services is to be recommended, but it is unrealistic to expect this to become the state of the art universally overnight. The true challenge is to build the required infrastructure, in terms of equipment resource and adequate training and expertise. Although the magnitude of this challenge should not be underestimated, the published evidence [2, 14] points the way to widespread implementation of spirometry in primary care. The community of respiratory health professionals is at the start of a journey; the goals being to address the global burden of COPD as outlined by GOLD. Spirometry by family physicians, with due consideration to quality assurance, is quintessential to this process.

Table 1. – Advantages and disadvantages of different alternatives for organising spirometry in primary care

<table>
<thead>
<tr>
<th>Where spirometry performed</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice surgery</td>
<td>Least barriers to access</td>
<td>Reliability of measurements less certain</td>
</tr>
<tr>
<td></td>
<td>No extra healthcare costs</td>
<td>Extra workload for family practices</td>
</tr>
<tr>
<td></td>
<td>Least travelling distance for patients</td>
<td>Changes in practice organisation (often) necessary</td>
</tr>
<tr>
<td></td>
<td>Minimises number of patient visits (“one-stop shop”)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Results of spirometry integrated into first consultation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enables FPs to acquire expertise</td>
<td></td>
</tr>
<tr>
<td>Nurse-run asthma/COPD clinic</td>
<td>Good reliability of measurements</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Few access limitations</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
<tr>
<td></td>
<td>No extra workload for family practices</td>
<td>Timely feedback of spirometry results to family practice crucial</td>
</tr>
<tr>
<td></td>
<td>No high demands on spirometry expertise in family practices</td>
<td></td>
</tr>
<tr>
<td>PCG-commissioned spirometry service</td>
<td>Good reliability of measurements</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Few access limitations</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
<tr>
<td></td>
<td>No extra workload for family practices</td>
<td>Timely feedback of spirometry results to family practice crucial</td>
</tr>
<tr>
<td></td>
<td>No high demands on spirometry expertise in family practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Centralisation of interpretation of spirometry</td>
<td></td>
</tr>
<tr>
<td>Hospital-based pulmonary function laboratory</td>
<td>Optimum reliability of measurements</td>
<td>Possible access limitations a</td>
</tr>
<tr>
<td></td>
<td>No extra workload for family practices</td>
<td>Limited capacity next to regular tasks</td>
</tr>
<tr>
<td></td>
<td>No high demands on expertise in family practice</td>
<td>Extra healthcare costs</td>
</tr>
<tr>
<td></td>
<td>Facilitates consultation of specialist respiratory services a</td>
<td>(Considerable) travelling distance for patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Timely feedback of test results to family practice crucial</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; PCC: primary care group; FP: family practitioner. a depending on local cooperation with secondary care chest physicians. Table modified from [10].
true potential will only be achieved by ensuring that quality spirometry is widely available in primary care. This is a vital prerequisite to the success of both World Chronic Obstructive Pulmonary Disease Day and the larger Global Initiative for Obstructive Lung Disease (GOLD) strategic plan. Never before have all parties involved been better positioned to contribute towards this collective goal.

References

Chapter 7

Referral and consultation in asthma and COPD: an exploration of pulmonologists’ views

Published in: Neth J Med 2003;61(3):71-81
Referral and consultation in asthma and COPD: an exploration of pulmonologists’ views

T. Schermer, F. Smeenk, C. van Weel

ABSTRACT

Background: The burden of asthma and chronic obstructive pulmonary disease (COPD) on national healthcare systems is expected to increase substantially in future years. Referral guidelines for general practitioners (GPs) and pulmonologists may lead to more efficient use of healthcare facilities. We explored the prevailing views of pulmonologists regarding referral and once-only consultation in asthma and COPD, and compared these views with recently published transmural referral guidelines for GPs and pulmonologists.

Methods: Cross-sectional multiple case study. Twenty-nine Dutch pulmonologists working at non-university hospitals or specialised chest clinics participated in group discussion sessions.

Results: The outcome of the discussions and recently published referral guidelines for GPs and pulmonologists showed considerable similarity, but also some marked discrepancies. During the discussions, the main points of disagreement among the pulmonologists were: 1) should GPs or pulmonologists add long-acting $\beta_2$-agonists to asthma treatment regimens; 2) should the current cut-off point ‘predicted FEV$_1$ $<$50%’ for referral of COPD patients be increased to 60 or 70%; and 3) should an annual exacerbation rate of two episodes a year be used as an undifferentiated referral criterion for COPD patients? For asthma, proposed back-referral (i.e. from pulmonologist to GP) criteria rested on: required dose of inhaled steroids, persistent need for long-acting $\beta_2$-agonists, duration of clinical stability and persistence of airway obstruction. Back-referral criteria for COPD rested on age, blood-gas abnormalities and ventilatory limitations. Primary care monitoring facilities and ‘shared-care’ constructions were considered to be facilitating conditions for back-referral.

Conclusions: This explorative study provided insights into how pulmonologists visualise a rational referral policy for patients with asthma or COPD. These insights can be taken into consideration in future revisions of referral and back-referral guidelines for GPs and pulmonologists.

INTRODUCTION

Over the next few years, it is expected that a sharp increase will occur in the incidence and prevalence of asthma and chronic obstructive pulmonary disease (COPD) in many Western countries. Consequently, patients with these chronic pulmonary diseases will make steadily increasing demands on healthcare services. General practitioners (GPs) and pulmonologists will soon become aware of this, owing to the increasing time investment in these categories of patients. One of the major challenges for the near future is to achieve efficient use of available care facilities for asthma and COPD patients. Adequate referral policies from the GP to pulmonologist and back-referral to the GP form an inextricable part of this challenge. Although the theme ‘referral in asthma and COPD’ has been receiving increasing attention in the literature over the past few years and various guidelines have been put forward that contain concrete referral criteria, no research has been performed into the effectiveness of (alternative) referral policies for the two diseases. Nevertheless it is
METHODOLOGY

Between March 1999 and April 2000, four group discussion sessions were held with pulmonologists working at non-university hospitals or specialised chest clinics in four different regions of the Netherlands, to make an inventory of prevailing views within this professional group and to compare these views to the expert consensus recently reached in the national transmural agreements for asthma and COPD.11,12 As there is very little evidence-based information on which to base concrete referral criteria, these agreements (developed in the light of empirical findings and expert consensus) are the highest attainable at the present time. In the development of guidelines, it is of decisive importance to have intimate knowledge of daily practice; experts are often inclined to make too little allowance for this. In addition, it is important to be able to anticipate how new guidelines will be accepted by the workforce.13

A series of postgraduate courses enabled us to study the views of pulmonologists, regarding referral, back-referral and once-only consultation in asthma and COPD. The aim of the study was to make an inventory of prevailing views within this professional group and to compare these views to the expert consensus recently reached in the national transmural agreements for asthma and COPD.11,12

To ensure that a number of previously determined issues would be dealt with during the course of the discussions, two standardised cases were developed: one for asthma (see Table 1) and one for COPD. Step by step, a specific part of the initial case description was modified using a standard set of overhead sheets. In this semi-structured manner, two of the authors (F. Smeenk and C. van Weel) were able to bring various issues under discussion that play a role in referral and back-referral in asthma and COPD. Criteria from the general practice guidelines were incorporated into the discussions. The asthma case was always discussed first, followed by the COPD case. This approach was tested and modified in a pilot discussion session held with pulmonologists working in the Nijmegen region. With the pulmonologists’ consent, the discussions were recorded on audiotape. After the recordings had been typed out, two of the authors (T. Schermer and F. Smeenk) independently extracted conclusions from the discussions and classified them per theme. The themes for

<table>
<thead>
<tr>
<th>Table 1</th>
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</thead>
<tbody>
<tr>
<td>Asthma case used to structure group discussion sessions</td>
</tr>
</tbody>
</table>

**INITIAL CASE DESCRIPTION**

A 24-year-old non-smoking female cashier with a history of childhood asthma and atopic rash consults a GP. Renewed onset of respiratory symptoms (intermittent dyspnoea attacks, max. once a week) at age 20. Adequate symptom relief on salbutamol on an as-needed basis.

Should a GP refer this patient to a pulmonologist?

**FIRST MODIFICATION**

Additional diagnostic information is available: FEV₁ 2.56 l (73% of predicted value), FEV₁ reversibility after salbutamol 20% of predicted value, allergic response to house dust mite and pollen.

Should a GP refer this patient to a pulmonologist?

**SECOND MODIFICATION**

Frequency of respiratory symptoms increases from once a week to daily and symptoms are more severe. Salbutamol is needed every day.

Should a GP refer this patient to a pulmonologist?

**THIRD MODIFICATION**

Respiratory symptoms and salbutamol use are less frequent (once a week) with addition of budesonide 400 μg twice a day. Tapering off the budesonide dose is unsuccessful.

Should a GP refer this patient to a pulmonologist?

**SUBSEQUENT MODIFICATIONS COVER THE FOLLOWING ISSUES**

- Persistent or deteriorating airway obstruction
- (High) dose of inhaled corticosteroids
- Addition of a long-acting β₂-agonist
- Rapid deterioration of asthma condition
- Frequent asthma exacerbations
- Current smoking
- Food allergy
- Occupational exposure

reasonably to assume that if GPs follow an efficient referral policy, then superfluous specialist care will be prevented, while patients who do require specialist care will receive it all the sooner. If, at the same time, pulmonologists endeavour to refer patients back to their GPs as soon as they consider it medically justified, then optimal use will be made of their valuable time. Guidelines that dictate when referral is indicated contribute to more effective care. However, incorrect guidelines or recommendations that are poorly linked with daily practice can have an unfavourable effect.19 Therefore, the Dutch professional organisations of GPs and pulmonologists recently developed two transmural ‘agreements’, in which concrete recommendations are made about referral and back-referral of patients with asthma and COPD.7-9 As there is very little evidence-based information on which to base concrete referral criteria, these agreements (developed in the light of empirical findings and expert consensus) are the highest attainable at the present time. In the development of guidelines, it is of decisive importance to have intimate knowledge of daily practice; experts are often inclined to make too little allowance for this. In addition, it is important to be able to anticipate how new guidelines will be accepted by the workforce.13

A series of postgraduate courses enabled us to study the views of pulmonologists, regarding referral, back-referral and once-only consultation in asthma and COPD. The aim of the study was to make an inventory of prevailing views within this professional group and to compare these views to the expert consensus recently reached in the national transmural agreements for asthma and COPD.11,12 As there is very little evidence-based information on which to base concrete referral criteria, these agreements (developed in the light of empirical findings and expert consensus) are the highest attainable at the present time. In the development of guidelines, it is of decisive importance to have intimate knowledge of daily practice; experts are often inclined to make too little allowance for this. In addition, it is important to be able to anticipate how new guidelines will be accepted by the workforce.13

A series of postgraduate courses enabled us to study the views of pulmonologists, regarding referral, back-referral and once-only consultation in asthma and COPD. The aim of the study was to make an inventory of prevailing views within this professional group and to compare these views to the expert consensus recently reached in the national transmural agreements for asthma and COPD.11,12
asthma were medication and treatment targets, titration of the dose of inhaled corticosteroids, diagnosis and monitoring, and asthma exacerbations. The themes for COPD were lung function, exacerbations, treatment options, and diagnosis. Spirometry in general practice was considered as a separate theme. The results section describes the content of the discussions held in one or more of the sessions. The most important conclusions about referral and once-only consultation are summarised in tables. Explicit mention is made of all divergent views that became apparent during the discussion sessions. For the sake of simplicity, ‘he’ (read: he or she) is used in the text to refer to GPs, pulmonologists and patients.

RESULTS

Characteristics of the pulmonologists

All 29 pulmonologists were working at non-university hospitals or specialised chest clinics (28 men, one woman; mean age 46 ± 5.2 years; mean time since specialist qualification 14 ± 6.7 years). All indicated that they were familiar with the asthma and COPD guidelines issued by the Dutch College of General Practitioners. The pulmonologists estimated that on average, formal back-referral to general practice occurred in 51% (range 15 to 82%) of their asthma and COPD patients. Table 2 presents the criteria used for back-referral, subdivided into ‘global’ and ‘specific’ criteria. Existing arrangements with GPs regarding the reason for referral and consultation were once-only consultation to determine diagnosis (38%), assistance with spirometry interpretation (20%), shared-care (20%) and local protocol for referral/back-referral (7%).

Issues on referral and consultation in asthma

Medication and treatment targets

Referral by GP to pulmonologist: In the case of intermittent or mild asthma with (reversible) airway obstruction, GPs have sufficient means at their disposal to initiate treatment. If the treatment does not lead directly to visible improvement, a GP should not be too hasty in referring the patient to a pulmonologist: a minimum evaluation period of six months was recommended. If the a priori set treatment targets (table 3) are not reached within this period, then the GP can

### Table 2

Global and specific criteria used by participating pulmonologists (n=29) to refer asthma and COPD patients back to general practice care

<table>
<thead>
<tr>
<th>GLOBAL CRITERIA</th>
<th>ASTHMA</th>
<th>SPECIFIC CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable asthma condition</td>
<td>(13, 45%)</td>
<td>P_{C_{20}} &gt; 8 mg/ml (4, 7%)</td>
</tr>
<tr>
<td>Lung function parameters</td>
<td>(7, 25%)</td>
<td>Stable lung function &gt; 1 year (4, 7%)</td>
</tr>
<tr>
<td>Well-regulated medication use</td>
<td>(4, 14%)</td>
<td>Competence of GP in question (2, 7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLOBAL CRITERIA</th>
<th>COPD</th>
<th>SPECIFIC CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable COPD condition</td>
<td>(13, 45%)</td>
<td>FEV₁ &gt; 60% of predicted value and clinically stable (2, 7%)</td>
</tr>
<tr>
<td>Lung function parameters</td>
<td>(7, 25%)</td>
<td>FEV₁/VC &gt; 50% of predicted value (2, 7%)</td>
</tr>
</tbody>
</table>

Figures in brackets represent the number and proportion of participants that indicated the particular criterion, respectively.

### Table 3

Treatment targets and indications for (once-only) consultation with a pulmonologist in adult patients with asthma, according to the national guidelines of the Dutch College of General Practitioners

<table>
<thead>
<tr>
<th>TREATMENT TARGETS IN PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No, or only minor asthma symptoms, acceptable night’s rest, (nearly) normal daily activities</td>
</tr>
<tr>
<td>As few interventions as possible, minimal or no side effects of asthma medication</td>
</tr>
<tr>
<td>Prevention or timely treatment of asthma exacerbations</td>
</tr>
<tr>
<td>Achieving and preserving optimal lung function</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INDICATIONS FOR (ONCE-ONLY) CONSULTATION WITH A PULMONOLOGIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent use of high-dose inhaled steroids without being able to taper off; treatment targets cannot be achieved on this regimen</td>
</tr>
<tr>
<td>Continuous use of high-dose inhaled steroids or moderately high dose of inhaled steroids combined with a long-acting β₂ agonist</td>
</tr>
</tbody>
</table>
increase the dose of inhaled steroids or add a long-acting β₂-agonist. If no progress is made during the new evaluation period with this combination therapy, then referral to the pulmonologist is indicated. The phase in which lung medication is initiated depends on the degree to which the GP decides to extend the medication himself. In one of the discussion groups, the prevailing view was that (partial) substitution of an inhaled steroid for a long-acting β₂-agonist should be performed by the pulmonologist, not by the GP.

In any case, before deciding to administer long-acting medication, the GP should first reconsider his diagnosis of asthma. If after repeating the anamnesis and supplementary peak flow measurements there is still doubt about the accuracy of the diagnosis, then a once-only diagnostic consultation with the pulmonologist can be requested.

**Tapering off the dose of inhaled steroids**

Referral by GP to pulmonologist: The maintenance dose of inhaled steroids is in itself a factor that should play a role in the GP’s decision as to whether or not to refer the patient. Upper dose limits of 800 to 1000 µg of budesonide or beclomethasone, or 500 µg of fluticasone a day, as recommended in the current Dutch GP guidelines, were considered to be acceptable referral criteria by the pulmonologists. At higher doses, the risk of systemic side effects can form an indication for referral.

Several of the pulmonologists had the impression that GPs are often reluctant to administer long-term maintenance treatment with inhaled steroids; they seem to have the tendency to prematurely taper off the dose. Once again, the factor time should play a role. If a GP decides to taper off a moderately high maintenance dose (800 to 1000 µg a day) in a stable asthma patient, but is unable to do so over a period of two years, then the risk of long-term side effects can form an indication for referral. Most pulmonologists were of the opinion that if the GP is certain of the diagnosis and has excluded all possible trigger factors, he can first add a long-acting β₂-agonist and then subsequently try to taper off the dose. If it still proves impossible to reduce the dose of steroids, then a once-only consultation with the pulmonologist can be requested to check whether any trigger factors have been missed. Several of the discussions revealed that owing to the fact that referral information from the GP does not always offer sufficient footing, it might not be possible to gain an adequate overview during a once-only consultation.

Back-referral from pulmonologist to GP: During consultation with an asthma patient, the pulmonologist provides further confirmation of the diagnosis and treatment, and establishes the minimum required maintenance dose of medication. On the basis of the histamine threshold, he evaluates whether the inhaled steroid dose can be tapered off. In the majority of cases, it is possible to refer the patient back to the GP with clear treatment instructions and recommendations for frequency-of-monitoring visits. Adaptation of a medication regime by the pulmonologist should always include a period of intensive spirometry or peak flow measurements which, in principle, the GP can undertake. When a patient in the care of a pulmonologist has become clinically stable on an 800 to 1000 µg daily dose of inhaled steroids, he can normally be referred back to his GP.

Even at higher doses, back-referral does not need to be a problem if the patient has been stable for some time. In only one of the discussion groups was the term ‘stable’ further specified as: normal lung function and very few respiratory symptoms, while the steroid dose is clearly based on the minimum required dose. The main reasons mentioned by the pulmonologists for not referring asthma patients back to the GP are given in *table 4*. If a patient is using an inhaled steroid dose of more than 800 to 1000 µg a day (with or without addition of a long-acting β₂-agonist) the pulmonologist can decide to monitor the patient himself. However, cooperation with the GP in the form of a shared-care construction is also possible, although structured communication between the pulmonologist and GP is essential in this situation.

**Diagnosis and monitoring**

Referral by GP to pulmonologist: In the majority of cases, the GP can make the diagnosis of asthma himself using peak flow measurements. Spirometry in patients with suspected asthma only has additional value when previously conducted peak flow measurements have shown that the patient has reversible airway obstruction or day-night variability. In asthma patients who have very few respiratory symptoms but show persistent airway obstruction, despite adequate treatment with inhaled steroids, there seems to be an indication for referral. Stipulations for referral are that the obstruction must in principle be fully reversible and there must be an obvious discrepancy between lung function and respiratory symptoms. Relatively young patients with persistent airway obstruction that does not subside after a ‘diagnostic’ course of oral steroids should be referred to the pulmonologist for further testing. Other reasons mentioned for referral are given in *table 4*.

Back-referral by pulmonologist to GP: The discussions showed that pulmonologists do not tend to refer patients back to general practice on the basis of hard evidence alone. The feeling that the pulmonary condition is stable plays a more important role. When the pulmonologist refers the patient back, he expects the patient to be monitored by his GP in accordance with the current asthma guidelines for GPs. It therefore depends on the GP in question whether the pulmonologist refers the patient back or not, especially in patients whose monitoring is of an urgent nature.
### Table 4

**Summary of statements concerning referral and once-only consultation in asthma, derived from four discussion sessions with non-university pulmonologists (n=29)**

<table>
<thead>
<tr>
<th>DESCRIPTION OF STATEMENT</th>
<th>NO. MEETINGS IN WHICH ITEM CAME UP⁴</th>
<th>PRO/CON⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Situations in which GPs should consider (once-only) consultation with a pulmonologist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider referral if:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attempts to taper off a high dose of inhaled steroids (&gt;800-1000 µg budesonide or beclomethasone, &gt;500 µg fluticasone) are unsuccessful after two years</td>
<td>4</td>
<td>(4/0)</td>
</tr>
<tr>
<td>(Partial) substitution of inhaled steroids by a long-acting β₂-agonist is considered</td>
<td>4</td>
<td>(1/3)</td>
</tr>
<tr>
<td>Poor medication compliance, ill-avoided lifestyle or other patient-centred causes for recurrent exacerbations despite sufficient attention from the GP</td>
<td>4</td>
<td>(4/0)</td>
</tr>
<tr>
<td>Persistent asthma symptoms coinciding with normal lung function, despite otherwise adequate treatment with inhaled steroids</td>
<td>3</td>
<td>(3/0)</td>
</tr>
<tr>
<td>≥3 asthma exacerbations a year, each requiring treatment with oral prednisolone, without an identified trigger for the high exacerbation rate</td>
<td>3</td>
<td>(3/0)</td>
</tr>
<tr>
<td>No clinical improvement is observed six months after adjustment of the asthma medication regime</td>
<td>2</td>
<td>(2/0)</td>
</tr>
<tr>
<td>Consider once-only consultation if:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent diagnostic uncertainty, even after repeating medical history taking, elimination of all possible trigger factors and additional peak flow monitoring</td>
<td>4</td>
<td>(4/0)</td>
</tr>
<tr>
<td>Doubt about the feasibility of tapering off inhaled steroids</td>
<td>4</td>
<td>(4/0)</td>
</tr>
<tr>
<td>Persistent airway obstruction after a diagnostic prednisolone course at relatively young age</td>
<td>3</td>
<td>(3/0)</td>
</tr>
<tr>
<td>Drastic allergen avoidance measures are inevitable</td>
<td>2</td>
<td>(2/0)</td>
</tr>
<tr>
<td><strong>Situations in which pulmonologists should consider back-referral to a GP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider referring back if:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A patient has been clinically stable for 1.5 to 2 years on a low to moderately high dose of inhaled steroids (≥800-1000 µg budesonide/beclomethasone, ≥500 µg fluticasone)</td>
<td>3</td>
<td>3/0</td>
</tr>
<tr>
<td>A patient has been clinically stable for 1.5 to 2 years on a high dose of inhaled steroids (&gt;800-1000 µg budesonide/beclomethasone, &gt;500 µg fluticasone), with or without a long-acting β₂-agonist, provided that the GP supervises the monitoring schedule, or a solid shared-care construction is available</td>
<td>3</td>
<td>3/0</td>
</tr>
<tr>
<td>None of the following are applicable:</td>
<td>1</td>
<td>1/0</td>
</tr>
<tr>
<td>Persistent necessity for the combination high-dose inhaled steroid + long-acting β₂-agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent airway obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma-related hospital admission &lt;1.5 to 2 years ago</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statements are ranked by the number of meetings in which each particular issue was discussed. ¹ Minimum 1, maximum 4. ² PRO-prevailing view during session in favour of statement; CON-prevailing view during session against statement; ³ in one session specified as ‘normal lung function, few respiratory symptoms and inhaled steroids adjusted to the lowest possible effective dose’.*

### Asthma exacerbations

Referral by GP to pulmonologist: If an asthma patient is undergoing optimal monitoring by the GP but suffers three or more exacerbations a year that require prednisolone, then referral to a pulmonologist is indicated. In cases with a clear explanation for the recurrent exacerbations, referral does not seem to be so worthwhile. If the GP is unable to identify the triggering factor in a patient with recurrent exacerbations, then referral is indicated. Two of the discussion sessions revealed that some of the pulmonologists felt that particularly patients with persistent symptoms were referred to them relatively quickly, whereas patients who needed several courses of prednisolone a year but expressed very few respiratory symptoms were not referred until the prednisolone became less effective.

Several pulmonologists suggested that GPs are sometimes too premature with administering courses of prednisolone, without first attempting to identify the underlying cause of the exacerbation. If there is no relevant improvement or persistent deterioration occurs while a patient is receiving optimally regulated maintenance treatment, then the GP should not wait too long before referring the patient to a pulmonologist.
Although the current GP guidelines recommend that an asthma patient should be referred to a pulmonologist in the case of two or more exacerbations a year, it seems to be difficult – if not impossible – in practice to establish a general absolute cut-off point. The specific circumstances of the patient and the existence of a possible explanation for a high exacerbation rate are strong determinants. In addition, the degree to which the asthma patient himself is responsible for ‘aggravating’ his asthma can play a role in the GP’s decision whether or not to refer the patient.

Back-referral by pulmonologist to GP: If a patient has recently suffered an acute severe asthma attack, it is advisable for him to remain under the care of the pulmonologist for a fairly long time. An evaluation period of 18 to 24 months was mentioned as a rule of thumb in several of the discussion groups, irrespective of whether the patient has become clinically stable on a maintenance dose of inhaled steroids. After the evaluation period the pulmonologist can consider referring the patient back to the GP. If he decides to refer the patient back, he should preferably give the most concrete possible advice about the further management policy.

Conclusions regarding referral and consultation in asthma are summarised in table 4.

Issues on referral and consultation in COPD

Lung function, exacerbations and treatment options

Referral by GP to pulmonologist: In all discussion groups the pulmonologists made it clear that when making a referral decision, GPs should not only take the Dutch GP guidelines (table 5) into consideration, but also the respiratory symptoms and possible discrepancies between these symptoms and clinical presentation. In the GP guidelines, the lung function criteria for referral are an FEV1 <50% of the predicted value and/or an FEV1 <1.5 litres. An important point of discussion in relation to these criteria was that a COPD patient who has not (yet) dropped under these cut-off levels will develop problems at some stage, which will persist for the rest of his life. If the GP does not establish any relevant baseline values for lung function, then the pulmonologist should be given the opportunity to do that for him.

The pulmonologists held the view that COPD patients with moderate to severe airway obstruction, but a discrepancy between respiratory symptoms and clinical presentation, should always be referred. Although there is evidence in the literature that the prognosis deteriorates when lung function falls below the above-mentioned FEV1 cut-off levels, it is not clear whether earlier referral has any additional value. However, owing to the fact that, depending on the specific circumstances, multiple problems can be expected in patients with moderate to severe airway obstruction in a relatively early stage of the disease, earlier referral is desirable, for instance at FEV1 <60% of the predicted value. In any case, GPs must be encouraged not to wait until the FEV1 has fallen below 50% before they refer a COPD patient. A possible disadvantage of lowering the referral limit is the considerable increase in burden on specialist care. Furthermore, the pulmonologists agreed that GPs should not base their referral decision only on FEV1 values. FEV1 alone is not sufficient to characterise a COPD patient, although in practice, this is all the GPs have to go on. Discussions on the role of exacerbations revealed that in the case of frequent exacerbations (i.e. two or more exacerbations a year), there are two arguments in favour of referral by the GP: evaluation of the causal factors and the risk of side effects from frequent prednisolone courses.

Bronchial hyperresponsiveness in COPD patients not only forms a prognostic factor, it can also be used to identify the (relatively small) group of COPD patients that also have...
features of asthma. With changing insights into the role of inhaled steroids in COPD it remains to be seen whether in the future, GPs should also consider the degree of bronchial hyperresponsiveness in their decision to prescribe inhaled steroids. As pulmonologists are better able to distinguish between subgroups than the GP, some patients might not receive maximum benefit from the existing treatment options during the years that are lost prior to referral. In two of the sessions, discussion arose about whether pulmonologists have more means at their disposal than GPs to help COPD patients quit smoking. Perhaps pulmonologists in their capacity as medical specialists have greater authority in the patient’s view, but in principle, the GP should be able to achieve the same results.

Back-referral by pulmonologist to GP: Pulmonologists should include the factor (advanced) age in their decision about whether or not to refer COPD patients back to general practice. Otherwise there is the risk that the outpatient clinic will ‘fill up’ with elderly COPD patients. If these elderly patients can manage on their regular maintenance treatment supplemented with a course of prednisolone now and again, then the pulmonologist has little more to offer than the GP. However, it is better for patients with gas transfer abnormalities to remain under the care of the pulmonologist, although a shared-care construction can also be considered, in which the GP monitors the patient and specially trained COPD nurses provide assistance. If the pulmonologist refers a patient on oral theophylline back to his GP, then it is important that he realises that the GP guidelines do not contain any recommendations about this treatment. Therefore his advice should include clear instructions. If the pulmonologist has tried in vain to stop the theophylline, this should also be mentioned explicitly in the back-referral letter.

**Diagnosis**

**Referral by GP to pulmonologist:** Although the GP himself can refer a patient for supplementary tests (e.g. chest X-ray), referral to a pulmonologist might be worthwhile to exclude malignancy or to ‘map’ the patient’s status on the basis of carbon monoxide diffusion capacity, blood gases, respiratory mechanics and ergometry. In every COPD patient with moderately severe airway obstruction (FEV1 50 to 70% of the predicted value) the GP should consider referral for a once-only (diagnostic) consultation. The pulmonologist can map the patient’s lung function more extensively and evaluate unfavourable prognostic factors. When they refer a patient just for spirometry and the accompanying interpretation of the pulmonologist, GPs also expect to receive concrete information about the diagnosis and advice about treatment. As the pulmonologist only sees the spirometry test results and not the patient himself, this is not an ideal situation. Within the discussion groups the participants clearly expressed preference for ‘evaluation mapping’ by the pulmonologist in such circumstances, in which he personally sees the patient (at least) once.

Back-referral by pulmonologist to GP: A COPD patient cannot be referred back to the GP on the basis of lung function criteria alone. It is important for the pulmonologist to gain insight into the impact of COPD on the patient’s daily functioning so that he can give the GP more detailed advice about treatment. In the case of moderately to severely disturbed diffusion capacity, continuation of regular monitoring by the pulmonologist takes preference over referral back to the GP. Although the spirometry and ventilatory parameters might be borderline normal, these patients are approaching the level of permanent invalidity. In patients with ventilatory limitations, hypoxaemia and/or hypercapnia on exertion, it is preferable for the pulmonologist to continue seeing the patient for checkups. If the patient is subjectively and objectively stable and the pulmonologist considers it possible to transfer the checkups to the GP, then he can refer the patient back. The pulmonologist can, for example, advise the GP to refer the patient to a lung function laboratory for periodical supplementary testing.

Conclusions regarding referral and consultation in COPD are summarised in table 6, see page 78.

**Discussion**

The results of this explorative study sketch a useful profile of the views of Dutch pulmonologists regarding the widespread theme: referral and consultation in asthma and COPD. Although previous research has shown that questionnaires can be used to make such inventories, it has also become clear that they are unable to map nuances. The present qualitative study design offered the opportunity to explore the major issues and discussion points surrounding this complex theme in fairly great detail. However, it is possible that the selection of regions influenced the findings: our survey did not include all the separate regions of the Netherlands. If regionally determined variations exist in referral and back-referral policies and views, then this may have affected the direction of the results. In addition, the discussions, despite uniform structuring by means of the standardised case descriptions on an overhead sheet, were kept fairly open. It is therefore possible that not all prevailing views were expressed, as certain topics received less attention.

One of the most important findings in this study was that broadly speaking, Dutch pulmonologists approved
the contents of the GP guidelines and the transmural agreements published by their own, and the GPs' professional organisations. However, they clearly had their own professional views about referral by GPs and subsequent back-referral. Another important conclusion is that it is reasonably easy to formulate univocal referral criteria for asthma; the literature and empiricism offer sufficient points of application for this. In contrast, this task is much more complex for COPD. According to the pulmonologists, there are so many individual, patient-related factors that can play a role in the GP’s decision to refer a patient with COPD that it is very difficult to devise strict criteria. On the one hand, this situation is inconsistent with the referral limit of an FEV₁ <50% of the predicted value or FEV₁ <1.5 litre currently recommended, because this cut-off point still leads to many discussions between GPs and pulmonologists. On the other hand, it is not clear whether the pulmonologists justifiably expressed concern that GPs wait until the FEV₁ has deteriorated to the recommended cut-off point. A possible solution was the proposal to refer all COPD patients with an FEV₁ of 50 to 70% of the predicted value (‘moderate obstruction’) to a pulmonologist for once-only evaluation mapping of diffusion capacity, blood gasses, etc. This policy is in line with the position held by Dutch pulmonologists regarding detection of the group of COPD patients with moderate to severe bronchial hyperresponsiveness. In this way, pulmonologists can evaluate the presence of an asthma component in the cause of airway obstruction and the indication for inhaled steroid treatment.

Comparison with published Dutch transmural agreements
Nine months after the last discussion session was held, the Dutch professional organisations of GPs and pulmonologists published their joint transmural agreements for asthma and COPD, which include detailed recommendations on referral and back-referral for GPs as well as pulmonologists. In many respects, the contents of the transmural agreements are in line with the existing asthma and COPD guidelines for GPs. The outcomes of our discussion sessions and the transmural agreements showed considerable

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**Table 6**

**Summary of statements concerning referral and once-only consultation in COPD, derived from four discussion sessions with non-university pulmonologists (n=29)**

<table>
<thead>
<tr>
<th>DESCRIPTION OF STATEMENT</th>
<th>NO. MEETINGS IN WHICH ITEM CAME UP</th>
<th>PRO/CON</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Situations in which GPs should consider (once-only) consultation with a pulmonologist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider referral if: FEV₁ &lt;50% of predicted value or FEV₁ &lt;1.5 litre</td>
<td>4</td>
<td>3/1²</td>
</tr>
<tr>
<td>FEV₁ value ≥50% of predicted value or FEV₁ ≥1.5 litre, but persistent respiratory symptoms or a discrepancy between symptoms and the clinical profile</td>
<td>4</td>
<td>4/0</td>
</tr>
<tr>
<td>≥2 exacerbations a year, in order to evaluate causal factors and assess the risk of side effects due to frequent prescription of prednisolone courses</td>
<td>3</td>
<td>1/2²</td>
</tr>
<tr>
<td>Consider once-only consultation if: FEV₁ is 50 to 70% of predicted value, in order to enable the pulmonologist to map relevant baseline parameters (e.g. TLCO, blood gasses)</td>
<td>3</td>
<td>3/0</td>
</tr>
<tr>
<td>The GP anticipates that the probability of successful smoking cessation may be higher when supervised by a pulmonologist</td>
<td>2</td>
<td>2/0</td>
</tr>
<tr>
<td>Determine whether treatment with inhaled steroids is appropriate, based on measurement of bronchial hyperresponsiveness</td>
<td>2</td>
<td>2/0</td>
</tr>
</tbody>
</table>

| **Situations in which pulmonologists should consider back-referral to a GP** | | |
| Consider referring back if: None of the following are applicable: | 2 | 2/0 |
| Presence of moderate to severe gas transfer abnormalities (except when a high-quality shared-care construction is guaranteed) | |
| Presence of ventilatory limitations | |
| Presence of hypoxaemia and/or hypercapnia | |
| An elderly patient is managing sufficiently well on the established maintenance treatment and an occasional oral prednisolone course | 1 | 1/0 |

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Statements are ranked by the number of meetings in which each particular issue was discussed. Minimum 1, maximum 4. PRO=prevailing view during session in favour of statement; CON=prevailing view during session against statement; in two sessions, the participants were in doubt whether it is appropriate to assert one cut-off point concerning annual exacerbation rate in all patients with COPD; in one session a cut-off point of 60% of the predicted FEV₁ value was proposed; TLCO = diffusing capacity for carbon monoxide.
similarly, but also some marked discrepancies. For asthma, the most notable discrepancies were:

- the issue of tapering off inhaled steroids does not come up at all in the agreement, whereas it was a major issue in all discussion sessions;
- GPs should wait longer (i.e. six instead of three months) after adjustment of an asthma medication regime before concluding that no clinical improvement has been achieved;
- GPs should first try to identify underlying triggers for (recurrent) asthma exacerbations before referring a patient to a pulmonologist;
- GPs should refer an asthma patient for once-only consultation in case drastic allergen avoidance measures are planned;
- pulmonologists should take longer (i.e. 18 to 24 months instead of 3 to 12 months) before referring clinically stable asthma patients back to their GP, regardless of the maintenance dose of inhaled steroids.

The transmural COPD agreement comprises more (and far more detailed) recommendations regarding referral and back-referral compared with the pulmonologists’ views expressed during the discussion sessions. As indicated above, some notable additions were suggested: referral of patients with a predicted FEV\textsubscript{1} of 50 to 70% for once-only (diagnostic) consultation to map relevant baseline characteristics; once-only consultation of a pulmonologist to evaluate the indication for inhaled steroid treatment on the basis of bronchial hyperresponsiveness.

Referral and efficiency of care

Although there is only one indication in the literature that a structured referral policy can result in more efficient asthma care, we do not know which set of referral criteria leads to the most efficient care for asthma patients. No studies have been performed on COPD in this area. Therefore for the time being, guidelines for referral and consultation in asthma and COPD can be based solely on common sense and consensus. It is particularly for this reason that the findings in this study may offer useful leads for authors who are formulating or revising referral guidelines. The fact that the pulmonologists from the study regions could apparently hold different views about who should be responsible for substituting inhaled steroids for a long-acting \(\beta_2\)-agonist can in practice form a barrier against accepting asthma guidelines. Most pulmonologists agreed that an 800-1000 \(\mu\)g dose of inhaled steroids was a useful referral criterion, which provides support for the current GP guidelines and transmural agreement. The additional referral criteria for GPs proposed in the discussions about asthma (see Table 4) can be taken into consideration when devising or revising guidelines. It is possible that clear formulation of the reason for referral and clear presentation of the question – something that was often missing according to our study participants – would contribute to more efficient care. In the literature, it is stated that in at least 15% of all referrals, the nature of the problem remains obscure.

GPs’ diagnostic uncertainty and the value of spirometry

In one of the discussion groups it was stated that when asthma is suspected, spirometry only has supplementary value if the GP finds reversible airway obstruction or day-night variability using peak flow measurements. Because airway obstruction – or its reversibility – can be detected more effectively with spirometry than with peak flow measurements, this is doubtful. As a steadily increasing number of GPs are setting up their own spirometry facilities, the value of peak flow measurements is decreasing. However, negative findings on supplementary tests (i.e. normal peak flow, absent peak flow variability, normal spirometry), while the GP nevertheless has clinical suspicions of asthma, can form a relevant referral indication. In such a case, supplementary tests by the pulmonologist have clear additional value: if the histamine threshold is normal, then clinical asthma is almost certainly excluded and the GP can continue his search within the differential diagnosis. During the discussions, the pulmonologists laid great emphasis on the ‘degree of certainty’ about the diagnosis asthma. Recent studies have also shown that this should be an important point of attention for GPs. For instance, Marklund \textit{et al.} found that GPs’ diagnoses of asthma could not be confirmed by an allergologist in 34% of the patients. In addition, 77% of the patients were found to have a combined diagnosis of asthma and COPD, which the GP had not recognised. Primary care research by Pinnock \textit{et al.} showed that spirometric re-evaluation of COPD patients led to a different (spirometric) diagnosis in 35% of the cases.

Back-referral to general practice and ‘shared-care’

The suggestion made to stimulate pulmonologists to refer asthma patients back to general practice once their lung function has normalised, they have few respiratory symptoms and inhaled steroids have been reduced to the lowest possible maintenance dose is of particular interest. This also applies to the exclusion criteria mentioned in the discussions, an asthma-related hospital admission less than two years previously and the persistent need for combined treatment with high-dose inhaled steroids and a long-acting \(\beta_2\)-agonist. The support that seems to exist among pulmonologists for cooperation with GPs in the form of shared-care is an extra reason to stimulate such constructions for the group of more complex asthma and COPD patients. However, the term ‘more complex’ should be clearly defined, because research has shown that shared-care in a large group of asthma patients as a whole did not prove to be more effective than full specialist treatment, even though the financial cost was considerably lower.
In the discussion about when pulmonologists should refer COPD patients back to general practice, it was concluded that guidelines can only offer a certain amount of footing, because the pulmonologist's own 'feeling' must continue to play a major role. Although it is difficult to lay down hard criteria, the view that patients with moderately to severely disturbed diffusion capacity, ventilatory limitations, hypoxaemia and/or hypercapnia on exertion should remain under the care of the pulmonologist, is relevant within this framework.

Communication and mutual expectations by GPs and pulmonologists

Research into referral and consultation in patients with chronic respiratory diseases has received little attention in the literature. Recently, Li et al. performed a survey in the USA on 37 GPs to gather information on the prevailing customs, preferences and expectations when referring asthma patients. Although the GPs who participated were not at all representative for the 'average' GP (all the respondents had affiliations with the university that conducted the survey), a striking finding in the study was that the majority of referrals to pulmonologists were written at the patient's own request. A satisfied patient and clear, applicable recommendations from the pulmonologist appeared to be the prevailing expectations of the GPs. Research in Canada by Langley et al. showed that the geographic distance to specialist care and the relationship between GP and specialist were important factors in the GP's decision whether or not to refer a patient. The study concerned not only asthma and COPD patients, but referrals by GPs in general. The view expressed in the current study that pulmonologists should give clear advice about the treatment policy when referring patients back to the GP is in line with the findings in other studies. Williams et al. reported that pulmonologists and GPs in the USA are of the opinion that the information supplied when a patient is referred is too often inadequate or unclear.

Primary care research has shown that GPs follow referral guidelines for asthma and COPD only to a limited extent. Jans et al. reported that the guidelines for referral to the pulmonologist were followed by the GP in only 17% of the cases with an indication. Doubt about the value of referral in individual cases was the most important reason for this. Studies have also shown that referral behaviour of GPs can be influenced positively, although it is not yet clear which intervention method is the most effective.

CONCLUSION

This explorative study provided insight into how non-academic pulmonologists visualise a rational referral policy for asthma and COPD patients. Although the outcome of the discussions and the recently published GP guidelines and transmural agreements showed considerable similarity, we also observed some marked discrepancies. To achieve optimal integration of published referral guidelines into daily practice the insights of this study should be taken into consideration during future revisions of referral guidelines for patients with asthma or COPD.

ACKNOWLEDGEMENT

The authors wish to thank Novartis Pharma BV (Arnhem, the Netherlands) for initiating and organising the post-graduate courses for pulmonologists.

REFERENCES

Chapter 8

Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial

*Published in:* Thorax 2003;58:30–36
Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial

B P A Thoonen, T R J Schermer, G van den Boom, J Molema, H Folgering, R P Akkermans, R Grol, C van Weel, C P van Schayck

Background: A study was undertaken to determine the effectiveness of asthma self-management in general practice.

Methods: Nineteen general practices were randomly allocated to usual care (UC) or self-management (SM). Asthma patients were included after confirmation of the GP diagnosis. Follow up was 2 years. Patients kept diary cards and visited the lung function laboratory every 6 months. Outcomes were number of successfully treated weeks, limited activity days, asthma specific quality of life, forced expiratory volume in 1 second (FEV1), FEV1 reversibility, concentration of histamine provoking a fall in FEV1 of 20% or more (PC20 histamine), and amount of inhaled steroids.

Results: A total of 214 patients were included in the study (104 UC/110 SM; one third of the total asthma population in general practice); 62% were female. The mean percentage of successfully treated weeks per patient in the UC group was 72% (74/103 weeks) compared with 78% (81/105 weeks) in the SM group (p=0.003). The mean number of limited activity days was 1.2 (95% CI 0.5 to 1.9) in the SM group and 3.9 (95% CI 2.5 to 5.4) in the UC group. The estimated increase in asthma quality of life score was 0.10 points per visit in the UC group and 0.21 points per visit in the SM group (p=0.055). FEV1, FEV1 reversibility, and PC20 histamine did not change. There was a saving of 217 puffs of inhaled steroid per patient in favour of the SM group (p<0.05).

Conclusion: Self-management lowers the burden of illness as perceived by patients with asthma and is at least as effective as the treatment usually provided in Dutch primary care. Self-management is a safe basis for intermittent treatment with inhaled corticosteroids.

Asthma is a chronic inflammatory pulmonary disease which has a significant socioeconomic impact on patients and their families.1 The finding that airway inflammation is the key underlying process in asthma has led to recommendations that inhaled corticosteroids should be introduced early in the management of the disease.2–5 Despite these guidelines and increasing knowledge, asthma morbidity is still considerable. Poor compliance with prescribed inhaled treatment is an important cause of uncontrolled disease.6–10 Poor control of asthma is associated with an impaired quality of life11–13 and is calculated to be responsible for three quarters of the total costs of asthma.1 It is therefore likely that improving compliance with treatment will lead to improvements in asthma control and quality of life. Low compliance results in underuse of medication, but asthma is also characterised by overuse, particularly of inhaled medication. Overuse of inhaled steroids may increase the number of unwanted side effects without additional benefits. There are indications that inhaled steroids can be tapered off or stopped during certain periods,14 or at least reduced to the minimal effective daily dose that provides adequate control of the disease.15 Optimising treatment for the individual patient may balance benefits and risks and lead to a more efficient and cost effective treatment.

Patients with mild asthma treated by their general practitioner (GP) may be suitable for intermittent treatment,16 providing adequate control of their asthma is maintained. Implementing guided self-management takes a considerable effort17 and studies on effectiveness and use in general practice are needed. Most published studies have shown self-management to be effective in patients with more severe asthma or those with frequent exacerbations,18 and it is unknown whether guided self-management may also be effective in patients with milder asthma. Loss of asthma control occurs less frequently and there is lower impact on quality of life,19 leaving limited room for improvement. The aim of this study was to determine if guided self-management can provide a safe treatment strategy for asthmatic patients in general practice.

METHODS

Practices
General practices were recruited from two pools; the first were in and around the city of Eindhoven and the second were practices from our department’s academic research network. Recruitment was stopped when a sufficient number of participating practices was reached. Practices rather than individual patients were randomised to prevent contamination. To prevent management bias, stratified cluster randomisation was performed based on the type of practice (one GP, two GPs, group practice), the number of identified asthmatics (above or below the median number (14) of identified patients), and use of computerised prescriptions (yes, no).

Selection of patients
GPs identified all asthma patients aged between 16 and 60 years using problem list coding (ICPC), prescription data from practice records, the annual influenza vaccination campaign list, and prescription data provided by the local pharmacist. Identified patients received an invitation letter from their GP to participate in the study. Patients willing to participate were invited for assessment in a lung function laboratory. Inclusion and exclusion criteria are summarised in box 1. Inclusion criteria were measured for all patients without exclusion criteria. Patients with a pre-bronchodilator forced expiratory volume in 1 second (FEV1) of <80% predicted were treated with 800 μg budesonide twice daily during a 6 week run in period
Asthma patients as usual; for most GPs this is according to the national guidelines for treatment of asthma. Both groups received regular inhalation instructions.

Outcome measures
The main outcome measures of the study were asthma control, asthma specific quality of life, and lost activity days. Asthma control was defined using the following parameters:

- percentage of successfully treated weeks;
- changes in bronchodilator FEV₁ (800 µg salbutamol once daily through spacer);
- changes in reversibility of FEV₁ as percentage of the predicted value; and
- changes in concentration of histamine provoking a fall in FEV₁ of 20% or more (PC₂₀ histamine).

Patients visited the lung function laboratory every 6 months over a period of 2 years. Diary cards were collected and checked for errors. At each visit post-bronchodilator FEV₁, reversibility, and asthma specific quality of life were measured. PC₂₀ histamine was measured at baseline and after 2 years. Assessors were not blinded to study group allocation.

A successfully treated week was defined as a week in which acceptable asthma control in terms of perceived dyspnoea was maintained. Patients in both groups weekly recorded dyspnoea on a modified Borg scale ranging from 0 (no dyspnoea) to 10 (maximally severe dyspnoea). The median dyspnoea score of all individual recordings was considered as the cut off point between successfully and unsuccessfully treated weeks. Weeks with a dyspnoea score equal to or below this cut off point were counted as successful. Successfully treated weeks were calculated if patients had recorded at least 52 weeks. To correct for differences in the number of recorded weeks, successfully treated weeks were standardised to the percentage of recorded weeks. An example of this procedure is summarised graphically for one patient in fig 1. In addition to the dyspnoea scores, patients weekly recorded the number of days during which asthma symptoms were inadequately controlled. The dyspnoea score of 32 weeks were calculated if patients had recorded at least 52 weeks.

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observed standard deviation of 0.9, a power of 90% and an interclass correlation of 0.02. With an average inclusion of 10 patients per practice, we assumed being considered clinically relevant. Based on multilevel analysis, we assumed an average inclusion of 10 patients per practice and an interclass correlation of 0.02. With an observed standard deviation of 0.9, a power of 90% and an \( \alpha \) of 0.05 (two sided), 17 practices with a total number of 170 patients were needed. After taking into account a drop out rate of 20%, it was calculated that 213 patients were needed.

**Analysis of data**
Outcome parameters were evaluated on an intention to treat basis and by repeated measurement techniques.\(^7\) A random coefficient linear model (multilevel) with an autoregressive error structure was performed on post-bronchodilator FEV\(_1\) and AQLQ scores. Reversibility of FEV\(_1\) (\% predicted value) was analysed in a similar non-linear model. Baseline values, age, sex, and smoking were entered as possible confounders. All analyses were performed using the PROC MIXED procedures by SAS.\(^7\) Transformed PC\(_{20}\) values (\(\log \) PC\(_{20}\)) were compared with a Student’s \(t\) test. If there was a significant difference over time in any quality of life domain, the proportions of subjects with a relevant change over 2 years (MCID) were compared using \(\chi^2\) tests. The amounts of medication used in both groups and the percentages of successfully treated weeks were compared using a \(t\) test when normally distributed and a Mann-Whitney \(U\) test when not normally distributed.

**RESULTS**
Of 38 practices invited to participate in the study, 19 agreed to do so. Table 1 shows the characteristics of the participating practices in both treatment groups. The flow chart in fig 2 summarises the number of patients. During the pretreatment phase 15 patients dropped out of the programme and a further 5 dropped out before the first follow up assessment. A total of 193 patients (98 SM) were therefore included in the intention to treat analysis. The baseline characteristics of the patients included in the intention to treat analysis are shown in table 2. The treatment groups did not differ in general or clinical characteristics at baseline apart from a higher proportion of patients reporting a recent episode of aggravated asthma symptoms and lower AQLQ scores in the SM group. Reversibility of FEV\(_1\) and AQLQ scores. Reversibility of FEV\(_1\) (% predicted value) was analysed in a similar non-linear model. Baseline values, age, sex, and smoking were entered as possible confounders. All analyses were performed using the PROC MIXED procedures by SAS.\(^7\) Transformed PC\(_{20}\) values (\(\log \) PC\(_{20}\)) were compared with a Student’s \(t\) test. If there was a significant difference over time in any quality of life domain, the proportions of subjects with a relevant change over 2 years (MCID) were compared using \(\chi^2\) tests. The amounts of medication used in both groups and the percentages of successfully treated weeks were compared using a \(t\) test when normally distributed and a Mann-Whitney \(U\) test when not normally distributed.

**Table 1** Characteristics of participating practices

<table>
<thead>
<tr>
<th>Type of practices</th>
<th>Self-management</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 GP</td>
<td>2 (25%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>2 GPs</td>
<td>3 (37%)</td>
<td>5 (46%)</td>
</tr>
<tr>
<td>&gt;2 GPs</td>
<td>3 (38%)</td>
<td>5 (43%)</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>No (95% CI) of asthmatics per 1000 patients</td>
<td>7.6 (5.6 to 9.6)</td>
<td>9.0 (4.9 to 13.2)</td>
</tr>
</tbody>
</table>

**Figure 1** Calculation of successfully treated weeks for one patient in the usual care group. Number of registered weeks = 104; median dyspnoea score = 64; percentage of successfully treated weeks = \(\frac{64}{104} \times 100 = 61.5\%\).
had a period of several months with frequent but short
episodes of sick leave due to asthma, the other a 3 month epi-
sode of uninterrupted sick leave. In both cases irritant
exposure in the workplace explained the high counts. Because
of the clear work related cause and the disproportionate
impact of these two outliers on the group mean, we decided to
exclude subjects above the 98th percentile from the final cal-
culations in both groups. This resulted in a mean number of
limited activity days of 1.2 (95% CI 0.5 to 1.9) for the SM
group and 3.9 (95% CI 2.5 to 5.4) for the UC group.

Figure 2 Flow chart showing study participants.

Table 2 Baseline characteristics of study subjects included in the intention to treat analyses

<table>
<thead>
<tr>
<th></th>
<th>Self-management (n=98)</th>
<th>Usual care (n=95)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.6 (11.2)</td>
<td>39.3 (12.0)</td>
<td>0.859</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>34/64</td>
<td>40/56</td>
<td>0.394</td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>45 (46%)</td>
<td>54 (56%)</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>31 (32%)</td>
<td>21 (22%)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>22 (22%)</td>
<td>21 (22%)</td>
<td>0.254</td>
</tr>
<tr>
<td>Pack years*</td>
<td>5.8 (4.5)</td>
<td>5.7 (4.5)</td>
<td>0.881</td>
</tr>
<tr>
<td>Requiring pretreatment with budesonide†</td>
<td>34 (35%)</td>
<td>22 (23%)</td>
<td>0.077</td>
</tr>
<tr>
<td>% with asthma attack(s) in previous 6 months</td>
<td>48.5%</td>
<td>31.6%</td>
<td>0.017</td>
</tr>
<tr>
<td>FEV1 (% predicted value)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronchodilator (BD)**</td>
<td>84.0 (13.1)</td>
<td>86.9 (14.2)</td>
<td>0.141</td>
</tr>
<tr>
<td>Postbronchodilator (BD)</td>
<td>90.0 (12.1)</td>
<td>92.6 (12.9)</td>
<td>0.135</td>
</tr>
<tr>
<td>FEV1 reversibility (%) (median)‡ **</td>
<td>5.0 (8.6) IQR</td>
<td>5.4 (6.8) IQR</td>
<td>0.930</td>
</tr>
<tr>
<td>Bronchial hyperresponsiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC20 geometric mean</td>
<td>1.20</td>
<td>0.97</td>
<td>0.442</td>
</tr>
<tr>
<td>Initial dose of inhaled steroids</td>
<td></td>
<td></td>
<td>0.622</td>
</tr>
<tr>
<td>None</td>
<td>12 (12%)</td>
<td>16 (17%)</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;400 µg daily or equivalent)</td>
<td>36 (37%)</td>
<td>30 (32%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate (&gt;400 and &lt;800 µg daily or equivalent)</td>
<td>34 (35%)</td>
<td>37 (39%)</td>
<td></td>
</tr>
<tr>
<td>High (&gt;800 µg daily or equivalent)</td>
<td>16 (16%)</td>
<td>12 (12%)</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities domain</td>
<td>5.3 (1.03)</td>
<td>5.6 (0.77)</td>
<td>0.015</td>
</tr>
<tr>
<td>Emotions domain</td>
<td>5.8 (1.01)</td>
<td>6.2 (0.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptoms domain</td>
<td>5.3 (1.03)</td>
<td>5.6 (0.90)</td>
<td>0.074</td>
</tr>
<tr>
<td>Environment domain</td>
<td>5.3 (1.10)</td>
<td>5.5 (1.1)</td>
<td>0.165</td>
</tr>
<tr>
<td>Overall score</td>
<td>5.4 (0.872)</td>
<td>5.7 (0.771)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Figures are mean (SD) values unless stated otherwise.

FEV1=forced expiratory volume in 1 second in litres; FVC=forced vital capacity.
*Missing data (self-management 2; usual care 1); **missing data (self-management 2; usual care 2); †pretreatment consisted of 6 weeks budesonide 800 µg twice daily; ‡difference between FEV1 before and after bronchodilator/predicted FEV.
As shown in fig 3, the post-bronchodilator FEV₁ had an estimated decline rate of 0.048 l/year in the SM group and 0.026 l/year in the UC group (p=0.239). There were no between group differences in the estimated rate of decline in FEV₁, reversibility and PC₂₁ histamine.

Changes from baseline in overall AQLQ score are summarised in fig 4. Based on repeated measurements analysis, the estimated increase in overall asthma quality of life score was 0.10 points per visit in the UC group and 0.21 points per visit in the SM group (p=0.055). Changes in quality of life were also estimated for each of the sub-domains (emotions, activities, symptoms, and environment). There was a significant change between groups only in the emotions domain (0.02 points per visit in the UC group; 0.20 points per visit in the SM group; p=0.006). To determine whether statistically significant changes in quality of life were clinically relevant, we estimated increase in overall asthma quality of life score was not different from previously studied acceptance rates. Determinants of willingness to participate and their implications have been discussed extensively elsewhere. The main implication is that subjects with low or intermediate doses of inhaled corticosteroids at baseline may have been relatively felt less worried or insecure about the influence of their asthma on daily life. GPs did not diagnose more exacerbations, but the number of oral prednisolone courses was higher in the guided SM group. The study population consisted of approximately one third of all subjects initially identified by GPs. Determinants of willingness to participate and their implications have been discussed extensively elsewhere. The main implication is that subjects with low or intermediate doses of inhaled corticosteroids at baseline may have been relatively over-represented in this study. Based on initial levels of pre-and post-bronchodilator FEV₁, the observed reversibility and initial dosage of inhaled steroids, included patients appeared to be a representative sample of patients with mild to moderately severe asthma.

Half of all invited practices participated in this study, which does not differ from previously studied acceptance rates. Other practice characteristics (table 1) also suggest that participating practices were a representative sample of Dutch general practice, with the restriction that participants have a positive attitude towards self-management.

There have been few randomised controlled trials to date on the effects of guided self-management programmes in family medicine.

**DISCUSSION**

Findings from this study indicate that asthma control improved in the SM group in terms of a higher number of successfully treated weeks and fewer limited activity days. There were no major changes in lung function parameters. In the SM group there was a slight improvement in asthma specific quality of life with a clinically relevant improvement in the emotions domain, indicating that patients in this group felt less worried or insecure about the influence of their asthma on daily life. GPs did not diagnose more exacerbations, but the number of oral prednisolone courses was higher in the guided SM group. The study population consisted of approximately one third of all subjects initially identified by GPs. Determinants of willingness to participate and their implications have been discussed extensively elsewhere. The main implication is that subjects with low or intermediate doses of inhaled corticosteroids at baseline may have been relatively over-represented in this study. Based on initial levels of pre-and post-bronchodilator FEV₁, the observed reversibility and initial dosage of inhaled steroids, included patients appeared to be a representative sample of patients with mild to moderately severe asthma.

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There have been few randomised controlled trials to date on the effects of guided self-management programmes in family medicine.

### Table 3: Indicators of exacerbations (between group comparison using Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Exacerbations per patient per 2 years (p=0.678)</th>
<th>Self-management</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (% within group) with 0 exacerbations</td>
<td>29 (36)</td>
<td>33 (41)</td>
</tr>
<tr>
<td>No (% within group) with 1 exacerbations</td>
<td>28 (35)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>No (% within group) with 2 exacerbations</td>
<td>7 (9)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>No (% within group) with &gt;4 exacerbations</td>
<td>9 (11)</td>
<td>7 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral prednisolone courses per patient per 2 years (p=0.015)</th>
<th>Self-management</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (% within group) with 0 courses</td>
<td>64 (70)</td>
<td>80 (85)</td>
</tr>
<tr>
<td>No (% within group) with 1 course</td>
<td>19 (21)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>No (% within group) with 2 courses</td>
<td>6 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>No (% within group) with &gt;3 courses</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Courses of antibiotics per patient per 2 years (p=0.643)</th>
<th>Self-management</th>
<th>Usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (% within group) with 0 courses</td>
<td>71 (78)</td>
<td>71 (76)</td>
</tr>
<tr>
<td>No (% within group) with 1 course</td>
<td>13 (17)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>No (% within group) with 2 courses</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No (% within group) with &gt;3 courses</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
During the study long acting β agonists were introduced in updated Dutch guidelines on diagnosis and treatment of asthma. Treatment with long acting β agonists was initiated in a relatively higher proportion of patients in the SM group but numbers were too small to allow for reliable statistics. It is therefore unlikely that prescription of long acting β agonists substantially contributed to improvements in successfully treated weeks or quality of life in favour of the SM group.

Based on our findings, we conclude that self-management of asthma is at least equally effective as asthma treatment usually provided in Dutch primary care. Asthma self-management provides a safe basis for intermittent treatment with inhaled corticosteroids and lowers the burden of illness as perceived by patients. Observed patient related outcomes are those in which self-management distinguishes itself from usual asthma care, even under conditions where room for improvement initially seemed limited.

References


Conflicts of interest: none.

**Authors’ affiliations**

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J. Malema, H. Folgering, University Lung Centre Dekkerswald, University Medical Centre Nijmegen, The Netherlands.

R. Grol, Centre for Quality of Care Research, University of Maastricht and University Medical Centre Nijmegen, The Netherlands.

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Chapter 9

Randomized controlled economic evaluation of asthma self-management in primary health care

Published in: Am J Respir Crit Care Med 2002;166:1062-72
Randomized Controlled Economic Evaluation of Asthma Self-Management in Primary Health Care

Tjard R. Schermer, Bart P. Thoonen, Guido van den Boom, Reinier P. Akkermans, Richard P. Grol, Hans T. Folgering, Chris van Weel, and Constant P. van Schayck

In this randomized controlled economic evaluation we compared guided asthma self-management with usual asthma care according to guidelines for Dutch family physicians. Nineteen family practices were randomized, and 193 adults with stable asthma (98 self-management, 95 usual care) were included and monitored for 2 years. We hypothesized that introducing self-management would not compromise asthma control and cost would be equal to or lower than in usual care. Patient-specific cost data were collected, preference-based utilities were assessed, and incremental cost per quality-adjusted life year (QALY) and successfully treated week gained was calculated. Self-management patients gained 0.039 QALY (95% confidence interval [CI], 0.003 to 0.075) and experienced 81 (95% CI, 78 to 84) successfully treated weeks in 2 years' time; the corresponding figures for usual care were 0.024 (95% CI, −0.022 to 0.071) and 75 (95% CI, 72 to 78). Total costs were €1,084 (95% CI, 938 to 1,228) for self-management and €1,097 (95% CI, 933 to 1,260) for usual care. Self-management patients consumed 1,680 (95% CI, 1,538 to 1,822) puffs of budesonide, usual care patients 1,897 (95% CI, 1,679 to 2,115). Mean productivity cost due to limited activity days was €213 lower among self-management patients. When all costs were included, self-management was cost-effective on all outcomes. The probability that self-management was cost-effective relative to usual care in terms of QALYs was 52%. We conclude that guided self-management is a safe and efficient alternative approach compared with asthma treatment usually provided in Dutch primary care.

Keywords: asthma; economics, pharmaceutical; family practice; patient education; randomized controlled trial

A systematic review including 23 trials concluded that self-management programs are able to improve health outcomes in adult asthma if they include self-monitoring and are accompanied with written action plans and regular medical professional review (8). However, the trials included in this meta-analysis have been conducted mainly in selected (secondary care) patients.

When competing for scarce health care resources it is not sufficient to determine the effects of asthma self-management programs solely in terms of health outcomes. It is also important to analyze whether the costs of introducing self-management outweigh the—potential—subsequent savings in health care utilization and productivity (“indirect”) costs, the latter resulting from fewer days of limited activities and incapacity for work (9). If the savings do not outweigh the investments, it is essential to assess whether the additional—or incremental—costs of a self-management program can be justified by the health gains.

Meanwhile, several asthma guidelines recommend self-management (10, 11) and health professionals and patients with asthma themselves seem to appreciate the contemporary approach (12–14). A number of economic evaluations of asthma education and self-management have been published (15–27), but most authors have confined themselves to separate descriptions of costs and health effects without directly assessing their relationship by calculating summary ratios. Essential methodological shortcomings were the absence of a control group receiving an appropriate comparator treatment and a too-short duration of follow-up. None of the published economic studies included instruments to assess preference-based utilities (e.g., quality-adjusted life years [QALYs] or similar universal outcome measures) as is currently recommended for all economic evaluations (28, 29). Moreover, only a part of the studies used written action plans, which seems to be a prerequisite for a successful treatment result (8).

This article reports a state-of-the-art economic evaluation of a guided self-management program for adult patients with asthma treated in Dutch primary care. We compared the self-management program with the “best” generally available medical treatment for asthma (“usual care”) according to asthma treatment guidelines for family physicians (30, 31). Beforehand, we did not expect substantial differences in health outcomes because medical care for patients with asthma is already of a high standard in The Netherlands, with asthma-related hospital admissions and deaths almost becoming rare events (32). Therefore, the main objective of this evaluation was to investigate whether a family practice-based self-management program for adults with asthma provides an efficient treatment alternative in terms of health care utilization and absence from work, without asthma control being compromised.
METHODS

Study Design
The study was a randomized controlled parallel group multicenter clinical trial. Nineteen (19) Dutch family practices (49 family physicians) were randomly allocated to guided self-management or usual care. Randomization was stratified on type of practice, number of patients with asthma initially identified from the practice records, and use of a computerized prescription system. Duration of follow-up was 2 years per patient. Self-management and usual care were fully pursued by the family physicians; no other health professionals were involved. The study protocol was approved by the medical ethics committee of the University Medical Center St. Radboud (Nijmegen, The Netherlands). Patients gave written informed consent before study entry. The first subject entered the study in March 1996, and the last subject completed the study in June 1999.

Participants
The 49 family physicians involved in the study selected subjects with asthma, aged 16–60 years, who were to be treated with inhaled steroids according to national guidelines (30, 31). Identification of subjects was based on the following information sources: problem list coding (International Classification of Primary Care: R96); prescription of inhaled steroids or bronchodilators from practice or pharmacy records; and the annual influenza vaccination campaign list. Subjects willing to participate were included if (1) their FEV1 was less than 8 mg/ml and/or their reversibility of FEV1 was greater than 9% of the predicted value after 800 μg of salbutamol was administered as an aerosol by spacer; (2) they had a smoking history of less than 15 pack-years; (3) they were not currently treated by a chest physician; and (4) they were able to communicate in the Dutch language. Eligible patients with an initial FEV1 of less than 80% of the predicted value were pretreated with budesonide 800 μg twice daily for 6 weeks.

Guided Self-Management and Usual Care
All participants were prescribed budesonide administered by multidose dry powder inhaler (Pulmicort Turbuhaler, 200 × 200 μg; AstraZeneca, Zoetermeer, The Netherlands) by one of the investigators (B.T.). Participants received new budesonide inhalers and handed in used inhalers in 1997 (31). Usual care patients did not receive peak flow meters, nor was bronchodilator therapy prescribed. Family Physicians in 1992 (30) and to the revised guidelines issued in Zoetermeer, The Netherlands) by one of the investigators (B.T.). Participation in the study was optional for both patients and physicians, and it was left to the initiative of the family physician and patient if and when these visits took place. Training tools consisted of (1) a detailed manual for the physicians describing the educational topics to be discussed during the consecutive training sessions and instructions on how to teach patients self-management skills (i.e., peak flow measurement, proper inhalation technique, completing the self-management diary, and application of self-treatment guidelines); (2) checklists for patients and physicians to assess and record specific information needs of patients; (3) two booklets of the Dutch Asthma Foundation, one containing general information about asthma and the other containing information about asthma medication; and (4) diaries containing self-treatment guidelines, also used for data collection. Self-management patients were equipped with a portable peak flow meter (Asmaplan plus; Vitalograph, Buckingham, UK) and instructed to measure morning and evening peak expiratory flow rates once a week and record the best of three attempts in their diary. Self-treatment guidelines were based on peak flow values and severity of respiratory symptoms (Figure 1). Detailed information about the exact contents of the education program and self-treatment guidelines have been published elsewhere (33). Usual care physicians were instructed to adhere to the asthma treatment guidelines issued by the Dutch College of Family Physicians in 1992 (30) and to the revised guidelines issued in 1997 (31). Usual care patients did not receive peak flow meters, nor were they instructed on how to adjust their dosage of budesonide.

Clinical Effectiveness
Clinical effectiveness was evaluated on the basis of asthma control parameters and quality of life. Asthma control was expressed as the number of successfully treated weeks in 2 years of follow-up, changes in postbronchodilator FEV1, changes in FEV1 reversibility as a percentage of predicted value, and changes in PC20-histamine (34). Asthma-specific quality of life was assessed with the interview-administered 32-question Asthma Quality of Life Questionnaire (AQLQ) (35). This instrument assesses four domains: (1) asthma symptoms, (2) limitation of activity, (3) emotional dysfunction, and (4) responses to environmental stimuli, respectively. An overall score as well as separate domain scores were calculated.

Economic Evaluation: Data Collection and Resource Valuation
A societal perspective was adopted for the economic evaluation. Patient-specific resource use was measured in natural units if possible. Resource use was valued in monetary terms by multiplying the units consumed by the cost per unit. Three major cost categories were distinguished: program implementation, direct health care, and productivity (indirect) costs.

Data regarding bronchodilators and other prescribed nonsteroid asthma medication, over-the-counter medication, and limited activity days were extracted from the diary cards. A limited activity day was defined as any day on which a patient could not perform his or her usual (paid or unpaid) daily activities. Consumption of budesonide was assessed by counting the remaining puffs in the inhalers returned by the patient on the diary cards. We considered the puff counts as

Step-up instructions
- PEFR deteriorates <40% PEFR ≥60% of PBV for 3 consecutive days:
  - double* budesonide dosage
  - in case of insufficient response within three weeks: again double* budesonide dosage
- PEFR deteriorates <60% PEFR ≥40% of PBV for 2 consecutive days:
  - increase budesonide dosage to 800 micrograms b.i.d.
  - in case of insufficient response within two days: start course of oral prednisolone and contact your family physician
- PEFR deteriorates <40% of PBV for 3 consecutive days:
  - immediately contact your family physician

Step-down instructions
- PEFR improves ≥240% PEFR <60% of PBV:
  - continue the current budesonide dosage until your PEFR is >60% of PBV
- PEFR improves ≥260% PEFR <80% of PBV:
  - continue the current budesonide dosage until your PEFR is >80% of PBV
- PEFR improves ≥280% of PBV:
  - reduce budesonide dosage when PEFR >80% for a period of two weeks

Figure 1. Summary of step-up and step-down instructions for self-management patients regarding the use of budesonide. *If no budesonide was used at the time of deteriorating peak flow, the patient should commence with the lowest dose (200 μg, twice daily). Patients were not allowed to double their dosage of budesonide anymore, once the maximum dosage of 800 μg twice daily had been reached. Either morning or evening value. PBV = personal best value; PEFR = peak expiratory flow rate.
the most reliable source of information for estimating budesonide consumption (36). Patient out-of-pocket cost on house dust mite allergen avoidance measures and smoking cessation attempts were assessed retrospectively by an ad hoc questionnaire. Family physicians reported details of asthma-related consultations, medication prescriptions, influenza vaccinations, referrals, and diagnostic procedures on study report forms. Completeness of consultation data was verified after a patient had completed study participation.

The first-choice source for resource unit valuation was the sum charged by family physicians to privately ensured patients (including value-added tax and a mark-up for administrative expenses). Subsequent sources were annually updated drugs and diagnostic indexes (37, 38) and more recent recommendations regarding cost analysis (39) (all issued by the Dutch College of Health Insurance), study expense accounts, and patient questionnaires. The human capital approach (28) was adopted to value limited activity days. An individual hourly wage based on the gross monthly income and the number of hours of disbursed work was calculated for all participants in paid employment. The resultant average gross hourly wage ($9.53) was subsequently used to convert all activity days (8-hour workday) into monetary terms, regardless of the employment status or income of individual participants. All resources used were valued in Dutch guilders and converted to euros. For conversion to U.S. dollars, costs in euros should be multiplied by a factor of 0.912, based on the 2000 Purchasing Power Parities as issued by the Organisation for Economic Co-operation and Development (www.oecd.org). Purchasing Power Parities are the rates of currency conversion that equalize the purchasing power of different currencies, thus eliminating differences in price levels between countries. Neither costs nor effects were discounted for time preferences.

Cost-Effectiveness Analysis: Outcome Measures

We performed a “base case” cost-effectiveness analysis, as well as secondary cost-effectiveness analyses. With the term “base case” we refer to an analysis in which the direct health care cost, program implementation cost, and productivity cost of patients are included. Outcome for the base case analysis was defined in terms of QALYs. To calculate QALYs, preference-based utilities were assessed at baseline and half-yearly at the pulmonary function laboratory. An interval rating scale ranging from 0 to 1 was used for this purpose, and being equal to death and 1 being equal to perfect health (40). Participants first marked a standardized (hypothetical) reference health state on the rating scale and subsequently their own perceived health state.

The number of successfully treated weeks served as the main outcome for secondary cost-effectiveness analyses (9). Successfully treated weeks were defined on the basis of recorded scores for shortness of breath in the diaries (modified Borg interval scale scoring: 0 = no shortness of breath; 10 = maximal shortness of breath) (41). Any given week with a score higher than the individual’s median score over the total follow-up was considered an unacceptably low level of control of asthma symptoms and therefore counted as unsuccessful. Subtracting this figure from the individual’s total number of recorded weeks resulted in the proportion of weeks being treated successfully, which was eventually standardized to the number of successfully treated weeks per 2 years (104 weeks). Next to successfully treated weeks, the number of patients with a minimal clinically important difference (MCID) in quality of life between the baseline and final visit was studied as a secondary outcome. MCID was defined as a within-subject improvement of 0.5 unit on the overall AQLQ or domain scores (35).

Statistical Analysis

Patients were included in the intention-to-treat analysis if they had been present at the first follow-up visit at the pulmonary function laboratory after 6 months. Although distributions of resource units were skewed to the right for most cost components, arithmetic means and $t$ test-based 95% confidence intervals (95% CIs) were calculated to compare self-management and usual care groups (42). Within-group cost differences between the first and second study year were analyzed by paired, between-group differences by unpaired $t$ test. QALYs were determined by calculating the area under the curve (time × rating scale score) for each participant. Mean costs and effects were expressed as ratios with a constant of 100 to standardize for inequalities of group sizes. Because of that, cost-effectiveness results reflect a situation in which 2 groups of 100 patients each would receive either self-management or usual care. Consequently, the cost-effectiveness ratios of the AQLQ data should be interpreted as the incremental cost or net savings to improve quality of life in one patient. A treatment was qualified to be “dominant” when this particular treatment was both more effective and less costly than the alternative (29). Secondary analyses were performed by calculating cost-effectiveness ratios with exclusion of the productivity cost.

The SAS statistical software package (release 6.12 for Windows; SAS Institute, Cary, NC) was used for statistical analyses. Regarding the incremental cost per successfully treated week, a 95% CI was determined on the basis of the Fieller theorem (43). To express uncertainty in the estimated incremental cost per QALY, DATA for Healthcare software (DATA Pro; TreeAge, Williamstown, MA) was used to generate graphical representations of the cost-effectiveness plane and accompanying two-dimensional 90% and 95% confidence intervals. This was done by nonparametric bootstrapping (Monte Carlo simulation): resampling with replacement from the patient-level cost and QALY data from the two comparator groups (1,000 random samples with size $n = 100$ each). Each point in the result scatter plot represents the incremental cost-effectiveness ratio of one iteration of the Monte Carlo simulation. A diagonal line intersecting the origin of the plot simplifies identification of points for which the incremental cost-effectiveness ratio of self-management versus usual care is less than, or equal to, an $a priori$ specified societal “willingness-to-pay” limit (44) (a) to gain one additional QALY. Arbitrarily, $a$ was set to $22,500$. A graphic representation (“acceptability curve”) of the probability that a particular intervention is cost-effective over a range of increasing values for $a$ was generated (45). This Bayesian approach of the stochastic analysis provides information relevant to health care decision making.

RESULTS

Study Population and Clinical Effects

Ninety-eight (98) self-management and 95 usual care patients were included in the intention-to-treat analyses (Figure 2). Treatment groups did not differ on general or clinical characteristics at baseline, apart from a higher proportion of patients reporting a recent episode of aggravated asthma symptoms and lower AQLQ scores in the self-management group (Table 1). Fourteen self-management patients and 16 usual care patients did not use bronchodilator medication during the study. Twelve self-management and 5 usual care patients used a long-acting $B_2$-agonist, and theophyllines were used by 3 self-management patients only. The course of the pre- and postbronchodilator FEV1 breath in the diaries (modified Borg interval scale scoring: 0 = no shortness of breath; 10 = maximal shortness of breath) (41). Any given week with a score higher than the individual’s median score over the total follow-up was considered an unacceptably low level of control of asthma symptoms and therefore counted as unsuccessful. Subtracting this figure from the individual’s total number of recorded weeks resulted in the proportion of weeks being treated successfully, which was eventually standardized to the number of successfully treated weeks per 2 years (104 weeks). Next to successfully treated weeks, the number of patients with a minimal clinically important difference (MCID) in quality of life between the baseline and final visit was studied as a secondary outcome. MCID was defined as a within-subject improvement of 0.5 unit on the overall AQLQ or domain scores (35).

Cost Analysis

The total implementation cost of the self-management program amounted to $189 (95% CI, $179 to $199) per patient (Table 3). Time invested by family physicians and purchase of peak flow meters constituted the major part of the implementation cost (60 and 16%, respectively). Mean budesonide usage was 1,680 puffs (95% CI, 1,538 to 1,822) or €414 for self-management and 1,897 puffs (95% CI, 1,679 to 2,115) or €467 for usual care, indicating a saving of 217 puffs or €53 per patient during the 2-year follow-up (Table 4). Converted to the level of budesonide inhalers, 0.5 inhaler per year was saved by self-management patients. Costs of short-acting bronchodilators were significantly

98
lower for self-management, but this difference was largely compensated by the higher cost of long-acting $\beta_2$-agonists and theophyllines in this same group. During the study, 30 (31%) self-management and 10 (11%) usual care patients took domestic house dust mite avoidance measures (relative risk = 1.7; 95% CI, 1.3 to 2.2). Consequently, mean costs of domestic house dust mite allergen avoidance measures were significantly higher among self-management patients (€193 versus €109 for usual care, $p = 0.0015$). Although the cost of influenza vaccinations composed only a marginal proportion of the total direct cost, there were significantly more vaccinations in the self-management group (Table 4): 46 (47%) self-management and 27 (28%) usual care patients received at least one influenza vaccination during follow-up (relative risk = 1.5, 95% CI, 1.1 to 1.9). There were more referrals to chest physicians among self-management than among usual care patients: 9 (4.6%) and 1 (0.6%), respectively (p = 0.011). No asthma-related emergency unit visits or hospital admissions were reported. Mean direct health care cost aggregated to €809 (95% CI, 683 to 934) for self-management and €798 (95% CI, 682 to 914) for usual care (Table 4).

Sixty-two percent of self-management patients and 70% of usual care patients reported one or more limited activity days at some point during follow-up. The mean number of limited activity days was 1.9 (95% CI, 0.7 to 3.2) for self-management and 6.0 (95% CI, 2.6 to 9.4) for usual care, corresponding with mean productivity costs of €144 and €462, respectively. However, closer examination of the productivity cost data identified two distinct outliers in the usual care group, with a productivity cost of €10,831 (142 limited activity days) and €5,263 (69 limited activity days), respectively. One outlier had a period of several months with frequent but short episodes of sick leave due to asthma, and the other had a 3-month episode of uninterrupted sick leave. In both cases, irritant exposure in the workplace explained the high productivity cost. Because of the clear work-related cause and the disproportionate impact of these two outliers on the average productivity cost in the usual care group, we decided to exclude subjects above the 98th percentile of the productivity cost distribution from the final cost calculations in both groups. This resulted in an average number of limited activity days of 1.2 (95% CI, 0.5 to 1.9) for self-management and 3.9 (2.5 to 5.4) for usual care, corresponding to a €213 productivity cost saving for self-management (Table 4). We consider the productivity cost without the outliers as the main results.

The sum of direct health care and implementation costs amounted to a difference of €199 (95% CI, 70 to 328) in favor of usual care (Table 5). The between-group difference in the total cost of €13 was not statistically significant ($p = 0.906$). Analyzing the cost for the first and second year separately showed that, as expected, the major part (91%) of the program implementation cost was spent during the first study year (Figure 3). A significant reduction of the productivity cost from first to the second year was observed for self-management ($p = 0.036$) but not for usual care ($p = 0.487$). During the second year the total cost per patient was €147 ($p = 0.0013$) lower in the self-management group.

**Base Case Cost-Effectiveness Analysis**

The course of rating scale scores is given in Figure 4. The mean number of QALYs gained during the 2-year follow-up was 0.039 (95% CI, 0.003 to 0.075) for self-management and 0.024 (95% CI, −0.022 to 0.071) for usual care (Table 2). This would imply that in 100 patients with asthma, self-management is associated with a gain of 1.5 QALYs (95% CI, −1.4 to 4.4) relative to usual
<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Self-Management</th>
<th>Usual Care</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>39.6 (11.2)</td>
<td>39.3 (12.0)</td>
<td>0.859</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>34/64</td>
<td>40/56</td>
<td>0.394</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student, %</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Full-time or part-time job, %</td>
<td>66</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Unemployed or retired, %</td>
<td>29</td>
<td>30</td>
<td>0.953</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>45 (46%)</td>
<td>55 (56%)</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>31 (32%)</td>
<td>21 (22%)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>22 (22%)</td>
<td>21 (22%)</td>
<td>0.254</td>
</tr>
<tr>
<td>Pack-years number</td>
<td>5.8 (4.5)</td>
<td>5.7 (4.5)</td>
<td>0.881</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of asthma,* yr</td>
<td>21.0 (16.5)</td>
<td>18.1 (14.3)</td>
<td>0.232</td>
</tr>
<tr>
<td>Subjects with asthma attack(s) in previous 6 mo</td>
<td>47 (48%)</td>
<td>30 (32%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Allergy, number of positive skin prick tests†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (23%)</td>
<td>20 (26%)</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>37 (44%)</td>
<td>29 (38%)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>28 (33%)</td>
<td>27 (36%)</td>
<td>0.735</td>
</tr>
<tr>
<td>Lung function parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, post-BD % of predicted value</td>
<td>90.0 (12.1)</td>
<td>92.6 (12.9)</td>
<td>0.135</td>
</tr>
<tr>
<td>Median FEV₁ reversibility, %</td>
<td>5.0 (IQR 8.6)</td>
<td>5.4 (IQR 6.8)</td>
<td>0.930</td>
</tr>
<tr>
<td>PC20, geometric mean</td>
<td>1.20</td>
<td>0.97</td>
<td>0.442</td>
</tr>
<tr>
<td>Utilities and quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utilities</td>
<td>0.80 (IQR 0.15)</td>
<td>0.80 (IQR 0.16)</td>
<td>0.668</td>
</tr>
<tr>
<td>Quality of life</td>
<td>0.40 (IQR 0.30)</td>
<td>0.40 (IQR 0.20)</td>
<td>0.380</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AQLQ = Asthma Quality of Life Questionnaire; BD = bronchodilator; IQR = interquartile range.

* Missing in 17 self-management and 14 usual care patients.
† Missing in 14 self-management and 19 usual care patients.
‡ Difference between FEV₁% predicted before and after bronchodilator.

In terms of cost-effectiveness, self-management dominated usual care (Table 6). Uncertainty around the incremental cost per QALY point estimate is depicted in Figure 5. This scatter plot shows that the uncertainty around the cost–effectiveness estimate is large. In other words, the dominance of self-management cannot be firmly established. This is supported by the cost-effectiveness acceptability curve (Figure 6): regardless of the societal willingness to pay, the probability that self-management is cost-effective relative to usual care is about 52% when a prior probability of 50% is assumed.

### Table 2. Average and Incremental Effects of Self-Management and Usual Care in Adults with Asthma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Average Effect</th>
<th>Incremental* Effect of Self-Management in 100 Subjects Treated for 2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>QALYs (95% CI)</td>
<td>0.039 (0.003, 0.075)</td>
<td>0.024 (0.002, 0.071) +1.5 (1.4, 4.4)</td>
</tr>
<tr>
<td>Number of successfully treated weeks (95% CI)</td>
<td>81 (78, 84)</td>
<td>75 (72, 78) +600 (230, 970)</td>
</tr>
<tr>
<td>Proportion of subjects with MCID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQLQ total score† (95% CI)</td>
<td>39 (29, 48)</td>
<td>29 (20, 38) +10 (3, 23)</td>
</tr>
<tr>
<td>AQLQ activities domain† (95% CI)</td>
<td>42 (32, 51)</td>
<td>25 (16, 33) +17 (10, 24)</td>
</tr>
<tr>
<td>AQLQ emotions domain† (95% CI)</td>
<td>52 (42, 62)</td>
<td>39 (30, 49) +13 (1, 27)</td>
</tr>
<tr>
<td>AQLQ symptoms domain† (95% CI)</td>
<td>35 (26, 45)</td>
<td>28 (19, 37) +7 (6, 20)</td>
</tr>
<tr>
<td>AQLQ environment domain† (95% CI)</td>
<td>42 (32, 51)</td>
<td>39 (30, 49) +3 (11, 1)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; MCID = minimal clinically important difference; QALY = quality adjusted life year.

Results of the base case analysis are printed in **boldface. Incremental effects are standardized to 100 subjects per group treated for 2 years.**

* Self-management minus usual care.
† Final AQLQ measurement was missing in two self-management and six usual care patients.
### TABLE 3. BREAKDOWN OF THE IMPLEMENTATION COST OF THE SELF-MANAGEMENT PROGRAM FOR 98 ADULTS WITH ASTHMA TREATED FOR 2 YEARS IN EIGHT FAMILY PRACTICES

<table>
<thead>
<tr>
<th>Component of Cost</th>
<th>Source for Unit Valuation</th>
<th>Number of Units</th>
<th>Cost per Unit (€)</th>
<th>Total Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prestudy training and instruction of family physicians</td>
<td>* Hours</td>
<td>23</td>
<td>73.53</td>
<td>1,691</td>
</tr>
<tr>
<td><strong>Application of self-management program</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational and self-management aids</td>
<td>† Set</td>
<td>98</td>
<td>14.25</td>
<td>1,396</td>
</tr>
<tr>
<td>Peak flow meters</td>
<td>† Meter</td>
<td>98</td>
<td>29.61</td>
<td>2,902</td>
</tr>
<tr>
<td><strong>Education sessions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family physician time</td>
<td>† Hours</td>
<td>151</td>
<td>73.53</td>
<td>11,075</td>
</tr>
<tr>
<td>Patient time</td>
<td>† Hours</td>
<td>151</td>
<td>9.531</td>
<td>1,436</td>
</tr>
<tr>
<td><strong>Total implementation cost:</strong></td>
<td></td>
<td></td>
<td></td>
<td>18,500</td>
</tr>
<tr>
<td>Average implementation cost per patient (95% CI):</td>
<td></td>
<td></td>
<td></td>
<td>189 (179, 199)</td>
</tr>
</tbody>
</table>

* Source used for unit valuation: Guidebook for Cost Investigation (Dutch College of Health Insurance [39]).
† Source used for unit valuation: retail prices (index year 2000).
‡ Set: all materials necessary to educate and train one patient, that is, information brochures, self-management diaries, and information feedback forms.
§ Source used for unit valuation: study-specific inquiry by questionnaire.
∥ Based on the average gross hourly wage of all employed participants.

### TABLE 4. MEAN AND INCREMENTAL PROGRAM IMPLEMENTATION, DIRECT HEALTH CARE, AND PRODUCTIVITY COST OF SELF-MANAGEMENT AND USUAL CARE PER PATIENT PER 2 YEARS

<table>
<thead>
<tr>
<th>Component of Cost</th>
<th>Source for Unit Valuation</th>
<th>Self-Management (n = 98)</th>
<th>Usual Care (n = 95)</th>
<th>Incremental Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Units (95% CI)</td>
<td>Cost (€)</td>
<td>Units (95% CI)</td>
</tr>
<tr>
<td>Program implementation cost†</td>
<td>a,b,c</td>
<td>98</td>
<td>189</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subtotal implementation cost:</strong></td>
<td></td>
<td>189 (179, 199)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Direct care cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs and other interventions</td>
<td></td>
<td>1,680 (1,538, 1,822)</td>
<td>414</td>
<td>1,897 (1,679, 2,115)</td>
</tr>
<tr>
<td>Budesonide, doses</td>
<td>d</td>
<td>469 (347, 591)</td>
<td>84</td>
<td>796 (526, 1,066)</td>
</tr>
<tr>
<td>Short-acting bronchodilators, doses</td>
<td>d</td>
<td>67 (10, 124)</td>
<td>51</td>
<td>30 (–6, 66)</td>
</tr>
<tr>
<td>Long-acting bronchodilators, doses</td>
<td>d</td>
<td>11 (–5, 26)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Theophylline, doses</td>
<td>d</td>
<td>0.33 (0.19, 0.46)</td>
<td>3</td>
<td>0.22 (0.08, 0.36)</td>
</tr>
<tr>
<td>Antibiotics, courses</td>
<td>d</td>
<td>0.28 (0.11, 0.44)</td>
<td>1</td>
<td>0.40 (0.19, 0.61)</td>
</tr>
<tr>
<td>Other asthma medication*</td>
<td>b,d,e</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Influenza vaccinations, number</td>
<td>d</td>
<td>0.72 (0.55, 0.90)</td>
<td>5</td>
<td>0.38 (0.25, 0.51)</td>
</tr>
<tr>
<td>Physiotherapy, courses</td>
<td>a</td>
<td>0.03 (0, 0.07)</td>
<td>4</td>
<td>0.01 (–0.01, 0.03)</td>
</tr>
<tr>
<td>Allergen avoidance measures†</td>
<td>c</td>
<td>NA</td>
<td>193</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Subtotal direct cost:</strong></td>
<td></td>
<td>809 (683, 934)</td>
<td>798 (682, 914)</td>
<td>+11</td>
</tr>
<tr>
<td><strong>Productivity cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited activity days, d§</td>
<td>c</td>
<td>1.2 (0.5, 1.9)</td>
<td>86</td>
<td>3.9 (2.5, 5.4)</td>
</tr>
<tr>
<td><strong>Subtotal productivity cost:</strong></td>
<td></td>
<td>86 (35, 136)</td>
<td>299 (191, 406)</td>
<td>–213</td>
</tr>
<tr>
<td><strong>Total cost:</strong></td>
<td></td>
<td>1,084 (938, 1,228)</td>
<td>1,097 (933, 1,260)</td>
<td>–13</td>
</tr>
</tbody>
</table>

* Both prescribed and over-the-counter medication.
† Purchase of house dust mite impermeable mattress covers, smooth floors, special vacuum cleaners and air cleaning equipment.
§ Cost of various pulmonary function and allergy tests, chest X-rays, and sputum cultures.
|| Highest two patients were excluded in both groups (see text).
| Self-management minus usual care.
| NA = not applicable.

Sources used for unit valuation: [a] guidebook for Cost Investigation (Dutch College of Health Insurance, reference [39]); [b] retail prices (index year 2000); [c] study-specific inquiry by questionnaire; [d] sum charged by family physicians to privately insured patients, including administrative expenses; [e] Pharmacotherapeutic Compass (Dutch College of Health Insurance, reference [37]); [f] Diagnostic Compass (Dutch College of Health Insurance, reference [38]).
Secondary Cost-Effectiveness Analyses

When productivity costs were excluded, the incremental cost per QALY of self-management relative to usual care was €13,267 (Table 6). Self-management dominated usual care with regard to successfully treated weeks and the proportion of patients with an MCID in quality of life. Without the productivity cost, the incremental cost–effectiveness ratio was €33 (95% CI, 4 to 99) to gain one successfully treated week due to self-management. Cost–effectiveness ratios based on the cost per patient with an MCID in quality of life preponderantly pointed to self-management as the dominant treatment, regardless of the inclusion or exclusion of productivity cost (Table 6).

DISCUSSION

This article reports the economic evaluation of a family medicine-based asthma self-management program, with “usual care” according to Dutch asthma treatment guidelines as the compara-

tor treatment. In summary, the results were as follows. Net savings in favor of self-management were observed in some of the direct health care cost components (i.e., use of budesonide and short-acting bronchodilators) and productivity (“indirect”) cost. When all costs were included, a mean net saving of €13 in favor of self-management was observed (not statistically significant). Despite the investment necessary for program implementation, the total costs for the self-management group were significantly lower during the second year of follow-up. The base case cost–effectiveness ratio pointed to self-management as a cost–effectiveness treatment option: self-management dominated usual care (i.e., was more effective and less costly). However, the graphic evaluation of uncertainty around the cost per QALY estimate showed that the observed dominance of self-management could not be firmly established. Overall, the secondary analyses based on successfully treated weeks and patients with a clinically important improved quality of life pointed to self-management as the dominant treatment option. When productivity costs were ignored, self-management was no longer dominant in the secondary analyses (€13,267 to gain 1 QALY and €33 to gain one successfully treated week).

Some comments on the methodology of the study need to be made before further discussing our findings. First, a disadvantage of using rating scales to value health states (and subsequently estimate QALYs) is that these instruments do not take risk aversion and uncertainty about future health outcomes into account. Therefore, rating scale utilities tend to produce higher quality weights than other techniques such as time-trade-off and standard gamble methods (46). Moreover, rating scale scores appear not to be a true interval scale of preference for certain health states. Unfortunately, in the current study we did not include a standard gamble or time-tradeoff instrument. The mean number of QALYs in both treatment groups may have been overestimated because of this, but the incremental difference between the groups is probably valid. However, this point should be kept in mind when comparing our QALY results with external information from other studies.

We did not randomize individual patients with asthma, but family practices. The reason for doing so was to avoid potential “contamination” of the usual care group by family physicians who had to practice both usual care and self-management simultaneously for different patients. Whereas in the clinical evaluation a multilevel analysis was used to address possible dependency in clustered observations induced by this kind of randomization (34), some influence on the cost data cannot be ruled out completely. For instance, prevailing habits and preferences in prescribing bronchodilators by family physicians may

<table>
<thead>
<tr>
<th>Direct Health Care</th>
<th>Program Implementation</th>
<th>Productivity</th>
<th>Average Total Cost (95% CI)</th>
<th>Incremental Cost of Self-Management per Subject Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1,084 (938, 1,228)</td>
<td>-13 (-252, 206)</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>—</td>
<td>997 (871, 1,124)</td>
<td>+199 (70, 328)</td>
</tr>
<tr>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>894 (751, 1,038)</td>
<td>-202 (-420, 16)</td>
</tr>
<tr>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>809 (683, 934)</td>
<td>+11 (-77, 99)</td>
</tr>
</tbody>
</table>

**Definition of abbreviation:** CI = Confidence interval.

Results of the base case analysis are printed in **boldface**. A plus sign indicates an expenditure due to the self-management program, a minus sign indicates a saving.

* In euros.
† Self-management minus usual care.
‡ Cost components included in the calculations of average costs.

**Table 5. Average and Incremental Cost During 2 Years of Self-Management and Usual Care in Adults with Asthma**

*Figure 3. Cost analysis for the first and second year of follow-up of self-management and usual care patients. Gray sections represent direct health care cost, black sections represent program implementation cost, and white sections represent productivity cost. The hatched area in the gray section of each column represents the patient out-of-pocket cost for domestic allergen avoidance measures. ^ Between-group difference in total cost for Year 2 (unpaired t test). *Within-group difference in productivity cost between Year 1 and Year 2 (paired t test).
Figure 4. Mean changes in rating scale scores for self-management and usual care groups adjusted for baseline level. Vertical bars represent standard errors. The gray area between the two lines represents the difference in QALYs between treatment groups. Because not all participants had their laboratory visits scheduled at exactly 6, 12, 18, and 24 months, this visual representation is an approximation of the exact sum of all individual QALYs as reported in text and in Table 2. Solid squares, self-management; solid circles, usual care.

have biased the results for this cost component to an unknown extent. The same argument holds for the promotion of influenza vaccination among individuals with asthma.

The baseline level of quality of life scores was higher in usual care patients, possibly leaving less room for improvement in this group. The comprehensive clinical evaluation of the data showed that the differences in AQLQ scores existing at baseline gradually disappeared during the 2-year follow-up period, which may indicate that quality of life was maximized in both groups (34). However, the observation that self-management patients experienced significantly more successfully treated weeks implies that the self-management program also had an independent effect, regardless of the health status differences present at baseline.

As a consequence of our study design, we cannot be sure which component of the self-management program in particular was responsible for the observed effects and savings: the (expensive) educational efforts made by the family physicians or the (relatively inexpensive) guidelines for self-monitoring and self-treatment. There is some evidence that addition of self-treatment guidelines to an asthma education program does yield extra effects in terms of health outcomes (47).

We have previously looked at the generalizability of our study population (48). Evaluation of the recruitment process showed that patients who use a low or intermediate dosage of inhaled steroids were more likely to participate in the study than patients receiving a high dosage or patients who did not use inhaled steroids at all (although, according to our national treatment guidelines [30, 31], they should have). Moreover, patients in paid employment were more likely to refrain from participation than those not in paid employment.

Regarding the cost analysis, several points need to be addressed. The most important expenditure necessary to implement the self-management program was the time spent by family physicians to educate and train their patients with asthma (€11005 per patient on average). Delegation of this task to, for instance, nurses specialized in respiratory care could reduce these costs considerably. Assuming delegation would not diminish program effectiveness, any reduction in the implementation cost would

| TABLE 6. INCREMENTAL COST-EFFECTIVENESS RATIOS FOR ASTHMA SELF-MANAGEMENT RELATIVE TO USUAL CARE DURING 2 YEARS OF FOLLOW-UP |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Incremental cost per QALY gained | Productivity Cost Included (95% CI) | Productivity Cost Excluded (95% CI) |
| Incremental cost per successfully treated week gained | Self-management dominant* | Self-management dominant |
| Observed incremental cost for one patient to experience an MCID, when 100 patients are treated: | | |
| AQLQ total score | Self-management dominant† | Self-management dominant |
| AQLQ Emotions Domain | Self-management dominant† | Self-management dominant† |
| AQLQ Activities Domain | Self-management dominant† | Self-management dominant† |
| AQLQ Symptoms Domain | Self-management dominant§ | Self-management dominant§ |
| AQLQ Environment Domain | Self-management dominant§ | Self-management dominant§ |

Definition of abbreviations: AQLQ = Asthma Quality of Life Questionnaire; MCID = minimal clinically important difference; QALY = quality-adjusted life year; 95% CI = 95% confidence interval.

Costs are in euros. Results of the base case analysis are printed in boldface.

* Dominant: treatment both more effective and less costly than the alternative treatment.
† Uncertainty in the base case cost per QALY estimate is depicted in Figure 5.
‡ Final AQLQ measurement was missing in two self-management and six usual care patients.
§ Because the cost per MCID estimates are based on group mean cost, it should be noted that uncertainty exists around the ratio estimates (results not presented).
obviously affect cost–effectiveness ratios in favor of self-management. Another advantage of transferring the actual pursuance of self-management training to other professionals would be the diminished impact on the (already) high workload of family physicians. Targeting the self-management intervention to patients with a high likelihood of treatment success could also enhance overall efficiency, although at this time it is unknown how these patients could be identified beforehand.

One of the most remarkable findings in this study was that the introduction of self-management led to substitution of particular cost components with other components. For instance, the financial saving due to reduced budesonide use and fewer activity days in the self-management group was outweighed for the greater part by the extra out-of-pocket cost for domestic allergen avoidance measures, and, although to a much lesser extent, more influenza vaccinations and referrals to chest physicians. These favorable “side effects” of the self-management program are probably explained by the emphasis put on the importance of healthy behavior (i.e., allergen avoidance, influenza vaccination, and smoking cessation) during the education sessions. The higher out-of-pocket cost for domestic allergen avoidance measures in the self-management group may be due to specific contents of our educational program. “Nature, cause and prevention of allergy or allergic symptoms,” “Hyperreactivity and personal triggers,” and “Allergen avoidance measures at home” were 3 of the 31 educational topics the family physicians discussed with their participants. One previous study has reported that asthma education may be effective in promoting house dust mite avoidance measures in patients with moderate to severe asthma (49). The extra attention focused on self-management patients as a consequence of the intensified doctor–patient relationship may have influenced the higher referral rate observed in the self-management group.

We observed significant differences in the use of asthma medication between self-management and usual care patients, especially for budesonide. This difference suggests a more efficient use of prophylactic medication due to self-management, a finding inconsistent with previously reported higher compliance rates regarding the use of inhaled steroids after introducing self-management (4, 50). However, use of the term “compliance” may be inappropriate when it comes to evaluation of self-management in patients with asthma. After all, the essence of the approach is to fine-tune the use of inhaled steroids to the actual need as determined by self-monitoring, without a prescribed (fixed) daily dose. For this reason, we anticipated a reduced consumption of

**Figure 6.** Acceptability curve reflecting the probability that asthma self-management is cost-effective relative to usual care given a societal willingness-to-pay (λ) value.
inhaled steroids in the intervention group beforehand, although it has been shown that self-management patients do not always adhere to their personalized self-treatment guidelines (4).

The main objective of any self-management program is to attain a long-wearing behavioral change in patients with regard to their disease. Once accomplished, this effect could be expected to persist for a longer period of time. Although in the current study we had to limit the time horizon to a maximum of 2 years, there was a tendency toward further productivity cost reduction during the second year of follow-up. Because we have no cost data from the years before the study at our disposal, we can only speculate about how the observed productivity cost for the first and second years relates to the annual productivity cost before the study. However, both Muhlhauser and coworkers (20) and Trautner and coworkers (25) have shown that significant changes in the pre-study situation may indeed be achieved. Moreover, findings reported by Trautner and coworkers (25) agree with our observation of a progressive reduction of productivity cost between the first and second year in self-management patients: they observed a 5% reduction in the number of days of absence from work during the first year, but an 18% reduction during the third year. This suggests that savings in productivity cost resulting from asthma self-management are retained in the long term.

Several other authors have reported significantly lower productivity costs due to self-management as well (17–19, 22, 23, 26, 27). The estimated savings from these studies range from 25 to 70% of the productivity costs observed in control patients. It should, however, be kept in mind that these studies were performed in populations with varying asthma severity, with diverse control groups, in different countries, and with different methods used for valuing productivity losses. Because there is no consensus in the literature as to what method is most suitable for valuing productivity losses, we applied the widely used human capital approach. An alternative method would have been the more advanced friction cost method as proposed by Koopmanschap and coworkers (51). The basic idea of this method is that the amount of production lost due to disease depends on the time span organizations need to restore the initial production level. This “friction period” is likely to differ by location, industry, firm, and category of worker, making the method rather complex. Had we used the friction cost method, our estimate of productivity cost would probably have been lower, as has been demonstrated for other health care programs (52).

It is generally recognized that a large proportion of the total cost of asthma is derived from treating the consequences of poor asthma control, such as emergency room use and hospitalizations (5). Therefore, improved asthma control is likely to reduce the number of acute asthma-related hospital admissions as well as the productivity costs resulting from the admission itself and recovery time after discharge. Although several authors have reported reductions in use of hospital services due to self-management, hospital admissions did not occur at all in our study and can therefore be no explanation for the lower number of study days observed in self-management patients. Thus, the effect of self-management on asthma-related activity days appears to be more subtle in patients with mild asthma under adequate control, like the patients involved in the current study.

Although the base case cost-effectiveness analysis demonstrated a 52% probability of the self-management program being cost-effective relative to usual care, we conclude that guided self-management is a safe and efficient alternative approach compared with asthma treatment usually provided in Dutch primary health care.

References

12. Thoonen BPA, Jones KP, Van Rooij HA, Van de Hout AC, Smeele I, Chardon L, Thomas RG, Starr-Schneidkraut N, Stancavage FB, et al. Evaluation of the efficacy and cost effectiveness of health education of self-management on asthma-related limited activity days observed in self-management patients. Thus, the effect of self-management on asthma-related limited activity days appears to be more subtle in patients with mild asthma under adequate control, like the patients involved in the current study.

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Short- and long-term efficacy of fluticasone propionate in subjects with early signs and symptoms of chronic obstructive pulmonary disease. Results of the DIMCA study

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Short- and long-term efficacy of fluticasone propionate in subjects with early signs and symptoms of chronic obstructive pulmonary disease. Results of the DIMCA study

Pierre van Grunsven, Tjard Schermer, Reinier Akkermans, Mieke Albers, Guido van den Boom, Onno van Schayck, Cees van Herwaarden, Chris van Weel

Summary

**Background.** Early treatment with inhaled corticosteroids may prevent progression of irreversible obstruction in COPD, especially in patients with bronchial hyperresponsiveness. We investigated the clinical effects of early introduction of inhaled steroids in subjects showing early signs and symptoms of COPD without a prior clinical diagnosis.

**Methods.** Study subjects were detected in a general population screening and monitoring program. Those with a moderately accelerated annual FEV₁ decline and persistent respiratory symptoms were invited to participate in a 2-year randomized controlled trial comparing fluticasone propionate DPI 250 μg b.i.d. with placebo. Pre- and post-bronchodilator (BD) FEV₁, PC₂₀ histamine, functional status (COOP/WONCA charts) and occurrence of exacerbations were periodically assessed. Subjects recorded respiratory symptoms. Post-BD FEV₁ decline served as the main outcome. Multivariable repeated measurements analysis techniques were applied.

**Results.** 48 subjects were randomized (24 fluticasone, 24 placebo). After 3 months, the post-BD FEV₁ had increased with 125 ml (SE = 68, P = 0.075) and the pre-BD FEV₁ with 174 ml (SE 90, P = 0.059) in the fluticasone relative to the placebo group. The subsequent post-BD and pre-BD FEV₁ decline were not beneficially modified by fluticasone treatment. There were no statistically significant differences in respiratory symptoms, functional status, or exacerbations favoring fluticasone. Subgroup analysis indicated that the presence of bronchial hyperresponsiveness modified the initial FEV₁ response on fluticasone, but not the subsequent annual FEV₁ decline.

**Conclusion.** Early initiation of inhaled steroid treatment does not seem to affect the progressive deterioration of lung function or other respiratory health outcomes in subjects with early signs and symptoms of COPD. In subjects at risk for, or in an early stage of COPD, long-term inhaled steroid treatment should not be based on a single spirometric evaluation after 3 months.
Introduction

Bronchial inflammation is the main cause of bronchial hyperreactivity and symptoms in asthma.\(^1\) As a consequence of inflammatory cell infiltration, goblet cell hyperplasia, basement membrane thickening and hyperplasia and hypertrophy of airway smooth muscle cells, persistent inflammation of the bronchial wall may cause irreversible loss of lung function.\(^2\) Although its pathogenesis is less well clarified in chronic obstructive pulmonary disease (COPD), bronchial inflammation also seems to play a significant role in this disease.\(^1\)

Treatment of asthma is directed at the inflammatory process and inhaled steroids are the cornerstone of asthma management.\(^3\) Although in patients with manifest COPD inhaled steroid treatment may reduce bronchial hyperresponsiveness\(^4\) and neutrophilic bronchial inflammation,\(^5\)–\(^7\) the benefits of maintenance treatment with inhaled steroids in COPD remain controversial.\(^8\) At this time, recent studies investigating the effectiveness of inhaled steroids in patients with manifest COPD\(^9\)–\(^12\) failed to demonstrate significant long-term effects on the decline of lung function, but there may be subgroups in which inhaled steroids are indeed effective in terms of prevention of lung function deterioration.\(^13\),\(^14\) Given the controversy of inhaled steroids in COPD, we hypothesized that initiation of this anti-inflammatory treatment in the earliest stages of the disease is critical for its efficacy in the long term. Because mild bronchial inflammation and airflow obstruction are not always accompanied by bronchial symptoms and go largely unnoticed by patients and primary care practitioners,\(^15\) study participants were selected from a general population screening program, which was initiated to detect subjects previously undiagnosed with COPD or asthma, but with early signs and symptoms of COPD.

Methods

Study design and recruitment of subjects

A 2-year randomized placebo-controlled double-blind trial was performed to compare fluticasone propionate with placebo treatment in subjects with mild but persistent signs of early COPD detected in the general population. Study subjects were selected through the two-stage detection strategy of the DIMCA program ("Detection, Intervention and Monitoring of COPD and Asthma", Fig. 1), which has been described in detail elsewhere\(^16\) but is summarized here. For the first stage of the detection strategy, in 10 Dutch general practices a random sample of all subjects aged 18–75 years without a prior diagnosis of COPD or asthma was invited for a screening visit. Screening took place in the general practices and consisted of spirometric assessment and a respiratory symptoms questionnaire. Subjects with chronic respiratory symptoms and signs of persistent airflow obstruction and/or bronchial hyperresponsiveness were included in the second stage of the DIMCA program, a 2-year monitoring phase. During the monitoring, lung function (including reversibility), bronchial hyperresponsiveness, occurrence of acute exacerbations and respiratory symptoms were assessed every 3 months. Based on the screening and monitoring findings, subjects were categorized into one of five groups: (1) persistent airflow obstruction (i.e., FEV\(_1\) < 80% of the predicted value after bronchodilation); (2) rapid decline in lung function (i.e., annual FEV\(_1\) decline > 80 ml); (3) persistent respiratory signs and symptoms (i.e., annual FEV\(_1\) decline 40–80 ml and bronchitis symptoms); (4) persistent mild symptoms and reversible airflow obstruction; (5) no abnormal respiratory signs or symptoms during monitoring ("screening false-positives").

Group 1–4 subjects were invited to participate in a series of randomized placebo-controlled trials in order to assess the efficacy of early initiated maintenance treatment with inhaled fluticasone.\(^15\) There was no evidence of recruitment or selection bias during the two stages of the detection program.\(^16\) An extensive description of reasons for non-participation to all different parts of the DIMCA program has been published elsewhere.\(^17\)

The current paper reports on the findings in Group 4, i.e. subjects with persistent respiratory signs and symptoms of early COPD. Subjects were included in the trial when, during the 2-year monitoring, they had reported chronic cough and/or sputum production for at least three consecutive months and showed an annual decline in pre-bronchodilator FEV\(_1\) of 40–80 ml. Subjects were
excluded in case of: previous diagnosis of a pulmonary condition; presence of a co-morbid condition with reduced life expectancy; intolerance for inhaled β₂ agonists; use of β-blocking agents; inability to use inhalation devices or peak-flow meters.

In the power calculation we assumed that the within-subject variation of FEV₁ measurement was 100 ml. A minimal detectable difference in annual FEV₁ decline of 60 ml due to fluticasone treatment was assumed. In an interim analysis of the first 16 subjects who finished the 2-year monitoring phase, the standard deviation (SD) of the mean annual FEV₁ decline was 66 ml. Thus, with α = 0.05, 1 − β = 0.80 and an anticipated 10% withdrawal rate, 18 subjects per treatment arm had to be recruited.

The study was approved by the medical ethics review board of the University Medical Center Nijmegen and all trial participants gave written informed consent.

Treatment arms and rescue medication

Subjects randomized to the active treatment group received fluticasone propionate (Flixotide) 250 μg b.i.d. by dry powder inhalation (Rotadisk) at each 3-monthly visit to the pulmonary function laboratory. Subjects were instructed to return all disks (full and empty) during the laboratory visits in order to assess treatment compliance. Individual compliance rates were determined by expressing the number of puffs consumed (number of dosages provided minus number of dosages returned) as a percentage of the amount prescribed during the trial. Treatment compliance and inhaler technique were checked half-yearly at the pulmonary function laboratory. When non-compliance was reported, a subject was reminded to use the study drug twice daily. In case of insufficient inhaler technique additional inhalation instruction was given.

Apart from short-acting ("rescue") bronchodilators in case of acute dyspnea, subjects were not
allowed to use other pulmonary medication. At each quarterly visit, consumption of rescue inhalations was recorded. At the start of the study, the participating GPs were reminded of the contents of the Dutch guidelines for management of asthma and COPD in general practice, which included a quit-smoking recommendation. In case of an acute exacerbation, GPs were advised to prescribe a 10-day course of prednisolone and a broad-spectrum antibiotic agent.

**Study outcomes and measurements**

The primary outcome of the study was the annual decline of the post-bronchodilator FEV1. Decline of pre-bronchodilator FEV1, PC_{20} histamine, exacerbation rate, number of episodes with aggravated symptoms, and use of rescue bronchodilators were studied as secondary outcomes. At the start of the trial and after 6, 12, 18 and 24 months, pre- and post-bronchodilator FEV1 and FVC were assessed by a trained lung function technician in a certified pulmonary function laboratory using a Microspiro HI-298 spirometer (Chest Corporation, Japan). Bronchial hyperresponsiveness was measured half-yearly as the concentration of histamine provoking a 20% fall in FEV1 (PC_{20}-histamine, procedure described by Cockcroft et al.) and estimated by linear interpolation. Pre- and post-bronchodilator FEV1 and FVC were also assessed in the general practices at 3, 6, 9, 15, 18 and 21 months using hand-held turbine spirometers (Microplus, SensorMedics, US). General practice assistants were thoroughly trained in performing spirometry. Following the criteria issued by the American Thoracic Society, the FEV1 from the maneuver with the highest sum of FEV1 and FVC out of three acceptable forced expiratory maneuvers was used for analysis. In case of >10% reproducibility (i.e., difference between the highest FEV1 value and the mean of all three maneuvers) an FEV1 value was excluded from the analysis. Post-bronchodilator FEV1 was assessed 15' after administration of 800 micrograms salbutamol by spacer. Measurements were only performed in exacerbation-free periods and not within 8 h of bronchodilator use.

Smoking history was assessed at the start of the trial and expressed as the number of pack-years smoked. Changes in smoking habit during the trial were expressed as the number of pack-years smoke. Subjects were considered to be allergic when the whealsize of ≥1 allergen exceeded 2/3 of the histamine control wheal.

Functional status was assessed at the quarterly general practice visits using the COOP/WONCA charts. This instrument consists of six domains ("physical fitness", "feelings", "daily activities", "social activities", "changes in health status", and "general health") with scores ranging from 1 ("very good") to 5 ("very bad").

Exacerbations were recorded by the GPs using standardized report forms. An exacerbation was defined as at least two positive answers on the following three items during a consultation: increased cough, wheezing and/or dyspnea; change in sputum color; use of bronchodilator rescue medication. Consultations with an interval <4 weeks were considered as pertaining to the same exacerbation.

In order to detect episodes with aggravated respiratory symptoms, subjects recorded symptom scores for dyspnea, cough, wheezing and phlegm on all days and/or nights during the past week. An episode was defined as either "increased cough, wheezing and/or dyspnea", "change in phlegm color", "increased use of rescue bronchodilators", and/or "having a cold". When in the next week no item was reported the episode was considered to have terminated. Information about serious and minor adverse events was collected.

**Statistical analyses**

The SAS statistical software package was used for analysis. All subjects with at least one follow-up measurement for the primary outcome (post-bronchodilator FEV1) were included in an intention-to-treat analysis. The effects of fluticasone versus placebo treatment on primary and secondary outcomes were analyzed using repeated measurements analysis of variance (PROC MIXED), in which subject, treatment, and time effects are analyzed simultaneously. Short-term responses (0-3 months) and long-term treatment effects (3-24 months) were analyzed in separate models. Baseline PC_{20} and number of packyears prior to the study were included in all models in order to adjust for their potential confounding effects. Based on the repeated measurements models, adjusted estimates of the long-term effect of fluticasone versus placebo on the decline of post-BD and pre-BD FEV1 were calculated for the 3-24 month data. Estimates for longitudinal changes in PC_{20} histamine were calculated using the full 2-year follow-up data.

A subgroup analysis was performed to investigate bronchial hyperresponsiveness (PC_{20}<8 versus
> 8 mg/ml) as a potential effect modifier of the short- and long-term efficacy of fluticasone treatment. This was done by including interaction terms in the repeated measurements models of the post- and pre-bronchodilator FEV1. PC20 values were log2 transformed before analysis. Consequently, changes in PC20 values are expressed as geometric means and should be interpreted as doubling doses of histamine. Between-group differences in the occurrence of acute exacerbations and episodes with aggravated symptoms were analyzed using Poisson tests, differences in functional status by Wilcoxon rank test. Between-group differences were considered to be statistically significant when \( P < 0.05 \).

## Results

### Study population and drop-outs

Seventy four (74) subjects met the inclusion criteria (Fig. 1). Of these subjects, 21 declined the invitation to participate in the trial, the main reasons being "general dislike of medication", "general dislike of medical testing", and "lack of time". Five subjects were excluded by the investigators (two used β-blockers, two moved away, and one wanted to become pregnant). The remaining 48 subjects were randomized to receive either fluticasone or placebo treatment for two years.

Demographic and clinical characteristics of participants and non-participants did not differ (results not presented). Table 1 shows the baseline characteristics of the trial participants by treatment group. Fluticasone group subjects had a higher number of pick-years compared to placebo group subjects (11.9 [SD 9.5] versus 5.8 [SD 8.4], respectively, \( P = 0.02 \)). Seven fluticasone and six placebo-treated subjects showed baseline bronchial hyperresponsiveness.

Twelve subjects (25% of the trial population) dropped out during the 2-year treatment period. Pharyngeal irritation and aversion to using pulmonary medication in the absence of respiratory symptoms were the main reasons for drop-out. Numbers of, and reasons for drop-out were equally distributed over the fluticasone and placebo groups. The overall compliance of the use of trial medication was 72% of the prescribed dose (range 7–102%). Compliance rates were similar in both treatment groups.

### Effects on FEV1 decline and PC20

The course of the post-bronchodilator FEV1, pre-bronchodilator FEV1, and PC20 in the treatment groups is depicted in Figs. 2–4. Three months after randomization, the mean post-bronchodilator FEV1 was 125 (SE 68) ml higher in the fluticasone-treated subjects compared to the placebo-treated subjects \( (P = 0.075, \text{Fig. 2}) \). During the 2-year follow-up the

| Table 1 Baseline characteristics of the study population by treatment group. |
|---------------------------------|-----------------|-----------------|
|                               | Fluticasone propionate (n = 24) | Placebo (n = 24) |
| Age (years)                   | 46 (10)          | 47 (11)          |
| Male/female                   | 12/12            | 13/11            |
| Smoker (yes/no)               | 12/12            | 8/16             |
| Pick-years                    | 11.9 (9.5)       | 5.8 (8.4)        |
| FEV1 pre-bronchodilator (l)   | 3.05 (0.70)      | 3.17 (0.76)      |
| as % predicted                | 95 (18)          | 98 (17)          |
| FEV1 post-bronchodilator (l)  | 3.16 (0.68)      | 3.19 (0.79)      |
| as % predicted                | 98 (15)          | 99 (18)          |
| FEV1/VC pre-bronchodilator (%)| 75 (10)          | 77 (6)           |
| FEV1 decline during monitor stage (ml/year) | 109 (46) | 124 (66) |
| FEV1 reversibility as % predicted | 4.0 (5.1) | 3.0 (4.0) |
| MEF50 as % predicted          | 65.6 (27.4)      | 68.5 (24.1)      |
| PC20 histamine\(^a\) (mg/ml)  | 14.2             | 9.2              |
| Allergy (yes/no/missing)      | 8/15/1           | 10/13/1          |
| Symptom score                 | 1.7 (1.5)        | 1.3 (1.3)        |

\(^a\)Geometric mean.
estimated annual decline of the post-bronchodilator FEV1 was $-93$ (SE 30) ml for fluticasone and $-14$ (SE 17) ml for placebo treatment ($P = 0.001$). For the pre-bronchodilator FEV1, the difference between fluticasone and placebo treatment was 174 (SE 90) ml after 3 months, favoring fluticasone treatment ($P = 0.059$, Fig. 3). The annual pre-bronchodilator FEV1 decline was $-85$ (SE 32) ml for fluticasone and $-38$ (SE 19) ml for placebo treatment ($P = 0.078$). At the end of the 2 year treatment period the difference in post-bronchodilator FEV1 was 47 (SE 63) ml in favor of placebo treatment ($P = 0.001$). For reason of clearness, the general practice measurements at 6 and 18 months are omitted from the figure (but not from the statistical analysis).

Figure 2 Short-term response and long-term course for the post-bronchodilator FEV1 in the fluticasone (—●—) and placebo (— – —) groups*. Vertical bars indicate standard errors. (* For reasons of clearness, the general practice measurements at 6 and 18 months are omitted from the figure (but not from the statistical analysis).)

Figure 3 Short-term response and long-term course for the pre-bronchodilator FEV1 in the fluticasone (—●—) and placebo (— – —) groups*. Vertical bars indicate standard errors. (* For reasons of clearness, the general practice measurements at 6 and 18 months are omitted from the figure (but not from the statistical analysis).)

Bronchial hyperresponsiveness as well as pack-years were confounders in the multivariable models for both the post- and pre-bronchodilator FEV1 decline. The subgroup analysis on baseline bronchial hyper responsiveness showed that, compared to placebo, fluticasone was significantly more efficacious in terms of the short-term (0–3 months) pre- and post-bronchodilator FEV1 response (Table 2). However, no modifying effect of bronchial hyperresponsiveness in favor of fluticasone treatment on
either the post- or pre-bronchodilator annual FEV\textsubscript{1} decline was observed (Table 2).

**Effects on exacerbations, respiratory symptoms and functional status**

Six exacerbations in five fluticasone-treated subjects and four exacerbations in three placebo-treated subjects were reported. In the fluticasone group, 127 episodes of increased respiratory symptoms were reported by 18 subjects, whereas 57 episodes in 17 subjects were observed in the placebo group ($P<0.001$). The number and severity of reported respiratory symptoms did not differ between the treatment groups, nor did the number of subjects who used rescue bronchodilators during the trial: seven subjects in the fluticasone group and eight subjects in the placebo group, respectively.

The baseline COOP/WONCA chart scores varied from 'not impaired' (1.2, SD 0.6 for social activities) to 'slightly impaired' (2.4, SD 1.2 for...
general health). The majority of subjects perceived no changes in COOP/WONCA charts score and differences between the fluticasone and placebo groups were never statistically significant (data not shown).

Adverse events

Four serious adverse events were reported during the trial: one diagnosis of polymyalgia rheumatica and three hospitalizations, one for severe headache, one for polyposis nasi, and one for uterus leiomyoma, none of which could be related to the trial medication. Fourteen subjects (29% of the trial population), equally distributed over the fluticasone and placebo groups, reported minor adverse events that could be related to the use of trial medication: dry mouth; hacking cough after inhalation of trial medication; sore throat or pharyngeal irritation; vomit; hoarseness; and loss of sense of taste. For five subjects (two fluticasone and three placebo) minor adverse events were the reason for dropping-out of the study.

Discussion

This study indicates that early initiation of regular treatment with fluticasone does have an initial and short-term effect, but does not seem to alter the subsequent course of lung function decline in subjects who are characterized by a moderately accelerated FEV\textsubscript{1} decline and persistent respiratory symptoms. The short-term effect of fluticasone appeared to be more pronounced in subjects with bronchial hyperresponsiveness. No long-term beneficial effects of fluticasone treatment on secondary health outcomes (i.e., bronchial hyperresponsiveness, exacerbations, respiratory symptoms, and health status) could be demonstrated.

We considered the post-bronchodilator FEV\textsubscript{1} to be the main outcome parameter in our study. Contrary to our initial hypothesis but in accordance with the results of previous long-term studies in subjects in different stages of COPD,\textsuperscript{9–12} the post-bronchodilator FEV\textsubscript{1} decline was not decelerated by inhaled steroid treatment. One could argue that the value of FEV\textsubscript{1} measurements in early or preclinical stages of COPD—as we would like to describe our study population—is doubtful. However, we observed a slight and statistically significant increase of FEV\textsubscript{1} in favor of fluticasone treatment after 3 months of study. A short-term increase of the FEV\textsubscript{1} during treatment with inhaled steroids, followed by a progressive decline parallel to placebo has also been reported by other authors.\textsuperscript{9,11} Although the FEV\textsubscript{1} has been widely accepted as the gold standard for measuring bronchial obstruction and thus of the severity of COPD, the value of FEV\textsubscript{1} measurements in very early stages of COPD is doubtful. The explorative subgroup analysis suggested that in the subjects with bronchial hyperresponsiveness, the short-term FEV\textsubscript{1} response due to fluticasone treatment was significantly larger than in subjects without bronchial hyperresponsiveness; this observation corresponds with findings reported for patients with manifest COPD.\textsuperscript{4–7} However, the presence (or absence) of bronchial hyperresponsiveness at baseline did not seem to influence the efficacy of fluticasone relative to placebo treatment with regard to the annual FEV\textsubscript{1} decline.

A substantial part of the FEV\textsubscript{1} measurements was performed in the general practices, and our findings rely heavily on the quality of these measurements. Repeated instructions of the practices’ staff resulted in reliable performances, with an average test reproducibility of 4%.\textsuperscript{23} Reanalyzing the data with only the measurements of the lung function laboratory did not change the main conclusions.

It has been hypothesized that subjects with mild obstructive airways disease, whose pathophysiologic abnormalities are predominantly present in the small airways, may remain undetected if no flow rates at low lung volumes are measured.\textsuperscript{28} Indeed, at the start of the trial the mid-expiratory flow (MEF) values were slightly impaired (below 70% of predicted values in both treatment groups), indicating (mild) obstruction of the peripheral airways. However, when we assessed the course of the pulmonary function on the MEF\textsubscript{25}, MEF\textsubscript{50}, or MEF\textsubscript{75} values, no effects of fluticasone in comparison to placebo on these indices were observed (results not presented).

In COPD, other characteristics of disease progression or monitoring of treatment like health status and exacerbations attract more and more attention.\textsuperscript{29} Impaired quality of life is more directly related to the use of general practitioners’ facilities than respiratory symptoms or a reduced lung function,\textsuperscript{30} and impaired quality of life may also be present in COPD with near normal spirometry.\textsuperscript{29} In the current study, no improvement in generic health status during treatment with fluticasone was observed, but this is probably due to the virtually undisturbed health status of the study subjects at the start of the trial. The rate of acute exacerbations was very low in both treatment groups, which may be expected in subjects who were not previously known by their GP as suffering
from chronic respiratory disease. Therefore, there was hardly any room for improvement on this particular outcome. The salient and statistically significant difference in the number of episodes with increased symptoms—one of the secondary study outcomes—in favor of placebo treatment was unexpected and we have no explanation for this observation. We conclude that, in the current study, we were unable to demonstrate significant long-term health benefits of early introduction of inhaled steroid treatment in subjects with early symptoms and signs of COPD. Primary care physicians should be careful to base maintenance treatment with inhaled steroids in subjects at risk for, or in an early stage of COPD on a single spirometric evaluation after 3 months. Implementation of screening or case-finding programs to detect subjects with early COPD cannot be justified on the basis of this study.

Acknowledgements

We are grateful to the general practitioners and practice assistants for monitoring the participants throughout the study and for dispensing the trial medication. We would like to thank Mrs. Lea Peters-van Gemert, Mrs. Lilian Bierman and Mrs. Vicky Verwaaijen-Larsson for their assistance in the data collection. We highly appreciate the assistance of Mrs. Twanny Jeijisman-Rouwhorst for her assistance in preparing this manuscript.

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Chapter 11

Probability and determinants of relapse after discontinuation of inhaled corticosteroids in patients with COPD treated in general practice

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Probability and determinants of relapse after discontinuation of inhaled corticosteroids in patients with COPD treated in general practice


Summary
Objective: The objective of the study was to assess the probability, and explore determinants of adverse respiratory outcome after discontinuation of inhaled corticosteroid (ICS) treatment in subjects with chronic obstructive pulmonary disease (COPD) diagnosed and treated in general practice. Design: Prospective unblinded ICS withdrawal study. Subjects: 201 ICS treated COPD patients with various degrees of airflow limitation from 45 Dutch general practices. Main outcome measures: Probability of and time to exacerbation or unremitting worsening of respiratory symptoms after ICS discontinuation. Results: Mean age was 60.6 (S.D. 9.5) years, post-bronchodilator forced expiratory volume in 1 s (FEV₁) 65.6 (S.D. 15.7) % predicted. Overall probability of adverse respiratory outcome after ICS discontinuation was 0.37 (95% confidence interval (CI) 0.31, 0.44). Survival analysis showed that age, gender, smoking status and reversibility of airflow limitation were independent predictors of adverse respiratory outcome. For females, the adjusted hazard ratio was 2.14 (95% CI 1.31, 3.50) compared to males. For age, the hazard ratio was 1.05 (95% CI 1.02, 1.08) per year lived. Conclusion: Discontinuation of inhaled corticosteroids may harm patients with COPD. The probability of an adverse respiratory outcome may be higher in women, elderly patients, smokers and patients with higher bronchodilator reversibility while on inhaled steroid treatment.

Introduction
Despite a number of recent clinical studies [1–4], the benefits of inhaled corticosteroids in patients with chronic obstructive pulmonary disease (COPD) are still debated. No effect on lung function decline has been established, but inhaled steroids seem to
slow-down health status deterioration and reduce acute exacerbations [1,4]. According to recent global guidelines for COPD management, inhaled steroids should be reserved for symptomatic patients with a documented spirometric response to steroids and for those with moderate to severe airflow limitation and repeated exacerbations which require antibiotic and/or prednisolone treatment [3]. At this time, however, many more patients with COPD in general practice are treated with inhaled corticosteroids, most of them for a number of years already [6,7]. Regular inhaled steroid treatment is probably superfluous in a considerable number of patients and ought to be discontinued. This may cause problems, however, as adverse effects of withdrawal of inhaled steroid therapy in patients with COPD have been reported [8—10], making it likely that at least some patients are harmed. For that reason, the possibility to predict adverse respiratory outcome would enable a more rational and safe way of withdrawing inhaled steroids in order to modify current ineffective prescription practices. Therefore, the objectives of this study were to assess the probability of an adverse respiratory outcome after discontinuation of regular inhaled steroid treatment in primary care patients with COPD, and to explore patient characteristics associated with the probability of exacerbation or relapse after inhaled steroid withdrawal.

Methods
Subjects and recruitment
We studied 232 subjects with COPD diagnosed and treated by their general practitioner (GP) (Fig. 1). All subjects entered the washout phase of the COPD on Primary Care Treatment (COOPT) trial [11], which investigates the effectiveness of inhaled fluticasone propionate and oral N-acetylcysteine in COPD. Study participants were recruited from 45 general practices in the south-eastern part of The Netherlands. Eligibility criteria were: chronic dyspnea, sputum production requiring an exacerbation during this period. The steroid washout formally terminated on the day of the visit at the lung function laboratory where the exacerbation was diagnosed and treated by his or her general practitioner and/or chest physician; or (2) an episode of unremitting worsening of respiratory symptoms of at least three consecutive days which led the subject to seek medical attention from his or her general practitioner and which resulted in relapse into inhaled steroid treatment.

General practice staffs were trained in performing spirometry before the study and were equipped with an electronic spirometer (Micro Medical Ltd., Rochester, Kent, UK) and spirometry software (Spiare®; Diagnostica Ltd., Oslo, Norway). Spirometry was performed before and after administration of 400 μg salbutamol dosaerosol by spacer (Volumatic®, GlaxoSmithKline, Zeist, The Netherlands). Reversibility of airflow limitation was calculated as the percentage change between pre- and post-bronchodilator FEV1 values and as the difference between the pre- and post-bronchodilator percentage predicted FEV1 [13].

Study procedures and measurements
The study was approved by the medical ethics review board of the University Medical Centre, Nijmegen. All subjects gave written informed consent. In order to be able to assess eligibility of subjects for the subsequent clinical trial, those on inhaled steroids had to go through a steroid washout of at least 3 months. Trial candidates requiring a washout were categorized as: low inhaled steroid dosage (<500 μg fluticasone propionate, <800 μg budesonide or beclomethasone dipropionate per day); intermediate dosage (fluticasone propionate 500—1000 μg, budesonide or beclomethasone dipropionate 800—1600 μg); high dosage (≥1000 μg fluticasone propionate, ≥1600 μg budesonide or beclomethasone dipropionate).

Subjects were instructed to contact their GP if they noted a worsening of their respiratory symptoms for at least three consecutive days. Subjects had to have been clinically stable for at least 6 weeks prior to steroid withdrawal, i.e. should not have had an exacerbation during this period. The steroid washout formally terminated on the day of the visit at the lung function laboratory where the eligibility criteria for trial participation were verified. Adverse respiratory outcome was defined as either

(1) The occurrence of an acute exacerbation of COPD, diagnosed and treated with prednisolon and/or a course of antibiotics by a general practitioner or chest physician; or
(2) an episode of unremitting worsening of respiratory symptoms of at least three consecutive days which led the subject to seek medical attention from his or her general practitioner and which resulted in relapse into inhaled steroid treatment.

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Study procedures and measurements
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Figure 1  Subject recruitment and drop out during inhaled steroid washout (*) including 11 subjects lost to follow-up, 17 subjects without confirmation of inhaled steroid discontinuation and 3 subjects where a general practitioner or chest physician advised against inhaled steroid withdrawal (†) including (n = 75) adverse respiratory outcome.

Statistical analysis

SPSS for Windows (Release 9.0.1) was used for analyses. Appropriate statistical tests were used to compare baseline characteristics between steroid dosage subgroups and subjects with and without adverse respiratory outcome. The relationship between the time to adverse respiratory outcome after steroid withdrawal and a number of explanatory variables was analysed using multivariable Cox proportional hazards modelling [14]. Survival time was defined as the number of days between the start of steroid withdrawal and onset of adverse respiratory outcome. Those withstanding the washout period without adverse respiratory events were treated as right censored cases. Explanatory variables included in the multivariable model were: age; gender; smoking status (current/former); duration of disease; self-reported exacerbation rate in the previous 2 years (0, 1, or ≥2 exacerbations); FEV1 as percentage predicted; FVC as percentage predicted; FEV1/FVC ratio ≥70% or <70%; reversibility of FEV1 <9% or ≥9%. Backward elimination was used to remove covariates with a Wald statistic test probability ≥0.10 from the model.

A priori, we suspected confounding by indication [15] with regard to the dosage of inhaled steroids before discontinuation: subjects on a high dose of inhaled steroids were more likely to be in a worse respiratory condition than subjects using a low or intermediate dosage. Therefore, a proportional hazards model containing all first order interaction
terms with baseline inhaled steroid dosage and the explanatory variables was considered first. Because this model showed significant interaction for age, reversibility and FEV1/FVC, we decided to construct separate models for each of the three inhaled steroid dosage subgroups, next to the model applicable to the total study population.

Results

Population characteristics and inhaled steroid withdrawal

Discontinuation of inhaled steroid treatment was intended in 232 subjects (Fig. 1). Eleven (5%) subjects were lost to follow-up. In 17 (7%) subjects, the actual discontinuation of inhaled steroid treatment could not be confirmed. In three (1%) subjects, withdrawal of inhaled steroids was advised against by a consulting chest physician. Table 1 shows baseline characteristics of the remaining 201 subjects by subgroup of inhaled steroid dosage. Most subjects (54%) were on a moderately high dosage of inhaled steroids. Significant airflow limitation (post-bronchodilator FEV1 < 80% of predicted value) was present in 156 (78%) subjects. Forty-six (23%) subjects had mild, 105 (52%) moderate, and 50 (25%) severe airflow limitation. Baseline steroid dosage was significantly related to pre- and post-bronchodilator FEV1 and FEV1/FVC values (Table 1).

Adverse respiratory outcome

Of the 201 study subjects, 86 (43%) dropped out after inhaled steroid treatment was discontinued, 75 (87%) due to respiratory causes and 11 (13%) for other reasons. Other reasons for dropping out were: lack of motivation (8); acute and serious illness of spouse (1); intervening elective surgery (1); and diagnosed malignancy (1). Of the respiratory dropouts, 54 (72%) were due to an acute exacerbation and 21 (28%) due to unremitting worsening of respiratory symptoms. Of all adverse respiratory outcomes, 11 (15%) occurred in the low, 43 (57%) in the intermediate and 21 (28%) in the high steroid dosage subgroup (Table 2). The overall probability of dropping out due to respiratory causes was 0.37 (95% confidence interval (CI) 0.31,

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of subjects with a general practice-based diagnosis of COPD and confirmed discontinuation of inhaled steroid treatment by baseline dosage of inhaled steroids. Values are means (S.D.) unless stated otherwise.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline dosage of inhaled steroids</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Gender (% female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Diseased lifeyears (%)</td>
</tr>
<tr>
<td>Smokers (% current)</td>
</tr>
<tr>
<td>Simultaneous NAC withdrawal (%)</td>
</tr>
</tbody>
</table>

Exacerbations in previous 2 years (%)

- None: 31.6 | 22.9 | 20.4 | 23.9 |  
- 1 | 7.9 | 21.1 | 20.4 | 18.4 |  
- ≥ 2 | 60.5 | 56.0 | 59.3 | 57.7 | 0.377 |

FEV1, pre-bronchodilator (l) | 2.02 (0.70) | 1.70 (0.68) | 1.68 (0.58) | 1.76 (0.67) | 0.024 |
Percentage of predicted value (%) | 67.6 (16.3) | 58.0 (17.4) | 56.9 (17.0) | 59.5 (17.5) | 0.006 |

FEV1, post-bronchodilator (l) | 2.18 (0.68) | 1.89 (0.64) | 1.85 (0.60) | 1.93 (0.64) | 0.028 |
Percentage of predicted value (%) | 72.8 (13.3) | 64.5 (15.6) | 62.7 (17.1) | 65.6 (15.7) | 0.006 |

FEV1 reversibility from baseline (%) | 9.6 (12.8) | 14.0 (15.2) | 11.4 (9.9) | 12.4 (13.5) | 0.309 |

FVC post-bronchodilator (l) | 3.31 (1.08) | 3.13 (0.84) | 3.01 (0.77) | 3.13 (0.88) | 0.324 |
FEV1/FVC post-bronchodilator (%) | 66.9 (10.5) | 60.5 (12.6) | 61.3 (12.3) | 61.9 (12.3) | 0.019 |

NAC: N-acetylcysteine; FEV1: forced expiratory volume in one second; FVC: forced vital capacity.

Significance level of difference between inhaled steroid dosage subgroups.

Number of years since initial diagnosis of COPD as a proportion of age.

Self-reported by study subjects.
Table 2  Univariate comparison of subjects with and without an adverse respiratory outcome after discontinuation of inhaled steroid treatment. Values are means (S.D.) unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>Adverse respiratory outcome</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 75)</td>
<td>No (n = 126)</td>
</tr>
<tr>
<td>General characteristics</td>
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<tr>
<td>Gender (% female)</td>
<td>40.0</td>
<td>27.0</td>
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<tr>
<td>Age (years)</td>
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<td>59.4</td>
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<tr>
<td>Smokers (% current)</td>
<td>47.6</td>
<td>50.7</td>
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<tr>
<td>Years since diagnosis* (%)</td>
<td>11.6 (9.2)</td>
<td>13.4 (13.2)</td>
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<tr>
<td>Exacerbations in past 2 years b (%)</td>
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<td></td>
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<tr>
<td>None</td>
<td>23.0</td>
<td>25.3</td>
</tr>
<tr>
<td>1</td>
<td>17.5</td>
<td>20.0</td>
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<tr>
<td>2 or more</td>
<td>59.5</td>
<td>54.7</td>
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<tr>
<td>Withdrawal of medication</td>
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<tr>
<td>Dosage inhaled steroids at time of withdrawal (%)</td>
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<tr>
<td>Low</td>
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<td>Simultaneous NAC withdrawal (%)</td>
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<tr>
<td>FEV1 reversibility (baseline) (%)</td>
<td>14.9 (16.5)</td>
<td>11.0 (11.3)</td>
</tr>
<tr>
<td>FEV1 reversibility (predicted) (%)</td>
<td>7.13 (7.38)</td>
<td>5.48 (5.66)</td>
</tr>
<tr>
<td>FEV1 pre-bronchodilator (l)</td>
<td>1.69 (0.68)</td>
<td>1.85 (0.64)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>57.1 (17.8)</td>
<td>60.9 (17.2)</td>
</tr>
<tr>
<td>FEV1 post-bronchodilator (l)</td>
<td>1.79 (0.66)</td>
<td>2.01 (0.62)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>64.3 (16.7)</td>
<td>66.4 (15.5)</td>
</tr>
<tr>
<td>FVC pre-bronchodilator (l)</td>
<td>2.64 (0.90)</td>
<td>2.98 (0.81)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>76.1 (17.2)</td>
<td>79.0 (15.6)</td>
</tr>
<tr>
<td>FVC post-bronchodilator (l)</td>
<td>2.93 (0.90)</td>
<td>3.25 (0.84)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>84.4 (16.3)</td>
<td>86.0 (15.2)</td>
</tr>
<tr>
<td>FEV1/FVC pre-bronchodilator (%)</td>
<td>60.7 (13.1)</td>
<td>62.0 (11.9)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>79.4 (17.0)</td>
<td>80.5 (14.9)</td>
</tr>
<tr>
<td>FEV1/FVC post-bronchodilator (%)</td>
<td>61.5 (12.5)</td>
<td>62.2 (12.2)</td>
</tr>
<tr>
<td>Percentage of predicted value (%)</td>
<td>80.3 (15.9)</td>
<td>80.8 (15.2)</td>
</tr>
</tbody>
</table>

NAC: N-acetylcysteine; FEV1: forced expiratory volume in 1s; FVC: forced vital capacity.

* Number of years since initial diagnosis of COPD as a proportion of age.

b Self-reported by study subjects.

0.44). Within the low, intermediate and high steroid dosage subgroups this probability was 0.29 (95% CI 0.15, 0.43), 0.39 (95% CI 0.30, 0.48), and 0.39 (95% CI 0.26, 0.52), respectively. The median (interquartile range) number of days until adverse respiratory outcome was 43 (66), 42 (49) and 22 (53) for the low, intermediate and high steroid dosage subgroups (P = 0.456), respectively.

Explanatory variables associated with adverse respiratory outcome

Univariately, gender, age, reversibility of airflow limitation and pre- and post-bronchodilator FEV1 and FVC values differed between those with and without adverse respiratory outcome (Table 2). Subjects experiencing an adverse respiratory outcome tended to be more often female, were older, showed a higher baseline bronchodilator reversibility and had lower FEV1 and FVC values. Multivariable survival analysis indicated that the risk of adverse respiratory outcome was higher for females and that the risk increased with progressing age (Fig. 2). The hazard ratio for females was 2.14 (95% CI 1.31, 3.50) compared to males (Table 3). For age, the hazard ratio was 1.05 (95% CI 1.02, 1.08) per year of increased age. When analysed separately for the baseline inhaled steroid dosage subgroups, age, gender, smoking status and reversibility were independent predictors for adverse respiratory outcome in one or more subgroups (Table 3).
Figure 2. Adjusted survival curves after discontinuation of inhaled steroid treatment in subjects with a general practice based diagnosis of COPD (n = 201) by age quartile.

Table 3. Results of multivariable proportional hazards analyses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference category</th>
<th>β coefficient</th>
<th>P-value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study population (n = 201)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 (37%) adverse outcome</td>
<td>Age 1 year increase</td>
<td>0.048</td>
<td>&lt;0.001</td>
<td>1.05</td>
<td>1.02, 1.08</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>0.762</td>
<td>0.002</td>
<td>2.14</td>
<td>1.31, 3.50</td>
</tr>
<tr>
<td>By inhaled steroid dosage subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dosage (n = 38)</td>
<td>Age 1 year increase</td>
<td>0.109</td>
<td>0.008</td>
<td>1.11</td>
<td>1.03, 1.20</td>
</tr>
<tr>
<td>11 (29%) adverse outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate dosage (n = 109)</td>
<td>Age 1 year increase</td>
<td>0.056</td>
<td>0.005</td>
<td>1.06</td>
<td>1.02, 1.10</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>0.810</td>
<td>0.022</td>
<td>2.25</td>
<td>1.13, 4.49</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker</td>
<td>0.718</td>
<td>0.030</td>
<td>2.05</td>
<td>1.07, 3.93</td>
</tr>
<tr>
<td>High steroid dosage (n = 54)</td>
<td>Gender</td>
<td>0.970</td>
<td>0.033</td>
<td>2.64</td>
<td>1.08, 6.45</td>
</tr>
<tr>
<td>21 (39%) adverse outcome</td>
<td>Reversibility</td>
<td>1.166</td>
<td>0.013</td>
<td>3.21</td>
<td>1.28, 8.05</td>
</tr>
</tbody>
</table>

CI: confidence interval.

Discussion

This study adds information to the limited body of knowledge with regard to the effects and risks of discontinuation of inhaled steroid treatment in patients with COPD. To our knowledge, no previous withdrawal studies have been performed in a primary care COPD population. All subjects in our study matched the ‘classic’ clinical profile of COPD, i.e. reported chronic sputum production and persistent cough for at least the previous 2 years. Moreover, some degree of persistent airflow limitation was present in all subjects and all were current or former smokers. We aimed to avoid inclusion of subjects with unambiguous asthma by excluding those previously treated for asthma, allergic rhinitis or atopic rash. Still, as both COPD and asthma show a high prevalence in the general practice population and smoking occurs in both groups of patients [16,17], coexistence of COPD and clinical features of asthma in the same subject is likely to have occurred in this study. Because asthma
and COPD share clinical similarities, it is virtually impossible to differentiate patients with chronic bronchitis and/or emphysema who have partially reversible airflow obstruction and bronchial hyper-reactivity from patients with asthma whose airflow obstruction does not remit completely [18]. Therefore, when it comes to deciding if inhaled steroid treatment is appropriate in a particular subject with apparent chronic obstructive airways disease, a pragmatic approach—which does not necessarily require definitive diagnostic labelling—is needed to support GPs' decision-making.

In the current study, neither patients nor GPs were ‘blinded’, so both were well aware of the fact that inhaled steroid treatment was discontinued. Although from a methodological point of view a double-blind withdrawal trial would have been the preferred design, the results of such a trial would not reflect what happens in daily general practice if inhaled steroid treatment is discontinued in a subject with apparent COPD. As a consequence of our unblinded design patients may have been more perceptively to changes in respiratory symptoms which they normally would have ignored had their regular pharmacotherapy not recently been modified.

After inhaled steroid withdrawal, more than one-third (39%) of our study subjects experienced an adverse respiratory outcome. This figure is very similar to findings reported by Jarad et al. [8], who observed that in a group of patients with COPD 38% experienced an exacerbation within 8 weeks after regular inhaled steroid treatment had been discontinued in an unblinded manner. In their double-blind randomised controlled fluticasone propionate withdrawal trial, van der Valk et al. [10] observed a 48% exacerbation rate and an increased risk of recurrence during 6 month follow-up of their 142 patients with moderate to severe COPD recruited from hospital and outpatient records. O'Brien et al. [9] found that in elderly patients with severe irreversible airflow limitation, withdrawal of inhaled steroid therapy led to deterioration in ventilatory function and increased exercise-induced dyspnea. However, the heterogeneous primary care COPD population in our study will generally suffer from less severe disease and is likely to comprise more subjects with coexisting asthma features.

So far, only one subgroup analysis with regard to adverse effects of inhaled steroid withdrawal in COPD has been reported [8]. In this study of 272 patients with apparently irreversible COPD, no demographic or lung function variables predicted the risk of exacerbation after discontinuation of inhaled steroid treatment. Several large prospective placebo-controlled trials have explored the relative efficacy of inhaled steroids in subgroup analyses [1—3]. These subanalyses all considered heterogeneity of treatment effect with regard to the progressive FEV1 decline, but never explored the occurrence or frequency of exacerbations as an outcome of interest. In one study it was observed that inhaled steroids decelerated FEV1 decline in the subgroup with the least smoking history [2]. Other subject characteristics like age, gender, baseline FEV1, presence of serum IgE antibodies, reversibility of airflow limitation, or response to an oral corticosteroid trial did not predict the long-term treatment result of inhaled steroids in COPD, at least not in terms of FEV1 decline [1—3]. A small study performed in a mixed primary care population of patients with COPD and asthma indicated that current smoking, higher bronchodilator reversibility, low FEV1/FVC ratio and high annual lung function decline were related to a more progressive decline of FEV1 while on inhaled steroid treatment [19]. A recent subgroup analysis of a large inhaled steroid trial in secondary care patients suggest that the effects of inhaled steroids on exacerbations may be seen predominantly in patients with moderate-to-severe COPD who experienced recurrent exacerbations [20]. Considering all published evidence on subject characteristics related to inhaled steroid treatment efficacy, there is some overlap with our findings: we observed that—next to gender and age—smoking status, degree of reversibility of airflow limitation and FEV1/FVC at the time of inhaled steroid withdrawal were related to adverse respiratory outcome.

In conclusion, when treatment with inhaled steroids is discontinued in patients with COPD, the probability of an adverse respiratory outcome is rather high, but it may be mediated by age, gender, smoking status and degree of reversibility of airflow limitation. Although the severity of airflow obstruction and the past exacerbation rate did not determine the probability of adverse outcome in our population, other studies have shown that these factors may be important determinants of relapse after inhaled steroid withdrawal as well. If a patient with COPD discontinuation of inhaled steroid treatment is intended, a thorough prior assessment of potential determinants and careful monitoring of early signs and symptoms of an adverse respiratory response is well-advised.

Announcement

As a GP you will learn from our paper that discontinuation of prophylactic inhaled steroid treatment may harm patients with COPD, and that certain patient characteristics (i.e. age, gender, smoking status, severity and reversibility of airflow
limitation, past exacerbation rate) may predict adverse outcome after discontinuation of inhaled steroids in this group of patients.

Acknowledgements

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References

Exacerbations and associated healthcare cost in patients with COPD in general practice

submitted
Exacerbations and associated healthcare cost in patients with COPD in general practice

TRJ Schermer, CGJ Saris, WJHM van den Bosch, NH Chavannes, CP van Schayck, PNR Dekhuijzen, C van Weel

Abstract

**Objective** - To investigate the occurrence rate, treatment, and healthcare costs of exacerbations in patients with chronic obstructive pulmonary disease (COPD) in Dutch general practice.

**Methods** – Baseline data from the COPD on Primary Care Treatment (COOPT) trial were used. Details on the occurrence and management of exacerbations were collected by systematic medical record review for the 2-year period preceding trial inclusion.

**Results** - Mean age of the 286 study subjects involved was 59.2 (SD 9.6) years, postbronchodilator FEV₁ 67.1% (SD 16.2) of predicted. Following ERS criteria, subjects suffered from: no (26%); mild (19%); moderate (40%); or severe (15%) airflow obstruction. Overall mean and median annual exacerbation rates were 0.88 (SD 0.79) and 0.5 (IQR 1.0), respectively. Eexacerbation rate was not related to severity of airflow obstruction (p=0.628). Mean annual exacerbation costs per subject were €40, €53, €61 and €92 for the respective severity subgroups (p=0.012). The increase of costs in the more severe subgroups was mainly attributable to more physician consultations, diagnostic procedures, and prescription of reliever medication (e.g., bronchodilators, cough preparations).

**Conclusion** – Occurrence of exacerbations did not depend on the severity of airflow obstruction, whereas the healthcare cost associated to exacerbations increased along with the severity of the disease.
Introduction
Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality world-wide(1). In Western countries, the burden of COPD on society is expected to increase substantially over the next decades(2;3). Apart from the accelerated decline in lung function, an important and characteristic clinical feature of COPD is the occurrence of exacerbations, i.e. recurrent episodes of acute deterioration of the disease caused by infectious agents or other trigger factors(4). Exacerbations have been shown to contribute substantially to the impaired health status observed in patients with COPD(5-7). Moreover, several studies suggest that the occurrence of exacerbations may influence the long-term prognosis in terms of lung function and health status decline, and survival(8-11). Published reports indicate that there may be large variation in the occurrence rate of exacerbations among patients with COPD. Estimates range from one to three exacerbations per patient per year(12-18), although there is evidence of substantial underreporting by patients(14). Differences in the populations studied and the absence of a definition for exacerbations generally agreed upon hampers direct comparison of studies.
Acute exacerbations are responsible for a large proportion of the healthcare cost due to COPD and disease severity seems to be the major driver of costs, especially while expenditures for physician time, emergency room visits, hospital admissions, oxygen therapy, and nursing home stays increase as the disease becomes more severe(19-22). However, most published studies have recruited patients in secondary care settings and, consequently, predominantly included patients suffering from severe to end-stage COPD. This subgroup of patients, which comprise only a relatively small proportion of all patients with COPD in the general population, suffer from frequent and severe exacerbations and are responsible for a substantial part of the healthcare cost attributable to COPD. Patients with mild to moderate disease, which are much larger in number, are typically treated in primary care and are less well studied with regard to their exacerbations.
Therefore, the objectives of the current study were to investigate the occurrence rate and management of acute exacerbations in patients with COPD treated in Dutch general practices, and to assess the exacerbation related healthcare cost in different stages of severity of airflow obstruction.
Methods

Study subjects and design
The study consisted of a systematic medical record review over the past 2 years in 286 subjects with physician-diagnosed COPD recruited from 46 general practices in the Netherlands. All subjects participated in the COPD on Primary Care Treatment (COOPT) study, a randomised controlled trial evaluating the effectiveness of N-acetylcysteine and fluticasone propionate in a primary care COPD population(23). General practitioners (GPs) identified subjects with a diagnosis of COPD using existing diagnostic labels and drug prescription records. Subjects identified as suffering from COPD were invited for a screening visit to the general practice. Subsequently, eligibility for trial participation was verified in a certified pulmonary function laboratory. Trial inclusion criteria were: age 35-75 yrs; current or ex-smoker; chronic dyspnea, sputum production and cough for at least three consecutive months per year during the previous two years(24); either post-bronchodilator (BD) FEV₁ (forced expiratory volume in one second) <90% of the predicted value or post-BD FEV₁/FVC <88% (89% for women) of the predicted value; no previous treatment for asthma, allergic rhinitis or atopic rash; no severe comorbid conditions. Subjects with FEV₁ <40% of predicted post-BD were excluded. The study was approved by the medical ethics review board of the University Medical Centre Nijmegen, the Netherlands. All subjects gave written informed consent.

Data collection
GPs identified all contacts related to acute deterioration of the respiratory condition during the two years preceding the date of trial inclusion from the subjects’ medical record using a standardised data extraction form. For each study subject the exact time frame was individually marked out by providing the GP with the begin and end dates of the observation period. Inquired details for each contact were: date, time, and type of contact (office consultation, telephone consultation, home visit); changes in respiratory symptoms (i.e., increased dyspnea, cough, amount of sputum); objective signs (sputum colour, sputum consistency, fever); drugs prescribed (dosage and brand of oral glucocorticoids, antibiotic agents, inhaled steroids, bronchodilators, mucolytics, cough preparations); diagnostic tests (chest X-rays, pulmonary function tests, sputum cultures, blood tests); referrals to respiratory consultants; emergency room visits; and hospital admissions (including length of stay). The information on changes in respiratory symptoms as recorded in the GPs files was often
incomplete and therefore not used in the current evaluation. Separate contacts pertaining to one and the same exacerbation episode were marked as such by the reporting GP. Completeness of the reported contacts was verified by one of the investigators in a ten percent (n=29) random sample of study subjects. In this sample, completeness of reporting turned out to be 100%.

Spirometry was performed in a pulmonary function laboratory in all subjects following the European Respiratory Society (ERS) standards(25). Following the protocol of the subsequent clinical trial (23), subjects were categorised according to severity of airflow obstruction using criteria issued by the ERS (postbronchodilator FEV$_1$ as percentage of predicted value $\geq 80%$: no obstruction; $\geq 70%$ and $<80%$: mild obstruction; $\geq 50%$ and $<70%$: moderate obstruction; $<50%$: severe obstruction)(24). History of cigarette smoking was assessed by standardised interview and quantified as the number of packyears smoked.

**Cost calculations**

Use of healthcare resources was assessed by counting the number of units consumed. Subsequently, units were converted into monetary values. Drug prescriptions were converted to costs using the March 2000 table of the Royal Dutch Association for the Advancement of Pharmacy and included taxes and pharmacist fee. Cost of diagnostic tests were calculated using tariffs published by the Dutch Council of Health Insurances(26;27). Referrals to respiratory consultants, emergency visits, and hospital admissions were valued using results of a cost investigation from a secondary care population of patients with COPD(28). Cost of referrals included the time spent by respiratory consultants and additional diagnostic procedures requested by the consultants. Costs were calculated as the cost per exacerbation episode as well as the annual exacerbation cost per subject. All cost are expressed in Euro’s (€). The year 2001 was taken as the index year for all cost, regardless of the calendar year in which an exacerbation had actually occurred.

**Analyses**

The SAS statistical software package (version 6.12 for Windows) was used for analysis. Differences in baseline characteristics between the categories of obstruction severity were analysed using analysis of variance (ANOVA) and $\chi^2$ tests. Mean and median annual exacerbation rates were calculated for the four categories of obstruction severity and compared by ANOVA and Kruskal-Wallis tests. Differences in the occurrence of exacerbations by calendar month were analysed by $\chi^2$ test. Although the cost data distribution
was skewed towards the left, \( t \) test based 95 percent confidence intervals (95% CIs) were calculated for total cost and separate cost components(29). Differences in exacerbation related cost between obstruction severity subgroups were compared using ANOVA.

Results

Study population

Demographic and clinical characteristics of the study population are given in table 1. Age and packyears of smoking were highest for the subjects with more severe obstruction (both \( p<0.001 \)), whereas the body mass index (BMI) was lowest in the more severe subgroups (\( p=0.042 \)). Reversibility as percentage of predicted FEV\(_1\) ranged from 5.5 (SD 6.2) percent in subjects without obstruction to 8.0 (SD 5.8) percent in subjects with moderate obstruction (\( p=0.044 \)). Long-acting bronchodilators and inhaled steroids were more often prescribed in the more severely affected subgroups (\( p=0.003 \) and \( p=0.019 \), respectively). Comorbidity was present in 109 (38%) subjects, hypertension being the most prevalent condition (16% of all subjects) followed by ischaemic heart disease (15%), atherosclerosis (11%), cardiac arrhythmia (6%), and diabetes mellitus (5%). Presence of relevant comorbid conditions did not differ between the categories of obstruction severity.
Table 1. Demographic and clinical characteristics of the study population (n=286) by severity of airflow obstruction* at the end of the 2-yr retrospective observation period. Values are means (standard deviation) unless stated otherwise.

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>No obstruction</th>
<th>Mild obstruction</th>
<th>Moderate obstruction</th>
<th>Severe obstruction</th>
<th>Total</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>75 (26)</td>
<td>53 (19)</td>
<td>114 (40)</td>
<td>44 (15)</td>
<td>286 (100)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.6 (9.8)</td>
<td>57.6 (9.6)</td>
<td>59.7 (8.8)</td>
<td>64.3 (9.2)</td>
<td>59.2 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Males (%)</td>
<td>54 (72)</td>
<td>32 (60)</td>
<td>90 (69)</td>
<td>32 (73)</td>
<td>209 (73)</td>
<td>0.097</td>
</tr>
<tr>
<td>Paid work (%)</td>
<td>32 (43)</td>
<td>15 (28)</td>
<td>36 (32)</td>
<td>6 (14)</td>
<td>89 (31)</td>
<td>0.011</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>42 (56)</td>
<td>33 (62)</td>
<td>60 (53)</td>
<td>26 (59)</td>
<td>160 (56)</td>
<td>0.675</td>
</tr>
<tr>
<td>Cigarette smoke exposure, Packyears</td>
<td>25 (14)</td>
<td>24 (14)</td>
<td>29 (20)</td>
<td>37 (17)</td>
<td>28 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8 (4.5)</td>
<td>27.6 (5.1)</td>
<td>25.8 (3.7)</td>
<td>25.5 (4.6)</td>
<td>26.4 (4.4)</td>
<td>0.042</td>
</tr>
<tr>
<td>Comorbid conditions (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>53 (71)</td>
<td>31 (58)</td>
<td>73 (64)</td>
<td>20 (45)</td>
<td>177 (62)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (20)</td>
<td>12 (23)</td>
<td>24 (21)</td>
<td>15 (34)</td>
<td>66 (23)</td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>7 (9)</td>
<td>10 (19)</td>
<td>17 (15)</td>
<td>9 (21)</td>
<td>43 (15)</td>
<td>0.181</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On inhaled corticosteroids (%)</td>
<td>26 (35)</td>
<td>27 (51)</td>
<td>51 (45)</td>
<td>28 (64)</td>
<td>132 (46)</td>
<td>0.019</td>
</tr>
<tr>
<td>Bronchodilator treatment (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bronchodilator</td>
<td>30 (40)</td>
<td>10 (19)</td>
<td>24 (21)</td>
<td>5 (11)</td>
<td>69 (24)</td>
<td></td>
</tr>
<tr>
<td>Short-acting†</td>
<td>37 (49)</td>
<td>34 (64)</td>
<td>63 (55)</td>
<td>26 (59)</td>
<td>160 (56)</td>
<td></td>
</tr>
<tr>
<td>Long-acting‡</td>
<td>8 (11)</td>
<td>9 (17)</td>
<td>27 (24)</td>
<td>13 (30)</td>
<td>57 (20)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebronchodilator FEV₁, litres</td>
<td>2.54 (0.56)</td>
<td>2.06 (0.51)</td>
<td>1.61 (0.39)</td>
<td>1.03 (0.26)</td>
<td>1.85 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>as % predicted</td>
<td>81.6 (8.7)</td>
<td>68.1 (7.5)</td>
<td>51.9 (8.8)</td>
<td>36.4 (7.4)</td>
<td>60.3 (17.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postbronchodilator FEV₁, litres</td>
<td>2.72 (0.55)</td>
<td>2.26 (0.47)</td>
<td>1.85 (0.36)</td>
<td>1.20 (0.24)</td>
<td>2.05 (0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>as % predicted</td>
<td>87.1 (6.1)</td>
<td>74.9 (3.1)</td>
<td>59.8 (5.6)</td>
<td>42.2 (5.7)</td>
<td>67.1 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postbronchodilator FVC, litres</td>
<td>3.95 (0.97)</td>
<td>3.36 (0.85)</td>
<td>3.21 (0.82)</td>
<td>2.45 (0.56)</td>
<td>3.32 (0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>as % predicted</td>
<td>102.4 (14.5)</td>
<td>90.6 (13.7)</td>
<td>82.7 (14.3)</td>
<td>68.8 (13.0)</td>
<td>87.2 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postbronchodilator FEV₁/FVC, %</td>
<td>69.9 (7.6)</td>
<td>68.4 (9.1)</td>
<td>59.1 (10.3)</td>
<td>50.4 (11.8)</td>
<td>62.3 (11.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁ reversibility, %‡</td>
<td>5.5 (6.2)</td>
<td>6.8 (8.0)</td>
<td>8.0 (5.8)</td>
<td>5.9 (4.3)</td>
<td>6.8 (6.2)</td>
<td>0.044</td>
</tr>
<tr>
<td>Annual exacerbation rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean rate</td>
<td>0.75 (0.63)</td>
<td>0.85 (0.76)</td>
<td>0.97 (0.88)</td>
<td>0.89 (0.78)</td>
<td>0.88 (0.79)</td>
<td>0.303</td>
</tr>
<tr>
<td>Median rate (IQR)</td>
<td>0.5 (1.0)</td>
<td>0.5 (0.7)</td>
<td>0.7 (1.0)</td>
<td>0.5 (1.4)</td>
<td>0.5 (1.0)</td>
<td>0.627</td>
</tr>
</tbody>
</table>

* no obstruction: FEV₁ >80% of predicted value; mild obstruction: FEV₁ 70-80% of predicted value; moderate obstruction: FEV₁ 50-69% of predicted value; severe obstruction: FEV₁ <50% of predicted value
† p-values indicate significance levels of differences between obstruction severity subgroups
‡ with or without additional short-acting bronchodilator
§ difference in FEV₁ % predicted between prebronchodilator and postbronchodilator measurement
IQR = interquartile range

135
Occurrence of exacerbations

A total of 507 exacerbations comprising 732 GP contacts were reported for the 286 subjects studied. In 227 (45%) exacerbations more than one contact with the GP had taken place. The number of GP contacts per exacerbation ranged from 1 to 7, with an average of 1.5 (SD 0.91) contacts. 220 subjects (77%) experienced at least one exacerbation during the two year period. Mean and median annual exacerbation rates did not differ between the severity subgroups (table 1). There was a dissimilar distribution in the occurrence of exacerbations throughout the year, with the majority of exacerbations reported in the months October through March (59% of all exacerbations) and July ($\chi^2$ test, $p=0.014$, figure 1).

Figure 1. Occurrence of exacerbations by calendar month in 286 subjects with COPD managed in general practice. The solid line represents the overall mean number of exacerbations per calendar month; the figure above each bar is the proportion of all reported exacerbations.

Management of exacerbations

A course of oral corticosteroids was prescribed in 26% of all exacerbations. Within the set of all reported exacerbations, the probability of an oral corticosteroid prescription increased
roughly along with the severity of obstruction of the subject concerned (no obstruction: 0.18, mild: 0.28; moderate: 0.28; severe: 0.32; $\chi^2$ test: $p=0.040$). Forty-seven percent of the exacerbations were treated with one or more antibiotic drugs, tetracyclines being the most frequently prescribed class of antibiotics (56%), followed by penicillins (27%), macrolides (12%), sulfonamides (4%), and quinolones (1%). Unlike oral corticosteroid prescriptions, the probability of an antibiotic being prescribed did not increase as obstruction became more severe ($\chi^2$ test, $p=0.747$). Hospital admission was reported for only one exacerbation; one other exacerbation necessitated an emergency room visit. Spirometry was performed in 173 (34%) of all exacerbations (94% performed in general practice, 6% in a pulmonary function laboratory). Chest radiographs were requested in 63 (12%) exacerbations, sputum cultures in 3 (1%). Referral to a respiratory consultant was reported for 25 (5%) exacerbations.

**Exacerbation related healthcare cost**

Table 2 shows the mean cost per exacerbation and the mean annual exacerbation cost per study subject. The total cost per exacerbation aggregated to €66 (95% CI 56, 76). The annual cost per subject attributable to exacerbations aggregated to €59 (95% CI 48, 69). Exclusion of the hospital admission cost resulted in €62 (95% CI 57, 67) per exacerbation, and €51 (95% CI 44, 57) for the annual exacerbation cost. There was no significant association between the annual exacerbation cost and age (Spearman: $r=0.027$, $p=0.654$) or gender (Mann-Whitney U, $p=0.492$). A consistent tendency towards increasing annual exacerbation cost within the more severely obstructed subgroups was observed (figure 2, $p=0.024$, and $p=0.060$ with the hospital admission cost excluded). The increasing cost were merely due to more GP consultations, diagnostic procedures requested, and prescriptions for reliever medication.
Table 2. Mean (95% CI) healthcare cost (in Euro’s) for exacerbations, and mean annual cost attributable to exacerbations in subjects with COPD.

<table>
<thead>
<tr>
<th>GP consultations</th>
<th>n° of units</th>
<th>Cost per exacerbation (n=507)</th>
<th>Annual exacerbation cost per subject (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office visits</td>
<td>681</td>
<td>22.6 (21.3, 23.8)</td>
<td>19.9 (17.7, 22.2)</td>
</tr>
<tr>
<td>House calls</td>
<td>35</td>
<td>1.7 (1.0, 2.5)</td>
<td>1.5 (0.8, 2.2)</td>
</tr>
<tr>
<td>Phone consultations</td>
<td>16</td>
<td>0.2 (0.1, 0.3)</td>
<td>0.2 (0.1, 0.3)</td>
</tr>
<tr>
<td><strong>Total GP consultation cost</strong></td>
<td></td>
<td><strong>24 (23, 26)</strong></td>
<td><strong>22 (19, 24)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug prescriptions</th>
<th>n° of units</th>
<th>Cost per exacerbation (n=507)</th>
<th>Annual exacerbation cost per subject (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic agents</td>
<td>260</td>
<td>5.7 (5.0, 6.4)</td>
<td>5.0 (4.1, 5.9)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>149</td>
<td>1.6 (1.4, 1.9)</td>
<td>1.4 (1.1, 1.8)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>106</td>
<td>7.1 (5.4, 8.7)</td>
<td>6.1 (4.3, 7.9)</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>179 †</td>
<td>5.7 (4.6, 6.8)</td>
<td>4.9 (3.7, 6.1)</td>
</tr>
<tr>
<td>Other reliever medication</td>
<td>17</td>
<td>0.4 (0.2, 0.7)</td>
<td>0.4 (0.2, 0.6)</td>
</tr>
<tr>
<td><strong>Total drug prescription cost</strong></td>
<td></td>
<td><strong>20 (18, 23)</strong></td>
<td><strong>18 (15, 21)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic procedures</th>
<th>n° of units</th>
<th>Cost per exacerbation (n=507)</th>
<th>Annual exacerbation cost per subject (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-rays</td>
<td>63</td>
<td>4.9 (3.7, 6.0)</td>
<td>4.3 (3.2, 5.4)</td>
</tr>
<tr>
<td>Lung function tests</td>
<td>173</td>
<td>5.7 (4.7, 6.8)</td>
<td>5.1 (3.9, 6.3)</td>
</tr>
<tr>
<td>Sputum cultures</td>
<td>3</td>
<td>0.1 (0, 0.2)</td>
<td>0.0 (0, 0.1)</td>
</tr>
<tr>
<td><strong>Total diagnostic procedure cost</strong></td>
<td></td>
<td><strong>11 (9, 12)</strong></td>
<td><strong>9 (8, 11)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary care</th>
<th>n° of units</th>
<th>Cost per exacerbation (n=507)</th>
<th>Annual exacerbation cost per subject (n=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation of respiratory consultant</td>
<td>25 ‡</td>
<td>6.0 (3.7, 8.3)</td>
<td>5.3 (3, 7.4)</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>1 ‡</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>1 &amp;</td>
<td>4.4</td>
<td>7.8</td>
</tr>
<tr>
<td><strong>Total secondary care cost</strong></td>
<td></td>
<td><strong>11 (2, 20)</strong></td>
<td><strong>10 (2, 17)</strong></td>
</tr>
</tbody>
</table>

**Total healthcare cost** | 66 (56, 76) | 59 (48, 69) |

* 76 (72%) new prescriptions, 30 (28%) increased dosage  
† 130 (73%) new prescriptions, 49 (27%) increased dosage  
‡ including cost of diagnostic procedures requested by the consultant  
§ cost of the ER visit were €161  
& cost of the hospital admission were €2237

**Discussion**

In this study we assessed the occurrence of exacerbations in a group of patients with COPD treated in Dutch general practice, and estimated the healthcare cost arising from these acute episodes. The noticeable observation that hospitalisations, emergency room visits and chest physician consultations were exceptional events illustrates the typical primary care nature of the patient population studied. The results also indicate that the healthcare cost induced by exacerbations of COPD in (Dutch) primary care may depend on the severity of airflow obstruction, whereas the occurrence rate of exacerbations itself does not seem to do so. The latter observation is in contrast with an earlier COPD study conducted in the Spanish primary care setting, in which an association was found between the severity of airflow obstruction.
Figure 2. Distribution of exacerbation related annual healthcare cost by subgroup of severity of airflow obstruction.

* $p=0.060$ with the hospital cost excluded
† bronchodilators, mucolytics, and cough preparations

and the risk of frequent exacerbations (30). On the other hand, our findings are in line with a study performed in a UK secondary care setting, in which patients with frequent or infrequent exacerbations were indistinguishable in terms of lung function (31). In the current study, the patients with more severe obstruction did not so much experience more exacerbations but once they suffered from one, the healthcare costs involved were higher than in those with less severe obstruction. The higher cost were caused primarily by more consultations, diagnostic tests, and prescription of reliever medication (i.e., bronchodilators, mucolytics, cough preparations) in the GPs management of exacerbations. A relationship between FEV$_1$ impairment and increased drug prescription in stable COPD has been reported previously (12), but our data suggest that this relationship may also apply to the primary care cost of treating acute exacerbations of the disease.

Studies in patients with COPD treated in secondary care have shown that the treatment cost of exacerbations are largely due to hospitalisations, emergency room visits, and domestic
oxygen therapy. Compared to these studies the exacerbation related costs in our study were rather low. This is easily explained by the fact that among all 507 reported exacerbations only one hospital admission and one emergency room visit had occurred. This further demonstrates the typical primary care nature of our study population: in the Netherlands, patients treated by GPs generally suffer from less severe disease and, consequently, require less intensive medical attention in case of an exacerbation compared to patients treated by secondary care chest physicians. The Confronting COPD survey has also demonstrated that the rate of unscheduled healthcare contacts is relatively low in the Netherlands.

One of the main reasons for Dutch GPs to refer patients with COPD to a chest physician appears to be the occurrence of recurrent or unresolving exacerbations. Once a patient with COPD has been admitted to hospital because of a (severe) exacerbation, it is rather common practice that a chest physician temporarily or permanently takes over the patients’ treatment after discharge from hospital. Because patients who were treated by chest physicians were less likely to be invited by the GPs for participation in the upcoming trial and because patients with FEV$_1$ <40% of predicted were excluded, those with frequent or severe exacerbations were probably underrepresented in our study population.

In order to avoid being forced to choose between existing definitions for exacerbations beforehand, we instructed the GPs to report any contact in which study subjects sought medical attention because of acute deterioration of their respiratory condition. Because of the differing definitions for exacerbation used in the literature, direct comparison of the exacerbation rate observed in our study with rates reported from previous studies is impeded. One method is to use prescriptions for courses of oral corticosteroids and antibiotics as a proxy measure for exacerbations. However, had we only used this proxy definition in the current study, we would have missed a substantial number of exacerbations, as in only a quarter of all episodes an oral corticosteroid was prescribed. With addition of antibiotic prescriptions to the proxy definition based oral corticosteroid prescriptions alone, 59 percent of all episodes would have been detected. Still, a substantial part (41 percent) of all episodes was managed without a course of oral corticosteroids or antibiotics, but merely with a -transient- increase of the dosage of inhaled corticosteroids and/or bronchodilators, or prescription of other reliever medication (i.e., mucolytics, cough preparations).

In the Netherlands each inhabitant can only be registered in a single general practice. Because of this, it is unlikely that we missed many exacerbations by using GP records as the only data source. However, we can only speculate on the number of exacerbations which were ‘self-managed’ by patients and were therefore not included in the GPs’ medical records. It has been
reported that patients with COPD may seek medical attention in only fifty percent of exacerbations(14). From a healthcare expenditure perspective these events are irrelevant as they do not result in any medical costs. However, the ‘productivity’ cost due to work absenteeism or incapacity for work may be relevant in these episodes. Because of the retrospective nature of our method for data collection we were not able to include the exacerbation related productivity cost in our calculations.

In conclusion, in the typical primary care population of patients with COPD studied we observed that patients with increasing severity of airflow obstruction did not experience more frequent, but more expensive exacerbations. The additional costs were mainly due to more physician consultations, requested diagnostic tests, and new prescriptions or adjustment of existing medication for relieve of respiratory symptoms. Although the probability of an oral corticosteroid prescription increased roughly along with the severity of airflow obstruction, a substantial number of exacerbations was not treated with either oral corticosteroids or antibiotics, which makes this healthcare utilisation based proxy measure a rather unreliable instrument for assessing exacerbation occurrence rates in primary care COPD studies.

References


General discussion
General discussion

The introduction of this thesis provided an inventory of the evidence regarding the efficacy (i.e., treatment effects in ideal experimental conditions) and effectiveness (actual treatment effect in real life conditions) of several interventions for COPD and asthma as established in 1997, and assessed the impact of a number of barriers towards optimal delivery of health care. Naturally, not all of the areas covered in the introduction could be elaborated on in this thesis. The two central topics that were investigated more profoundly in the preceding chapters were (I) aspects of utilization of spirometry in general practice; and (II) treatment with inhaled corticosteroids in different groups of patients with, or at high risk of chronic respiratory disease. These two topics are discussed below in the light of the results of the studies reported in this thesis.

I. Utilization of spirometry in general practice

Although it is obvious that spirometry does not capture the full impact of chronic airways disease on patients’ health, it remains the gold standard for diagnosing airflow obstruction and monitoring its progression. Spirometry is generally considered to be the best standardized and most reproducible measurement for this purpose currently available. Equipment is no longer a limiting factor for spirometry utilization in general practice, as rather inexpensive and reliable electronic spirometers have become available. According to the guidelines of the Dutch College of General Practitioners (NHG) and professional organisations in the field of respiratory care (e.g., the Global Initiative on Obstructive Lung Disease – GOLD) spirometry constitutes an essential tool to determine the presence and severity of airflow obstruction, and to distinguish between reversible and irreversible obstruction. The NHG guideline on COPD states that “the general practitioner (GP) can test and treat most patients with mild or moderately severe COPD, provided that the practice is in the possession of a spirometer and the GP is capable of interpreting the results of the lung function test”.

The first six chapters of this thesis dealt about different aspects of spirometry utilization in general practice. In the literature review reported in Chapter 1 it was concluded that application of spirometry in general practice may lead to better differentiation between COPD and asthma, which may bring about more adequate treatment targeting and, as a consequence, improved health status in patients. However, several years after the first chapter was written, there still is no firm scientific evidence that supports the presumption that the health of patients is indeed improved when GPs consistently apply spirometry while diagnosing and monitoring chronic
respiratory disease. Particularly the usefulness of monitoring spirometric indices as a routine part of the management of COPD may be exaggerated and has yet to be determined. Spirometry as an isolated tool for diagnosing and monitoring is unlikely to have an impact on patients’ health if the test results do not entail appropriate modification of the patients’ management. Because the treatment options recommended for COPD and asthma more and more diverge as new (pharmacological) interventions are introduced (e.g., long-acting bronchodilators) and established treatments and health care services are targeted to specific subgroups of patients partly on the basis of spirometric indices (e.g., indication for inhaled corticosteroids\(^5\), referral to secondary care - see Chapter 7), the relevance of broad implementation of spirometry in general practice increases.

If one is willing to accept the proposition that intensified use of spirometry for diagnostics and monitoring in primary care is indeed to the benefit of patients or to the efficiency of the health care system, one should at the same time be convinced of the feasibility of this type of lung function testing in the general practice setting. This point has been - and should remain to be – an important point of attention. After all, inadequate spirometric tests are likely to produce indices that are either too low (like, for instance, the FEV\(_1\)) or too high (the FEV\(_1\)/FVC ratio), which may result in false-positive or false-negative diagnoses or in overestimation or underestimation of the severity of airflow obstruction.

Chapter 1 highlighted some essential pre-conditions that should be met in a general practice when spirometry is to be implemented adequately. Whether general practice based spirometric tests are actually valid was the subject of investigation in the study reported in Chapter 2. In this study an effort was made to create the necessary pre-conditions in the involved general practices by providing spirometry training for practice staff, dispensing good quality spirometers, and arranging regular check-up of and maintenance service for the equipment. Contrary to our \textit{a priori} expectations the results of the study showed that a general practice spirometric test was on average not inferior to the same test conducted in a pulmonary function laboratory in the same patient when the same procedures and equipment were used. Apparently, with sufficient training of those executing the tests the current practice of performing spirometry in the general practice setting seems justifiable. This is an important observation, which provides a basis for initiatives to intensify the use of spirometers by GPs. Chapter 6 elaborated on some alternatives to arrange for spirometry facilities in primary care, and discussed the pros and cons of these alternatives.
Spirometry quality assurance

Ongoing spirometry quality standards are difficult to bring into the daily routine of general practice. Therefore, one should be aware of the fact that dwindling attention to quality assurance is a likely cause of declining quality of spirometric tests in general practice in the course of time. Even if those who execute the tests have been well trained initially, the relatively low rate of tests requested by GPs, the (often) limited number of staff members who have been trained to perform spirometry, the (often) limited attention to equipment calibration and maintenance, and the lack of any feedback on the quality of test performance are potential causes of decline of test quality.

Whether or not intensified guidance of the execution of tests could prevent the anticipated decline, a subanalysis of the study reported in Chapter 2 was performed to explore the effects of periodic supervision by lung function technicians on the achievements of general practices with regard to their spirometric tests. Intensified supervision and feedback has been shown to be effective in clinical trial settings and epidemiological studies. The results of the subanalysis reported in Chapter 4 indicate that even without additional quality assurance measures the overall performance of spirometric testing in general practice was quite acceptable a year after the initial training program. Nonetheless, periodic educational outreach visits did seem to contribute to maintaining the validity of the spirometric tests. Because of the labour-intensive nature of outreach visits, alternative options to maintain test validity may be more attractive. Making use of the possibilities that present-day spirometry software packages have to offer with regard to quality assurance may be an efficient way to keep those responsible for the execution of tests focussed on the quality of their work. The results of the small-scale study in healthy volunteers reported in Chapter 3 suggest that a simple intervention like exposing practice assistants to information from flow-volume curves may already lead to some improvement of spirometric test quality. Thus, even if a GP does not use flow-volume curves in his or her diagnostic evaluation of patients, the quality of spirometric tests is likely to benefit from critical assessment of the curves while executing a test. Therefore, if a general practice considers purchasing a spirometer, the device chosen should preferably display a real-time flow-volume curve. Another option for guidance of general practice spirometry quality assurance would be to receive feedback on tests that are send to a local lung function laboratory for judgement by an experienced technician. There are examples of general practices in the field that have established such a structure. Arrangements between a general practice and a local laboratories also offers the opportunity to institute periodic practice-teaching of nurse practitioners and practice assistants, and would also enable regular check-up and calibration of
spirometers. There are indications that primary care professionals fail to appreciate the importance of calibration, maintenance, and cleaning of spirometric equipment, especially in comparison with the stringent procedures that ought to be employed in lung function laboratories. Whether this apparent lack of attention towards equipment performance has consequences for the reliability of spirometric tests and, ultimately, for patient care in general practice is not known.

**Implementation of spirometry**

The maximum benefit of spirometry for primary care can only be achieved when GPs consistently integrate spirometric testing into their routine for diagnosing and managing patients with chronic respiratory disease. The apparent underutilization of spirometry in primary care is also illustrated by our experience that in a substantial number of subjects who are labelled by GPs as having COPD, no lung function testing has ever been carried out. In these subjects the assignment of the diagnosis COPD is not formally justified, as the presence of airflow obstruction has not been demonstrated. The degree to which spirometry is (under-)utilized is likely to vary from practice to practice and even from GP to GP. Implementation of spirometry could be enhanced by clearing away barriers that impede GPs to use spirometry. The essential first step is to aim for facilities for quality spirometry to be widely available and easily accessible: GPs and other primary health care professionals who are involved in the care for patients with respiratory disease should have access to spirometry, either for diagnosing and severity staging, for periodic monitoring of lung function, or both. It will depend on the local circumstances and preferences how spirometry can best be organized for a particular general practice: either in the practice itself, by means of centralized services like primary care group commissioned services, nurse-run asthma clinics or mobile community-based spirometry services, by arranging open access to pulmonary function laboratories, or a combination of these options (see Chapter 6). The transcripts of the discussion sessions with pulmonologists on which Chapter 7 was based also pointed to the indispensableness of spirometry to support GPs’ decisions whether or not to refer a patient to a pulmonologist, and the pulmonologists’ decision to pass on the patients’ management back to the GP when this is appropriate.

If a GP does not want to take up full diagnostic spirometry, he or she should at least consider the use of office screening spirometry, an approach that is also known as ‘exclusion spirometry’. A normal result from a (valid) screening test is probably sufficient to exclude respiratory impairment, except in asthma. An abnormal outcome of a screening test would require verification of the test outcome, or even additional diagnostic lung function testing by
using one of the services mentioned above (including a full diagnostic spirometry in the general practice itself). Although the diagnostic characteristics of this stepwise approach of using spirometry need to be evaluated before it can be recommended, it may be a rather efficient mode of applying spirometry in general practice. Screening spirometry can also be used to actively detect undiagnosed subjects with COPD in high-risk populations like, for instance, all former or current smokers, or smokers above a certain age. Although studies on the effects of this ‘case-finding’ approach are emerging, further research is needed to determine which combination of subject characteristics constitutes the most predictive and efficient profile to detect undiagnosed cases of COPD. Both the ethical and economic aspects of COPD case-finding in general practice also warrant further research attention.

Even with good accessibility of services there is no guarantee that GPs will indeed use spirometry in all cases in which this would be indicated. Little is known about the reasons why GPs choose to use spirometry or to refrain from it, but it is likely that a number of factors may play a role. The capability to organize spirometry, the possibility of delegation of tasks by GPs to practice assistants or practice nurses, the guaranteed availability of equipment on every occasion that it is needed, and lack of time are factors that are likely to be involved. Another factor which appears to be relevant is that a GP may simply be not convinced that spirometry adds relevant information to the usual routine of medical history taking and physical examination that he or she is acquainted with. Lack of self-confidence with regard to the interpretation of spirometric tests may also cause GPs to be reluctant to take up spirometry. In Chapter 5 of this thesis the achievements of GPs to interpret spirometric tests were investigated and although this simulation study does not necessarily reflect what happens in real life, some interesting observations were made. The results suggest that by using spirometry GPs may reduce their diagnostic uncertainty (or, in other words, narrow their differential diagnosis) but may also be inclined to confirm their diagnosis by requesting additional diagnostic testing, or by referring the patient to a pulmonologist. Whether remote support by a pulmonologist or by a computerized spirometry expert system can prevent this from happening in cases where it is not really necessary is currently being investigated in our department. Finally, the health economic consequences of enhanced implementation of spirometry in primary care are unclear. The question whether the extra costs of performing more spirometric tests in general practice are compensated by savings in other domains or by actual health benefits in patients has not been answered yet.

It will take time before all GPs have adopted spirometry as a self-evident part of their diagnostic repertory. The time that spirometers are as commonly used in general practices as
devices for measuring blood pressure is probably still years ahead of us. Facilitation of this development by means of financial and other incentives would be helpful to speed up this process.

II. Inhaled steroids in chronic respiratory disease

Asthma

Adherence and asthma self-management
Inhaled corticosteroids have been available for well over two decades now. For asthma the efficacy of these anti-inflammatory drugs has been demonstrated conclusively in the early nineties of the past century\(^{22-25}\) and the actual effectiveness has been confirmed in a large population based cohort study.\(^{26}\) Although new anti-inflammatory drugs have more recently been added to the available modes of therapy (e.g., leukotriene receptor antagonists) inhaled steroids still constitute the cornerstone of asthma management and are likely to keep this position for a number of years to come.

In a situation like this, in which a highly effective prophylactic drug is available for a particular chronic disease, GPs and other primary care professionals involved should try to optimize the actual utilization of these drugs in their practice population. In the case of inhaled steroids this can be achieved by neutralizing barriers that impede asthma patients to take maximum benefit from this prophylactic treatment, as was touched upon in the Introduction of this thesis. One of the barriers appears to be the well established observation that a substantial number of asthma patients do not use their inhaled steroids appropriately in terms of treatment adherence,\(^{27,28}\) or even quit using their prophylactic medication completely after a while.\(^{29-32}\) Although the evidence that this type of conduct actually compromises patients health mainly comes from retrospective and case-control studies in patients with rather severe asthma\(^{33-35}\), it is likely that non-adherence towards prescribed inhaled steroid treatment does indeed result in – potentially avoidable - morbidity. Thus, improving the actual utilization of inhaled steroids from the first prescription on in those patients that really need it is generally considered to be one of the main points of impact for improving asthma care.\(^{36}\)

A contemporary way to achieve this is to try and involve patients with asthma more closely in the management of their disease by equipping them with self-management skills.\(^{37}\) According to a recent meta-analysis the evidence on the isolated contribution of written self-management
plans in the known beneficial effects of comprehensive asthma care has not been firmly established.\textsuperscript{38} On the other hand, it has also been put forward that the use of individualised action plans is a pivotal factor in the success of self-management programs, especially when the action points for patients are based on personal best peak expiratory flow (PEF) rates and comprise inhaled as well as oral corticosteroid self-treatment of exacerbations.\textsuperscript{39}

The self-management study reported in Chapters 8 and 9 of this thesis included a written action plan that was based on personal best PEF and bronchial symptoms, and showed that the implemented self-management program was at least equally effective as the asthma treatment usually provided by Dutch GPs. Even while the actual benefit of the intervention of doubling the dose of inhaled steroids when asthma control starts to deteriorate has recently been questioned\textsuperscript{40}, self-management does seem to improve – or at least maintain - asthma patients’ health all the same. Moreover, it has been shown that by including a ‘step-down’ approach for the dose of inhaled steroids in the action plan a significant reduction in the use of inhaled steroids\textsuperscript{41} and bronchodilators\textsuperscript{42} can be achieved without compromising asthma control. (The sparing effect on inhaled steroids was also observed in the study reported in Chapters 8 and 9, whereas the effect on the use of bronchodilators was not.) The observation that patients continue to use self-management skills to one degree or another years after they have acquired these skills\textsuperscript{43} makes the initial investment worthwhile, as the cost of a self-management intervention seem to be recovered by savings in years thereafter.\textsuperscript{44} In the study in patients with mild to moderate asthma reported in Chapters 8 and 9 these savings were mainly due to the reduced use of inhaled steroids and the lower number of days with restricted activities. In patients with more severe asthma – a relatively small group in general practice - savings can also be expected in emergency visits and hospital admissions.\textsuperscript{45;46}

Combined with the argument that the self-management approach fits well in the present-day concept that patients should be more autonomous with regard to their treatment\textsuperscript{47}, the observed equivalence of self-management with, or even dominance over usual asthma care should be reason enough to facilitate implementation of self-management programs in general practice. By doing so, barriers of the constitutive kind (i.e., attitudes of patients and primary care professionals)\textsuperscript{48-50} and organizational kind (i.e., time, money, tools)\textsuperscript{51} that impede implementation can be expected. Practice nurses, a discipline that is increasingly seen in Dutch general practices\textsuperscript{52} and is expected to change usual general practice care for patients with chronic (respiratory) disease significantly, can play a central role in the implementation of self-management interventions for patients with asthma or other chronic diseases. The 2001 asthma treatment guidelines of the Dutch College of General Practitioners\textsuperscript{53} do not yet recommend the
use of written self-management action plans, but given the current state of evidence - to which
the study reported in this thesis contributed – the guideline appears to be outdated on this
specific point.

Even so, self-management will not be a suitable approach for all patients with asthma.54 Ideally
GPs should consider the appropriateness of a self-management intervention for each asthma
patient in their practice population, but directing self-management to those patients that are
likely to become successful ‘self-managers’ would be a more efficient and convenient way to
utilize this type of intervention. Although some work has been done in this area55-57, further
research is needed to establish the psychological, behavioural and other characteristics that
discriminate successful from unsuccessful self-managers among the patients with asthma
treated in general practice.

Self-management interventions have also been investigated in COPD, but the goals that are
pursued in COPD patients are quite different than for asthma, as are the points of impact that
patients have to self-manage their disease. For instance, inhaled steroid dose-adjustment when
disease control starts to deteriorate is not applicable in COPD, whereas in asthma this is one of
the core elements of self-management. In COPD self-management the focus is mainly on
teaching patients how to carry out their physical activities optimally given their physiological
impairment, and to prevent or decrease the severity of exacerbations through lifestyle
modification.58 A recent meta-analysis concluded that the current body of literature contains
insufficient data to give evidence-based recommendations on the efficacy of self-management
in COPD.59 Further research in this area is needed, particularly to establish the value of self-
management programs for patients with mild to moderate disease, who constitutes the major
part of all patients with COPD managed in general practice.12

Asthma self-management and combination treatment

The recent introduction of inhalation devices that contain the combination of an inhaled steroid
and a long-acting β2-agonist may be an attractive alternative treatment option in patients who
are not eligible for self-management. Although the final results of several recently finished
‘landmark’ trials will have to be awaited, evidence is accumulating that ‘single inhaler’
combined treatment with an inhaled steroid and a long-acting β2-agonist provides a superior
level of asthma control in the asthma populations studied.60-63 Although unquestionably more
convenient for the patient, a combination formulation has the potential to decrease the
flexibility required to successfully manage asthma over long periods of time.64 Thus, the
availability of single inhaler treatment requires asthma self-management interventions to be
repositioned. After all, the aim of guided self-management is to give patients the ability to control their own disease with guidance from a healthcare professional, and one of the keys to achieve this is to self-regulate the use of respiratory medication to the most adequate (or minimal) level that is required at a particular time. This implies that patients should have the possibility to be flexible in deciding how much of which drug is required. By using a single inhaler that contains two drugs with different treatment targets (inflammation and bronchodilation, respectively), this flexibility is no longer practicable because patients can no longer vary the dose of the prophylactic compound (the inhaled steroid) without simultaneously adjusting the compound for symptom relief (the long-acting bronchodilator). This seriously limits patients’ liberty to self-manage their disease. Because the regular use of a long-acting β₂-agonist in itself already seems to improve the adherence towards inhaled steroid treatment, the concern that this adherence will decrease under concomitant use of a long-acting β₂-agonist appears to be unfounded. Therefore, single inhaler treatment may better be reserved for those patients in whom other options— including self-management and the use of separate inhalers for administering inhaled steroids and (long-acting) β₂-agonists— fail or are inappropriate for other reasons, like for instance in case of insufficient and incorrigible perception of asthma control, or the presence of important comorbidity.

II.B. COPD

Inhaled steroids and exacerbations

In contrast with asthma, patients with COPD are generally much less responsive to the anti-inflammatory actions of inhaled steroids. Despite a number of large clinical studies that have been conducted in recent years the efficacy of inhaled steroids in COPD has not been established quite as unambiguously as in asthma. Two recent meta-analyses of published studies have indicated that there may be a small effect of inhaled steroids on the FEV₁ decline of 5 to 8 millilitres per year, but the clinical relevance of an effect this size remains questionable. The study reported in Chapter 10 indicates that initiating regular inhaled steroid treatment in an earlier or pre-clinical stage of the disease does not seem to provide a solution as well, as the progressive deterioration of lung function and other respiratory health outcomes were not beneficially affected. Chapter 11 and 12 presented data from the COPD on Primary Care Treatment (COOPT) study, a randomised controlled clinical trial performed by the departments of general practice of the University Medical Centre Nijmegen and Maastricht
This particular study aims to evaluate the effectiveness of an inhaled steroid (fluticasone propionate 500 microgram b.i.d.) and the anti-oxidative agent N-acetylcysteine (600 milligram o.d.) in former or current smokers with mild to moderate COPD or persistent symptoms of chronic bronchitis. The COOPT study concludes in 2004 and will provide complementary evidence on the position of inhaled steroids and N-acetylcysteine in the management of COPD.

In recent years, investigators involved in the evaluation of pharmacologic and non-pharmacologic treatment in COPD have shifted their attention from lung function decline as the primary outcome of interest to the occurrence of acute exacerbations and changes in health status. This shift was partly driven by the observation that inhaled fluticasone propionate was ineffective in decelerating the annual FEV\textsubscript{1} decline, but at the same time was effective in preventing acute exacerbations and slowing the deterioration of health status. The data on exacerbations reported in Chapter 12 show that in patients with COPD or chronic bronchitis who are treated in (Dutch) general practice, the annual occurrence rate of exacerbations is rather low. With a mean rate of less than one exacerbation per year and a quarter of all patients not suffering from a single exacerbation in the 2-year retrospective observation period, the room for improvement for any prophylactic treatment seems limited in this patient population.

On the other hand, it has been reported that many COPD exacerbations are not documented in medical records because patients do not necessarily contact their physician in case of worsening of their disease. This seems unfortunate, because timely intervention does seem to improve the course and recovery of exacerbations, which may subsequently affect the course of patients’ health status. However, exacerbation rate is a difficult outcome to measure in clinical studies, especially while proxy definitions based on health care utilization (which are quite frequently used) do not seem to be adequate. Therefore, better methods to assess the occurrence of exacerbations and to express their severity are required.

**Indications for inhaled steroid treatment in COPD**

As was noted in Chapter 7 priority should be given to identifying the (relatively small) group of patients with COPD that do benefit from regular inhaled steroid treatment. Current COPD management guidelines specify criteria for regular inhaled steroid treatment in patients with COPD. The table below summarizes the recommendations with regard to inhaled steroid treatment in the various guidelines.
Indications for regular inhaled steroid treatment in COPD guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year</th>
<th>Indication for regular inhaled steroid treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹</td>
<td>2003</td>
<td>Based on publications appearing since June 2000, the 2003 Report recommends use of inhaled glucocorticosteroids only in patients with severe or very severe (Stages III and IV) COPD and frequent exacerbations.</td>
</tr>
<tr>
<td>B National Institute for Clinical Excellence (NICE)⁷</td>
<td>2004</td>
<td>Inhaled corticosteroids should be prescribed for patients with an FEV₁ ≤ 50% predicted who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period.</td>
</tr>
</tbody>
</table>
| C American Thoracic Society (ATS) and European Respiratory Society (ERS)(3200) | 2004   | In patients with more advanced disease (usually classified as an FEV₁ <50% predicted) there is evidence that the number of exacerbations per year and the rate of deterioration in health status can be reduced by inhaled corticosteroids in COPD.  
... When therapy is thought to be ineffective, a trial of withdrawing treatment is reasonable. Some patients will exacerbate when this occurs, which is a reason for re-instituting this therapy. |
| D Dutch College of General Practitioners (NHG)³                          | 2001   | History of asthma and/or atopy, non-smoker: continue in case of (subjective) effect, discontinue when no effect.  
Frequent exacerbations (≥3 in last winter or year): continue in case of improvement (i.e., reduction of number of courses of prednisone or antibiotics or hospital admissions for COPD); discontinue if no effect. |

The table shows that the guidelines that have recently been issued by leading respiratory professional organisations (A, B, and C) are consistent in recommending that inhaled steroids should be prescribed in patients with advanced COPD who experience frequent exacerbations. It should be mentioned that For Dutch GPs this would mean that - at the most - one out of every five patients with COPD would have an indication for inhaled steroid treatment¹², and it is quite likely that in many of these cases pulmonologists have already taken over the patients’ treatment. Moreover, the clinical studies on which the recommendations in the guidelines are based have predominantly included patients with moderate to (very) severe disease. As a consequence, the milder side of the COPD severity spectrum has been underexposed while
establishing the efficacy of inhaled steroids in terms of prevention of exacerbations and other outcomes.

Still, it is rather unsatisfactory that the severity of airflow obstruction and the past rate of exacerbations should determine whether or not a patient with COPD should be prescribed an inhaled steroid. The question as to why patients with more severe disease show a treatment response and patients with less severe disease do not has not been answered. Apparently, with the current state of knowledge it is not possible to give more specific indications based on characteristics of the actual inflammatory process underlying the disease in a particular COPD patient.\textsuperscript{79} Meanwhile, the perception among Dutch pulmonologists that the presence of bronchial hyperresponsiveness in a COPD patient is a useful criterion to base regular inhaled steroid treatment on (see Chapter 7) does not seem to be well-founded. Bronchial hyperresponsiveness, which is often considered to be discriminative between asthma and COPD, can actually be present in both conditions.\textsuperscript{80} A 6-month follow-up study in COPD patients with bronchial hyperresponsiveness showed that fluticasone did have a positive effect on lung function indices compared with placebo, but that the hyperresponsiveness itself was not significantly reduced.\textsuperscript{81} This finding runs parallel with the subgroup analysis of the study reported in Chapter 10, in which it was observed that subjects with an accelerated lung function decline and bronchial hyperresponsiveness showed an FEV\textsubscript{1} response on fluticasone during the first few months, but no subsequent modifying effect of continued fluticasone treatment on the annual FEV\textsubscript{1} decline was observed. Thus, the limited evidence currently available contradicts the notion that it is useful to include the presence of bronchial hyperresponsiveness in the decision to prescribe inhaled steroid treatment in a particular patient with COPD.

Despite the lack of effect in terms of bronchial hyperresponsiveness, it has been shown that inhaled steroids may affect specific cellular and molecular aspects of the inflammation in the airways of patients with COPD. Beneficial effects on the numbers of mast cells, neutrophils and macrophages present in the bronchial wall tissue and bronchoalveolar lavage fluid as well as on levels of inflammatory mediators have been reported\textsuperscript{82-86}, although other authors have produced evidence against an anti-inflammatory action of inhaled steroids in COPD.\textsuperscript{87} During the last decade sputum induction has offered a rather save and noninvasive method to study the inflammatory process in the airways of patients with COPD.\textsuperscript{88} Induced sputum analysis can be used to distinguish between asthma and COPD\textsuperscript{89}, and there is some evidence that the absence of sputum eosinophilia is associated with steroid resistance.\textsuperscript{90} Determination of the presence of sputum eosinophilia or levels of specific inflammatory mediators may help physicians to identify the subgroup of COPD patients who are particularly responsive to inhaled steroid
treatment. Although the health outcomes of pharmacogenetics - an evolving and promising field of research - are largely untested, this technology may also have the potential to identify inhaled steroid responsive COPD patients. Hopefully, in future guideline revisions it will be possible to include a more sophisticated profile of those patients with COPD that are likely to benefit from long-term inhaled steroid treatment.

Discontinuation of inhaled steroids
From the discussion above it follows that regular inhaled steroid treatment is only indicated for a limited number of patients with COPD. Interestingly, it has recently been reported that GPs and pulmonologists in Belgium prescribe inhaled steroids considerably more often than guidelines recommend, although this finding is not per se generalizable to other countries. Even so, it is not surprising that in the year 2002 a substantial proportion (~60%) of all patients with COPD in the Netherlands received inhaled steroids on a regular basis. Chapter 11 of this thesis presented the results of a study in which inhaled steroid treatment was discontinued in a general practice population of patients with COPD and (ex-) smokers with chronic bronchitis. In this study 37% of the patients experienced an adverse outcome during the first three months after withdrawal, and although the study did not include a control group of patients who continued the use of their inhaled steroids, a relapse rate of ~40% has also been reported in another uncontrolled study and two studies that did include a cross-over control condition or a parallel control group.

Two of the guidelines referred to above provide recommendations on how to deal with discontinuation of inhaled steroid treatment in patients with COPD. In both guidelines a ‘trial and error’ approach is recommended. As long as the determinants of a long-term inhaled steroid treatment response are insufficiently underpinned, such a pragmatic approach - which does not necessarily require definite diagnostic labelling of patients - is required. A step-down scheme which permits an early check of whether an adverse response to inhaled steroid discontinuation is to be expected may be well-advised. Until better indications can be formulated to support the discontinuation (or, more importantly, the initiation) of inhaled steroid treatment in COPD, educational or other interventions aimed at GPs and pulmonologists are needed to reduce the number of patients in which this treatment is superfluous.
References


Summary
Summary

The introduction gives a summary of a comprehensive literature review on the efficacy and effectiveness of health care interventions for COPD (chronic obstructive pulmonary disease) and asthma. Barriers associated with the primary process of care delivery were also identified. These barriers comprised, among others, delayed contact of patients with the health care system, diagnosis of the respiratory condition, indications for pharmacological and non-pharmacological interventions, the actual execution of care and treatment compliance by patients. The literature review was performed as a part of the 1997 Public Health Status and Forecasts (PHSF) project enforced by the National Institute of Public Health and the Environment (RIVM).

In Chapter 1 the need for widespread use of spirometry in primary healthcare is appraised through a more specific literature review. The added value of spirometry for and the quality of measurements made by general practitioners (GPs), and the economic consequences of intensified use of spirometry in primary care are discussed. Appropriate application of spirometry in general practice may lead to improved health status of patients with COPD or asthma, but consistent attention to quality assurance measures is vital. If good quality cannot be guaranteed in the general practice setting, the reliability and validity of the tests is uncertain. Pulmonary function laboratories, nurse-run asthma clinics, primary care group commissioned and mobile community-based spirometry services may be other choices, but it depends on local availability as to which choice is most suitable for organising primary care spirometry.

The aim of the study reported in Chapter 2 was to investigate the validity of spirometric tests performed in general practice. A within-subject comparison of spirometric tests with a ‘gold standard’ (spirometric tests performed in a pulmonary function laboratory) was performed in 388 patients with COPD. GPs and practice assistants took part in a baseline spirometry workshop. Within subject differences in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) between laboratory and general practice tests were determined. Relevant spirometric indices measured by trained general practice staff were marginally but statistically significantly higher than those measured in pulmonary function laboratories, indicating consistently higher values for general practice measurements. The proportion of non-reproducible tests was very similar for the laboratory and general practice tests. Because of the limited agreement between laboratory and general practice values the use of these measurements interchangeably is probably better avoided, but with sufficient training of practice staff the current practice of performing spirometric tests in the general practice setting seems justifiable.
The study reported in Chapter 3 was performed to explore the effect of periodic educational outreach visits by lung function technicians on the validity of general practice spirometry in patients with COPD. ‘Intervention group’ practices were periodically visited by a lung function technician, who focussed on optimization of spirometric test performance. ‘Reference group’ practices were not visited. A baseline spirometry workshop was offered to both groups of practices. Outcomes were the within-subject differences in forced expiratory volume in 1 second ($\Delta FEV_1$) and forced vital capacity ($\Delta FVC$) between laboratory and general practice tests (practice minus laboratory value). Intervention and reference group practices differed in number and age of practice assistants and GPs’ attendance at the baseline spirometry workshops. In the first year evaluation the mean $\Delta FEV_1$ and $\Delta FVC$ favoured the general practice tests in both groups. A year later, $\Delta FEV_1$ and $\Delta FVC$ were higher in intervention group patients compared to reference group patients. Although initially the validity of spirometric tests was sufficient in the intervention as well as reference group practices, periodic educational outreach visits by lung function technicians seemed to prevent regression of test validity over time, especially in terms of FVC values.

In Chapter 4 it was investigated whether the use of feedback information provided by flow/volume curves during spirometry as performed by practice assistants improves spirometry test quality. To address this issue, a randomised controlled crossover study was performed in which general practice assistants performed spirometry in healthy volunteers in two different measurement conditions, one allowing viewing flow/volume curves during the tests (‘unblinded’), the other not (‘blinded’). Outcomes were differences in the most relevant spirometric indices and the repeatability and number of manoeuvres per test. Higher PEF (peak expiratory flow) values were observed for the unblinded condition, but the other outcomes (i.e., $FEV_1$, $FVC$, $FEV_1/FVC$) showed no differences. Two lung function technicians judged that the flow/volume curves obtained in the unblinded condition were somewhat better. This study in healthy subjects suggests that the use of information from flow/volume curves leads to a modest quality improvement of spirometric tests performed by practice assistants.

The aim of the study reported in Chapter 5 was to compare the achievements of trained GPs in spirometric diagnosis with an expert consensus panel, and to assess the influence of spirometry on the GPs decision-making. Twelve paper cases including a range of flow/volume curves were interpreted by 39 GPs as well as a by an expert panel. The results showed that normal curves and obstructive curves were reasonably well diagnosed, while rare and mixed disease patterns achieved considerably lower scores. Intermediate scores were obtained in the recognition of incorrect test manoeuvres. Spirometry influenced GPs decision-making in reducing the number of alternative diagnoses, but also increased referral rates to pulmonologists as well as the use of diagnostic predniso(lo)ne courses considerably. Trained
GPs were able to differentiate between normal and obstructive disease patterns, while curves suggestive of rare and mixed pathology were often missed. Spirometry also seems to influence the decision-making process of the GP.

Chapter 6 is an editorial on the annual World COPD Day which has been instituted by the Global Initiative for Chronic Lung Disease (GOLD). On this particular day people worldwide are encouraged to review their respiratory health status and consult a doctor in case of certain symptoms, especially when they are smokers. Spirometry would be regarded as an integral component of this consultation. Thus, a likely and desirable outcome of World COPD Day could be a considerable and perhaps dramatic increase in demand for spirometry. An essential requirement would seem to be the development of high quality spirometry by family physicians on a large scale. World COPD Day aims to promote public awareness of COPD, and it is to be hoped that early diagnosis of COPD will facilitate the prevention of further damage to the airways and lungs, predominantly by focusing on smoking cessation. Thus, spirometry, in conjunction with a commitment to smoking cessation initiatives, has the potential to impact significantly on global health. However, its true potential will only be achieved by ensuring that quality spirometry is widely available in primary care.

In Chapter 7 the prevailing views of pulmonologists regarding referral and consultation in asthma and COPD are explored and compared with published referral guidelines for GPs and pulmonologists. Twenty-nine Dutch pulmonologists working at non-university hospitals or specialised chest clinics participated in group discussion sessions. The outcome of the discussions and the published referral guidelines for GPs and pulmonologists showed considerable similarity, but also some marked discrepancies. The main points of disagreement among the pulmonologists were: 1) should GPs or pulmonologists add long-acting bronchodilators (β₂-agonists) to asthma treatment regimens; 2) should the current cut-off point for severity of airflow obstruction (‘predicted FEV1 <50%’) for referral of patients with COPD be increased; and 3) should an annual exacerbation rate of two episodes a year be used as an undifferentiated referral criterion for COPD patients? For asthma, proposed back-referral (i.e. from pulmonologist to GP) criteria rested on: required dose of inhaled steroids, persistent need for long-acting β₂-agonists, duration of clinical stability and persistence of airflow obstruction. Back-referral criteria for COPD rested on age, blood-gas abnormalities and ventilatory limitations. Primary care monitoring facilities and ‘shared-care’ constructions were considered to be facilitating conditions for back-referral. Overall, this explorative study provided insights into how pulmonologists visualise a rational referral policy for patients with asthma or COPD. These insights can be included in future revisions of guidelines for GPs and pulmonologists.
In Chapter 8 a study to determine the effectiveness of asthma self-management in general practice is reported. Nineteen general practices were randomly allocated to usual care or self-management and 214 adult asthma patients were included in the study. In the two year follow-up the proportion of successfully treated weeks per patient in the usual care group was 72% compared with 78% in the self-management group. The mean number of limited activity days was 1.2 in the self-management group and 3.9 in the usual care group. Lung function indices (i.e., FEV₁, reversibility) and bronchial hyperresponsiveness did not change. There was a saving of 217 puffs of inhaled steroid per patient in favour of the SM group. It was concluded that self-management lowers the burden of illness as perceived by patients with asthma and is at least as effective as the treatment usually provided in Dutch primary care. Moreover, self-management appears to be a safe basis for intermittent treatment with inhaled corticosteroids in patients with asthma.

Chapter 9 describes an extensive economic evaluation of the asthma self-management study reported in Chapter 8. We hypothesized that introducing self-management would not compromise asthma control while the cost would be equal to or lower than in usual care. Patient-specific cost data were collected, health preferences were assessed, and incremental cost per quality-adjusted life year (QALY) and per successfully treated week gained were calculated. Self-management patients gained more QALYs and experienced more successfully treated weeks during the 2-year observation period. Self-management patients consumed less puffs of budesonide compared to usual care patients. The productivity cost due to limited activity days were lower among self-management patients. When all costs were included, self-management was cost-effective on all outcomes studied. Thus, guided self-management is a safe and efficient alternative approach compared with asthma treatment usually provided in Dutch primary care.

In Chapter 10 the clinical effects of early introduction of inhaled corticosteroids (fluticasone propionate) in subjects showing early signs and symptoms of COPD without a prior clinical diagnosis were investigated in a randomised clinical trial. Subjects with an accelerated annual lung function decline and persistent respiratory symptoms were detected in a general population screening and monitoring program. Forty-eight subjects were randomized (24 fluticasone, 24 placebo). After 3 months, the forced expiratory volume in 1 second (FEV₁) before and after administration of a bronchodilator had increased in the fluticasone relative to the placebo group. However, the subsequent decline of the FEV₁ was not beneficially modified by fluticasone treatment. There were no differences in respiratory symptoms, functional status, or exacerbations favouring fluticasone treatment. The presence of bronchial hyperresponsiveness modified the initial FEV₁ response on fluticasone, but not the subsequent annual FEV₁ decline. Early initiation of inhaled steroid treatment does not seem to affect the
progressive deterioration of lung function or other respiratory health outcomes in subjects with early signs and symptoms of COPD.

The objective of the study reported in Chapter 11 was to assess the probability and explore determinants of an adverse respiratory outcome (exacerbation or increase of respiratory symptoms) after discontinuation of inhaled corticosteroid (ICS) treatment in patients with COPD. A prospective unblinded ICS withdrawal study was performed in 201 patients with COPD with various degrees of airflow limitation who were diagnosed and treated in general practice. The overall probability of an adverse respiratory outcome within three months after ICS discontinuation was 0.37. Age, gender, smoking status and reversibility of airflow limitation were predictors of adverse respiratory outcome. It was concluded that discontinuation of inhaled corticosteroids may harm some patients with COPD. The probability of an adverse respiratory outcome may be higher in women, elderly patients, smokers and patients with higher bronchodilator reversibility while on inhaled steroid treatment.

Chapter 12 reports on the occurrence rate, treatment, and healthcare costs of exacerbations in patients with COPD in Dutch general practice. The baseline data from the COPD on Primary Care Treatment (COOPT) trial were used. Details on the occurrence and management of exacerbations were collected by systematic medical record review for the 2-year period preceding trial inclusion. Following international criteria, subjects had chronic bronchitis without obstruction (26%), mild airflow obstruction (19%), moderate obstruction (40%) or severe obstruction (15%). The overall mean annual exacerbation rates was 0.88. Exacerbation rate was not related to severity of airflow obstruction. The mean annual exacerbation costs per patient were €40, €53, €61 and €92 for the respective severity subgroups. The increase of costs in the more severe subgroups was mainly attributable to more physician consultations, diagnostic procedures, and prescription of reliever medication (e.g., bronchodilators, cough preparations). It was concluded that in a general practice population of patients with COPD the occurrence of exacerbations does not depend on the severity of airflow obstruction, whereas the healthcare cost associated to exacerbations increase along with the severity of airflow obstruction.
Samenvatting
Samenvatting

De Introductie geeft een samenvatting van een uitgebreide literatuurstudie naar de werkzaamheid en doeltreffendheid van zorginterventies bij patiënten met chronic obstructive pulmonary disease (COPD, of ‘chronisch obstructief longlijden) en astma. Tevens werden barrières in het primaire proces van zorgverlening geïdentificeerd. Deze barrières omvatten onder andere verlaat contact van patiënten met het zorgsysteem, de diagnostiek van chronische luchtwegaandoeningen, indicatiestelling voor medicamenteuze en niet-medicamenteuze interventies, de feitelijke uitvoering van zorg en de therapietrouw van patiënten. De literatuurstudie was onderdeel van de Volksgezondheid Toekomst Verkenning 1997, uitgevoerd door het Rijksinstituut voor Volksgezondheid en Milieu (RIVM).

Aan de hand van een andere literatuurstudie wordt in Hoofdstuk 1 de behoefte van brede toepassing van spirometrie in de eerstelijns gezondheidszorg belicht. Spirometrie wordt steeds meer toegepast in huisartspraktijken en biedt daar een meerwaarde bij vooral de (vroeg-)detectie en behandeling van obstructieve longaandoeningen. De betrouwbaarheid van spirometrie verricht in de huisartspraktijk is minder gegarandeerd dan in longfunctie- of huisartsenlaboratoria, waardoor spirometrie in eigen beheer van de huisarts minder geschikt lijkt voor het monitoren van het longfunctiebeloop. Spirometrie kan wel een waardevol en haalbaar instrument zijn voor huisartsen, onder voorwaarde dat de uitkomsten adequaat geïntegreerd worden in het huisartsgeneesekundig denken en handelen. De economische consequenties van wijdverspreide toepassing van spirometrie in de huisartspraktijk zijn vooralsnog onduidelijk. Als een huisartspraktijk de kwaliteitsbewaking onvoldoende kan garanderen, kunnen longfunctie- en huisartsenlaboratoria een belangrijke plaatsvervangende of ondersteunende rol spelen.

Het doel van de studie in Hoofdstuk 2 was de betrouwbaarheid van spirometrietests zoals uitgevoerd in Nederlandse huisartspraktijken nader te bepalen. Hiertoe werden van 388 patiënten met COPD uit 61 huisartspraktijken de spirometrietests uit de huisartspraktijken vergeleken met de bestaande ‘standaardtest’: een spirometrietest verricht in een longfunctielaboratorium. Voor aanvang van het onderzoek volgden huisartsen en praktijkassistenten een spirometrie cursus. Binnenpersoonsverschillen tussen laboratorium- en huisartspraktijk tests in het geforceerde expiratoire volume in 1 seconde (ΔFEV₁) en de geforceerde vitale capaciteit (ΔFVC) werden per patiënt berekend als effectmaten. Uit de resultaten bleek dat de meetwaarden uit huisartspraktijken consistent hoger waren en dat het percentage niet-reproduceerbare tests, een kwaliteitsindicator, niet verschilde tussen de laboratorium- en huisartspraktijk tests. De conclusie van het onderzoek luidde dat relevante spirometrische meetwaarden door getrainde medewerkers in huisartspraktijken bepaald, marginaal (maar wel statistisch significant) hoger waren dan dezelfde waarden gemeten in een
longfunctielaboratorium. Vanwege de beperkte overeenstemming tussen de spirometrieuitslagen uit laboratoria en huisartspraktijken kan het afwisselend gebruik van metingen uit deze verschillende locaties beter worden vermeden. De resultaten van dit onderzoek lijken een ondersteuning voor de inmiddels wijdverspreide ontwikkeling om spirometrie in eigen beheer van de huisartspraktijk uit te voeren.

In **Hoofdstuk 3** wordt het effect van periodieke begeleidingsbezoeken door een longfunctielaborant op de betrouwbaarheid van spirometrietests bij COPD-patiënten in de huisartspraktijk bestudeerd. Praktijken in een ‘interventiegroep’ werden periodiek bezocht door een longfunctielaborant die zich richtte op het optimaliseren van de uitvoering van spirometrietests. Praktijken in een ‘referentiegroep’ werden niet bezocht. Huisartsen en praktijkassistenten uit beide groepen praktijken kregen vooraf een spirometrietraining aangeboden. Binnenpersoonsverschillen tussen laboratorium- en huisartspraktijktests in het geforceerde expiratoire volume in 1 seconde ($\Delta FEV_1$) en de geforceerde vitale capaciteit ($\Delta FVC$) werden per patiënt berekend als effectmaten en vergeleken tussen de interventie- en referentiegroepen. In een aantal opzichten (bijv. aantal en leeftijd van praktijkassistenten, bijwonen van de spirometrienascholing) waren de praktijken in de interventie- en referentiegroepen niet volledig met elkaar vergelijkbaar. In het eerste jaar van de evaluatie vielen de effectmaten ($\Delta FEV_1$ en $\Delta FVC$) in beide groepen ten gunste van de huisartspraktijken uit. Een jaar later waren de effectmaten echter beter in de interventiegroep dan in referentiegroep. Geconcludeerd werd dat - hoewel de betrouwbaarheid van de spirometrietests feitelijk toereikend was in beide groepen praktijken - periodieke begeleiding door een longfunctielaborant een terugval in de betrouwbaarheid van spirometrietests in de loop der tijd mogelijk kan voorkomen.

In **Hoofdstuk 4** werd onderzocht in hoeverre het gebruik van informatie die tijdens de uitvoering van spirometrietests voortkomt uit flow/volume curven de kwaliteit van door doktersassistenten uitgevoerde tests ten goede komt. Om dit te onderzoeken werd een gerandomiseerd, gecontroleerd experiment verricht. Daarin verrichten huisartspraktijkassistenten bij gezonde proefpersonen spirometrie onder twee verschillende meetcondities. Bij de ene conditie was de flow/volume curve zichtbaar tijdens de test (‘ongeblindeerd’), bij de andere conditie niet (‘geblindeerd’). Effectmaten waren de verschillen tussen de twee condities in de belangrijkste meetwaarden uit spirometrie, de reproduceerbaarheid van tests en het aantal blaaspogingen per test. Onder ongeblindeerde omstandigheden werden hogere pickstroomwaarden (PEF) gemeten; voor de overige effectmaten (d.w.z. FEV$_1$, FVC, en FEV$_1$/FVC) werden géén verschillen gevonden. Twee longfunctielaboranten oordeelden dat de flow/volume curven die waren verkregen onder de ongeblindeerde omstandigheden iets vaker van betere kwaliteit waren. Deze studie bij
gezonde proefpersonen duidt erop dat het gebruik van informatie uit flow/volume curven leidt
tot enige kwaliteitsverbetering bij spirometrietests zoals uitgevoerd door doktersassistenten.

Het doel van het in Hoofdstuk 5 beschreven onderzoek was om de prestaties van huisartsen
bij het diagnosticeren en interpreteren van spirometrie te vergelijken met de interpretatie van
een panel van deskundigen en de invloed van spirometrie op het proces van besluitvorming
van huisartsen vast te stellen. Twaalf ‘papieren’ casus, die een variëteit aan flow/volume
curven omvatten, werden door 39 huisartsen beoordeeld; onafhankelijk daarvan deed het
deskundigenpanel hetzelfde. De resultaten lieten zien dat normale curven en obstructieve
afwijkingen redelijk goed door de huisartsen werden herkend, terwijl dat bij minder
voorkomende en gemengde ziektebeelden veel minder het geval was. Redelijke prestaties
werden gevonden voor het herkennen van slecht uitgevoerde spirometrietests. Spirometrie
beïnvloedde het beslisproces van huisartsen, wat tot uiting kwam in een afname van het aantal
alternatieve diagnosen, een aanzienlijke stijging van het aantal verwijzingen naar longartsen
en het gebruik van diagnostische prednisontests. Geconcludeerd werd dat in spirometrie
nageschoolde huisartsen goed in staat bleken te differentiëren tussen normale curven en
obstructieve afwijkingen, terwijl curven die passen bij weinig voorkomende of gemengd
ziektebeelden relatief vaak verkeerd werden beoordeeld. Spirometrie leek tevens invloed te
hebben het beslisproces van huisartsen in termen van verwijzing en aanvullende diagnostiek.

Hoofdstuk 6 betreft een redactioneel artikel over de World COPD Day (‘Wereld COPD
Dag’), die is uitgeroepen door de Global Initiative for Chronic Lung Disease (GOLD). Op
deze jaarlijks terugkerende dag worden mensen wereldwijd aangemoedigd om aandacht te
schenken aan de toestand van hun longen en luchtwegen en om bij bepaalde symptomen een
arts te consulteren, vooral wanneer zij (nog) roken. Spirometrie maakt vervolgens integraal
onderdeel uit van zo’n consult. De - wenselijke - uitkomst van World COPD Day is derhalve
een substantiële toename in de vraag naar spirometrie. Een essentiële voorwaarde daarbij is
dat er op grote schaal hoogwaardige spirometriefaciliteiten voor huisartsen beschikbaar zijn.
‘Wereld COPD Dag’ richt zich op het stimuleren van de publieke aandacht voor COPD,
waarmee mogelijk door vroege herkenning en diagnostiek van COPD verdere schade aan de
longen en luchtwegen kan worden voorkomen. In combinatie met een verhoogde aandacht
voor stop-roken initiatieven heeft spirometrie de potentie om een forse impact te hebben op de
volksgezondheid van de wereldbevolking. Dit streven kan echter alleen worden gerealiseerd
indien er voldoende kwalitatief goede spirometriefaciliteiten voor de eerste lijn beschikbaar
zijn.

In Hoofdstuk 7 werden de visies van longartsen op verwijzing en consultatie bij astma- en
COPD-patiënten verkend en vergeleken met gepubliceerde transmurale richtlijnen voor huis-
en longartsen. Negenentwintig Nederlandse longartsen uit niet-academische ziekenhuizen en
gespecialiseerde longrevalidatiecentra namen deel aan groepsdiscussies. De uitkomsten van
de discussies en de gepubliceerde richtlijnen ten aanzien van verwijzing lieten duidelijke
overlap zien, maar ook enkele duidelijke discrepanties. De belangrijkste verschillen in
inzichten tussen de longartsen onderling waren: 1) moet de huisarts of de longarts een
langwerkende luchtwegverwijder (β₂-agonist) toevoegen aan het behandeling bij astma; 2)
moet het huidige afkappunt voor de ernst van luchtwegobstructie (‘voorspelde FEV₁<50%’) voor
verwijzing van patiënten met COPD omhoog worden bijgesteld; en 3) moet een
exacerbatiefrequentie van twee per jaar wel als een ongedifferentieerd verwijs criterium
gelden bij patiënten met COPD? Voor terugverwijzing van astmapatiënten door de longarts
naar de huisarts werden als criteria voorgesteld: de benodigde onderhoudsdosering
inhalatiesteroïden; een aanhoudende noodzaak voor gebruik van langwerkende β₂-agonisten;
duur van de periode waarin een patiënt ‘klinisch stabiel’ is; en het bestaan van een
persisteerende luchtwegobstructie. Als criteria voor terugverwijzing bij COPD werden
genomen: leeftijd, afwijkende bloedgaswaarden en ventilatoire beperkingen. Faciliteiten voor
monitoring in de eerste lijn en het bestaan van ‘shared-care’ constructies werden door de
longartsen beschouwd als omstandigheden die terugverwijzing van patiënten naar de huisarts
zouden bevorderen. Deze exploratieve studie verschafte inzicht in hoe longartsen aankijken
tegen een rationeel verwijsbeleid bij patiënten met astma of COPD. Deze inzichten kunnen
worden betrokken in toekomstige revisies van richtlijnen voor huis- en longartsen.

Hoofdstuk 8 betreft de evaluatie van een gerandomiseerde studie naar de effectiviteit van een
zelfmanagementprogramma voor patiënten met astma in de huisartspraktijk. Negentien
huisartspraktijken verstrekten ofwel ‘gebruikelijke huisartsenzorg’, ofwel ‘zelfmanagement’.
In totaal namen 214 volwassen astmapatiënten deel aan de studie. Tijdens de
observatieperiode van twee jaar bedroeg het gemiddelde percentage ‘succesvol behandelde
weken’ per patiënt 72% in de groep die gebruikelijk zorg ontving; in de zelfmanagementgroep
was dit 78%. Het aantal dagen waarop patiënten beperkingen in hun dagelijkse activiteiten
ondervonden was gemiddeld 1,2 bij zelfmanagement en 3,9 bij gebruikelijke zorg.
Longfunctiewaarden (d.w.z. FEV₁, reversibiliteit) en bronchiale hyperreactiviteit veranderden
niet. De conclusie luidde dat zelfmanagement tenminste even effectief was als de
gebruikelijke behandeling van astma die in de eerstelijns gezondheidszorg wordt verstrekt.
Zelfmanagement lijkt daarmee voor patiënten met astma een veilige basis te zijn voor
intermitterende behandeling met inhalatiecorticosteroiden.

Hoofdstuk 9 beschrijft een uitgebreide economische evaluatie van het
zelfmanagementprogramma voor astmapatiënten dat ook onderwerp van studie was in
Hoofdstuk 8. De hypothese vooraf was dat het introduceren van zelfmanagement niet ten
coste zou gaan van de mate van astmacontrole, terwijl de kosten gelijk of lager zouden zijn
dan bij gebruikelijke zorg. Er werden onder meer patiëntenspecifieke kostengegevens verzameld
en gezondheidsvoorkeuren gemeten. De meerkosten per gewonnen *quality-adjusted life year* (QALY) en per gewonnen ‘succesvol behandelde week’ werden berekend. Patiënten in de zelfmanagementgroep wonnen meer QALYs en hadden meer succesvol behandelde weken tijdens de 2-jaars observatieperiode. Er was sprake van een besparing in het gebruik van inhalatiecorticosteroïden in de zelfmanagementgroep. De kosten door verzuim van arbeid en andere dagelijkse activiteiten waren ook lager in de zelfmanagementgroep. Indien de medische kosten en de kosten door productiviteitsverlies werden meegenomen was zelfmanagement kosteneffectief voor alle bestudeerde effectmaten. Geconcludeerd werd daarom dat zelfmanagement een veilig en efficiënt alternatief is voor de astmazorg zoals die doorgaans vanuit de huisartspraktijk wordt verleend.

**In Hoofdstuk 10** werden de effecten onderzocht van het vroegtijdig starten van een behandeling met inhalatiecorticosteroïden (fluticason propionaat) bij personen met beginnende tekens en symptomen van COPD, maar bij wie deze diagnose nog niet was gesteld. Personen met een versnelde jaarlijkse daling van de longfunctie en aanhoudende luchtwegsymptomen werden door middel van een gericht bevolkingsonderzoek en daaropvolgende monitoring opgespoord. Achtenveertig personen werden betrokken in een placebo-gecontroleerd experiment; de ene helft werd twee jaar lang met fluticason behandeld, de andere helft met placebo. Na drie maanden was de eensecondewaarde (FEV\(_1\)) meer toegenomen in de fluticasongroep dan in de placebogroep. De daaropvolgende jaarlijkse daling van de FEV\(_1\) werd echter niet gunstig beïnvloed door fluticason, noch had deze behandeling een gunstig effect op luchtwegsymptomen, kwaliteit van leven of het optreden van exacerbaties. Na de eerste drie maanden verbeterde de FEV\(_1\) bij mensen die hyperreactiviteit van de luchtwegen vertoonden wel in de fluticasongroep, maar niet in de placebogroep. Bij de jaarlijkse FEV\(_1\)-daling had aanwezigheid van bronchiale hyperreactiviteit echter geen modificerende rol ten aanzien van de effectiviteit van de behandeling. Geconcludeerd werd dat vroegtijdige behandeling met inhalatiesteroïden geen gunstige invloed had op de progressieve longfunctiedaling of op andere respiratoire effectmaten bij personen met beginnend COPD.

Het doel van de in **Hoofdstuk 11** beschreven studie was te bepalen in hoeverre het stopzetten van een behandeling met inhalatiecorticosteroïden bij patiënten met COPD op de korte termijn leidt tot een negatieve uitkomst (d.w.z. een exacerbatie of verergering van luchtwegklachten). Het betrof een prospectieve ongeblindeerde stopstudie voor inhalatiesteroïden bij 201 COPD-patiënten met verschillende mate van ernst van luchtwegobstructie. De patiënten waren gediagnosticeerd en werden behandeld in de huisartspraktijk. De kans op een negatieve uitkomst in de eerste drie maanden na het stoppen van de inhalatiesteroïden was 0.37. Leeftijd, geslacht, rookstatus en reversibiliteit van luchtwegobstructie voorspelden de kans op een negatieve uitkomst. De conclusie luidde dat
het staken van een behandeling met inhalatiesteroïden bij een deel van de COPD-patiënten een negatief effect kan hebben. In dit onderzoek was de kans op een negatieve uitkomst groter voor vrouwen, ouderen en rokers en bij patiënten met een reversibele obstructie.

In *Hoofdstuk 12* werden de frequentie van optreden en de behandeling en medische kosten van exacerbaties bij patiënten met COPD in huisartspraktijken bestudeerd. Gegevens over het optreden en de behandeling van exacerbaties werden verzameld door middel van systematisch medisch dossier onderzoek over een periode van 2 jaar. Volgens internationale criteria hadden patiënten chronische bronchitis zonder obstructie (26%), milde luchtwegobstructie (19%), matige obstructie (40%) of ernstige obstructie (15%). De gemiddelde exacerbatiefrequentie was 0.88 exacerbaties per jaar. De frequentie van exacerbaties was niet gerelateerd aan de ernst van de luchtwegobstructie. De gemiddelde jaarlijkse exacerbatiekosten per patiënt bedroegen €40, €53, €61 en €92 in de opeenvolgende subgroepen qua ernst van obstructie. De stijging van de kosten in de subgroepen met ernstigere problematiek was vooral toe te schrijven aan hogere kosten door consulten bij een arts (huis- of longarts), diagnostische tests en recepten voor medicijnen ter verlichting van symptomen (met name luchtwegverwijders, hoestpreparaten). De conclusie luidde dat in de groep COPD-patiënten die behandeld wordt in de huisartspraktijk het voorkomen van exacerbaties niet afhangt van de ernst van de luchtwegvernauwing, maar dat de kosten die gepaard gaan met deze exacerbaties wel stijgen naarmate de longfunctie ernstiger gestoord is.
Dankwoord
Dankwoord

In de afgelopen jaren heb ik ervaren hoe complex en arbeidsintensief het doen van wetenschappelijk onderzoek in de Nederlandse huisartspraktijk is. De diverse onderzoeken waaruit dit proefschrift is voortgekomen hadden onmogelijk uitgevoerd kunnen worden zonder de toewijding en inzet van een groot aantal mensen. Ik ben de patiënten, huisartsen, praktijkassistenten, longfunctielaboranten en longartsen en alle andere mensen die bij de verschillende onderzoeksprojecten betrokken waren zeer erkentelijk voor hun onmisbare - en vaak belangeloze – inzet.

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Curriculum vitae
Curriculum vitae

Tjaarda Roland Jacob Schermer was born on 23 January 1967 in Ede, the Netherlands. In 1984 he obtained his secondary school diploma in Zevenaar and started a vocational physiotherapy training program in Arnhem one year later. After graduation as a physiotherapist in 1989 he practised physiotherapy full-time for three years. From 1991 to 1996 he studied Biomedical Health Sciences at the Medical Faculty of the Radboud University Nijmegen while still working part-time as a physiotherapist. During his study in Nijmegen he developed a special interest in the epidemiology of chronic diseases. In 1996 he started working for the COPD & Asthma Research Unit of the Department of General Practice of the Radboud University Nijmegen Medical Centre, first as a research assistant but after one year as a researcher. At present he is the coordinator of the COPD & Asthma Research Unit and executive project leader of a number of studies in the field of COPD and asthma.

He has a registered partnership with Nienke Bruins. Together they have two children, Jelte (1998) and Wyke (2001). They live in the city of Arnhem in the eastern part of the Netherlands.