Measurement and improvement of health status in patients with COPD

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Chapter 1

Introduction

1.1 Chronic Obstructive Pulmonary Disease (COPD)

Definition and diagnosis of COPD

COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as '*a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients*.'[1] In patients with symptoms of chronic progressive dyspnea, cough, sputum production and a history of exposure to risk factors (i.e. smoking history) for the disease, a diagnosis of COPD should be considered. To confirm the diagnosis a post-bronchodilator spirometry showing persistent airflow limitation should be present. The severity of COPD is partially based on the degree of airflow limitation, depicted in Table 1. Exacerbations and comorbidities contribute to the overall severity in individual patients.[1] Exacerbations in this thesis are defined as an acute event characterized by a worsening state of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.[2] They can be categorized as mild (increase of respiratory symptoms requiring change of inhalation medication), moderate (exacerbation requiring antibiotic and/or oral steroid treatment) and severe (exacerbation requiring hospitalization).[1] Common systematic manifestations and comorbidities in patients with COPD are skeletal muscle wasting, cachexia, ischemic heart disease, heart failure, pulmonary hypertension, osteoporosis, anemia and diabetes.[3] Patients with COPD with comorbidity have an increased risk of physical impairment, hospitalization, mortality and reduced health status.[4] The association between COPD and systematic manifestations can be explained by the increased systemic inflammation in patients with COPD.[3] Systematic inflammation is one of the factors that contribute to disease severity; other factors are clinical symptoms (i.e. chronic productive cough) and exacerbation frequency.

For the follow-up and treatment of patients with COPD, objective measurements such as spirometry alone, without patients' perceptions, are not enough to reflect the im-

TABLE 1: Severity of airflow limitation in COPD

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

Only to be used in patients with $FEV_1/FVC<0.70$. Based on post-bronchodilator FEV_1.

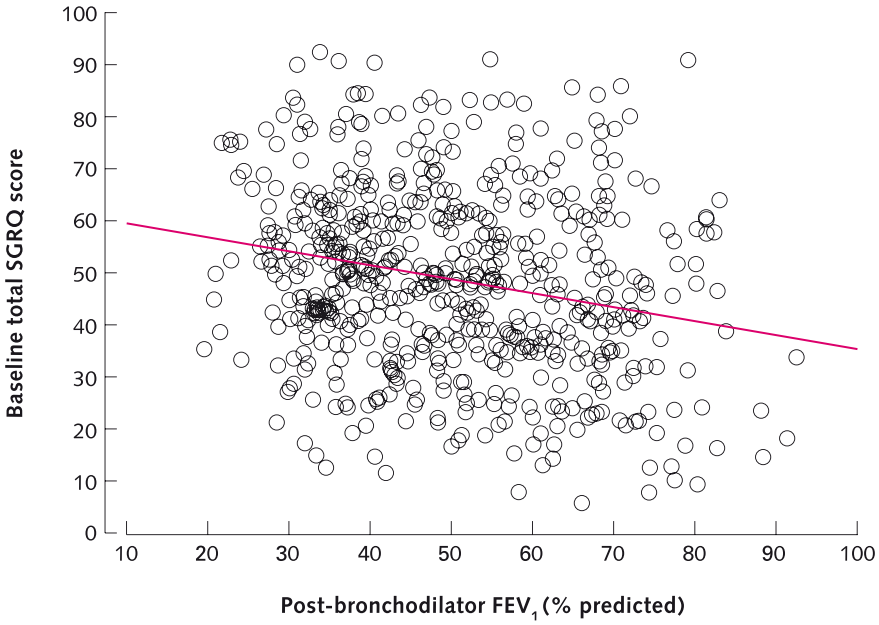
GOLD=Global Initiative for Chronic Obstructive Lung Disease

FEV_1=Forced Expiratory Volume in 1 second

FVC=Forced Vital Capacity

Adapted and with permission from www.goldcopd.org. Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Official Journal of the American Thoracic Society.[1]

FIGURE 1: Correlation between health status and spirometry



FEV_1=Forced Expiratory Volume in 1 second

SGRQ=Saint George's Respiratory Questionnaire

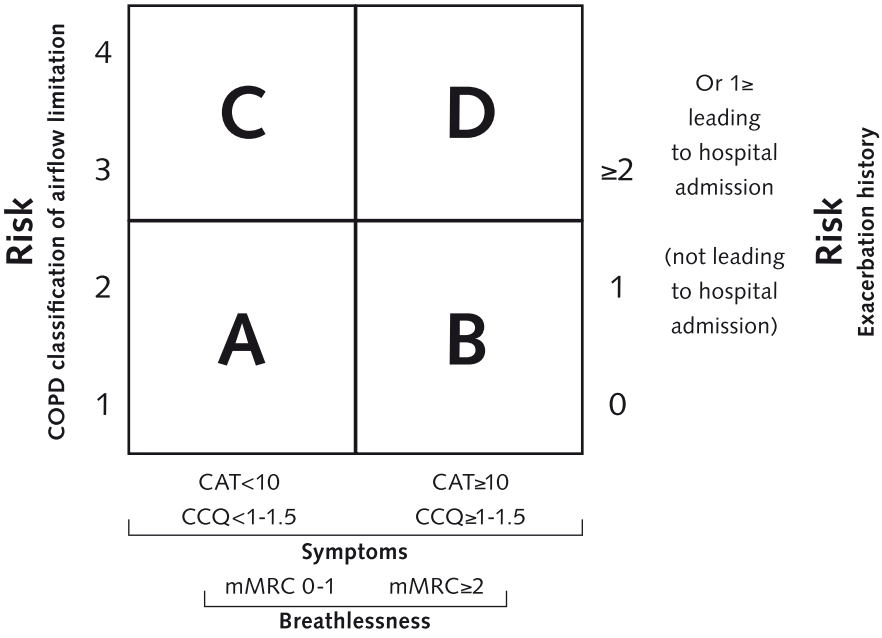
Relationship between health status as measured by the SGRQ, FEV_1 and GOLD stage. Patients' perception of symptoms and health status, as assessed by the SGRQ, were not well correlated with FEV_1 and GOLD stage. Adapted from Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001; 56: 880-887 with permission from the BMJ publishing Group limited.[48]

pact of COPD on a patient. Especially, the forced expiratory volume in 1 second (FEV_1) is not well correlated at all with patients' health status, Figure 1.[5] Similarly, exacerbation frequency and severity of symptoms are not well correlated with health status.[1;6;7] Therefore, it is widely propagated to include a determination of health status in the assessment of COPD in clinical practice. This has been carried a step forwards by the GOLD guidelines committee when defining four elements of disease severity[1]:

1. Symptoms, impact of the disease on the patient's health status
2. Severity of airflow limitation
3. Risk of future events (exacerbations, hospitalizations, mortality)
4. Presence of comorbidities

The combined assessment of COPD is summarized in Figure 2, in which four groups can be identified; Group A: low risk, low symptoms, Group B: low risk, more symptoms,

FIGURE 2: Combined COPD assessment



CAT=COPD Assesment Test

CCQ=Clinical COPD Questionnaire

GOLD=Global Initiative for Chronic Obstructive Lung Disease

mMRC=modified Medical Research Council

When assessing risk, choose the highest risk according to GOLD spirometric grade or exacerbation history and health status. Adapted and with permission from the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: http://www.goldcopd.org/. Copyright © 2014[1]

Group C: high risk, less symptoms, Group D: high risk, more symptoms. The treatment of COPD should, according to the GOLD committee, be aimed at reducing current symptoms (impact) and reducing future risk (most notably exacerbations). The advantage of the combined assessment of COPD is that all treatment goals are taken into account in the assessment of severity of COPD, and therefore is a better reflection of the complexity of COPD.[1] However, a recent study showed that both COPD classifications, the combined assessment of COPD with the A-D classification and the old GOLD classification of obstruction only, had comparable predictive abilities for hospitalizations and mortality.[8] The benefits of the A-D classification over the old GOLD 1-4 classification will be examined in the coming years. This thesis was started before the release of the new classification of the GOLD guidelines of 2011 and the research protocols were not designed for this new A-D classification. To adjust for this new A-D

classification, data should be collected prospectively. Therefore we decided to use the GOLD 1-4 classification in the chapters of this thesis instead of the new A-D classification.

The burden of COPD

The prevalence of COPD is still increasing and putting pressure on outpatient clinics.[9;10] Currently, pulmonologists decide when and how many outpatient visits are needed for a COPD-patient per year. This manner of pre-planned outpatient visits is not guided by actual variations in symptoms or complaints of the patient. Nevertheless, COPD has varying and unpredictable frank acute exacerbations.[11] Therefore outpatient visits often occur when patients are stable and thus when little action is required. By contrast, when urgent attention is needed, it is frequently a struggle in the current system to respond to this request because the outpatient clinic is fully booked. Therefore, we believe the current system of outpatient visits does not fit the demands of COPD patients and can be optimized with more flexibility to respond to urgent attention. Two different systems of outpatient visit management were successfully employed in other chronic diseases. The first system, telemedicine, was assessed in patients with heart failure and diabetes mellitus. The telemedicine system led to early discharge from the hospital and reduction of readmission rates and healthcare expenditure compared to usual care.[12;13] Furthermore, diabetic patients[14] had a better self-care, glycemic control and reported fewer symptoms of depression. Several studies examined[15-18] telemedicine in patients with COPD, however the net effects of telemedicine on healthcare utilisation and health status are still under debate. The second system was an open access system, or an on-demand-system. In this on-demand system the patient is the center of attention and determines when an outpatient visit is needed. This system showed promising results in patients with inflammatory bowel disease and rheumatoid arthritis, i.e. fewer outpatient appointments in the on-demand group.[19-21] Thus theoretically, a care-on-demand-system and/or a telemedicine-system has the potential to improve continuity of care, increase efficiency of outpatient-management, and prevent deterioration of health-status in patients with COPD.

1.2 Health status

Definition of health status

In recent years, health status is increasingly becoming an important determinant of care, and instruments to measure it are more and more important in the treatment and follow up of patients with COPD. To date, there is no uniformity of nomenclature and different definitions and terms are used to describe related patient reported outcomes. The most common definitions are: quality of life, health-related quality of life and health status. A graphical visualization of the definitions used in this thesis is shown in Figure 3.[22] Quality of life is the overarching term, which includes health status, health-

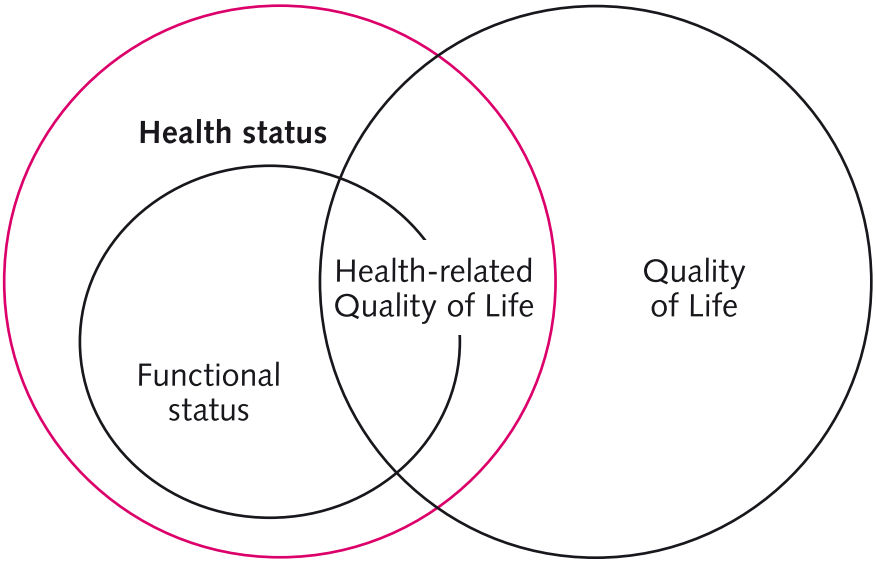
related-quality of life and functional status. It is defined as the self-determined evaluation of the quality of a person's life influenced by health but also by financial status, employment and social network.[23] Health-related quality of life is the quality of life or an individual's satisfaction or happiness with domains of life insofar as they affect or are affected by health.[24] Functional status is an individual's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being, which is the ability of a person's daily performance. The definition that we used in this thesis is health status. Health status encompasses functional status, health-related quality of life and partly quality of life, i.e. the effect of a person's health on the ability to perform and enjoy activities of daily life.[22]

COPD and health status

Optimal health status is one of the treatment goals in the assessment of COPD.[1] It gives information about the way patients experience their symptoms and the impact of COPD in daily life.[25]

The perception of health status of patients with COPD differs from that of their clinicians. More specifically, clinicians underestimate the impact of COPD on a patients daily life[26], and explicit and standardized measurement as patient reported outcome is therefore essential. COPD-specific health status questionnaires reflect the health status

Figure 3: Conceptual model of patient-assessed health outcomes



Conceptual model of the overlapping realms of common terms describing patient reported health outcomes.
With permission from Professor J. Randall Curtis.[22]

of patients with COPD for symptom, functional and mental domains.[27] In clinical practice all three domains are important and should be discussed. This leads to improvement of patient satisfaction, prevents misunderstanding and improves compliance.[26] Use of health status questionnaires is therefore recommended in clinical practice.
There are at least 13 different disease-specific health status questionnaires for patients with COPD available.[28] The most frequently used questionnaire for clinical research is the Saint George's Respiratory Questionnaire (SGRQ).[29] The SGRQ is a long and time-consuming questionnaire and therefore not very practical in daily clinical practice. The Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT) are much shorter questionnaires. The CCQ can be completed in 134 (29-307) seconds and the CAT in 107 (43-210) seconds, as compared to 578 (300-960) seconds for the SGRQ.[30] The most frequently used COPD-specific questionnaire in clinical practice in the Netherlands is the CCQ, developed in 2003.[27] In 2009 the CAT was developed and this COPD-specific questionnaire is used more frequently worldwide.[30-32] To assess which one of these questionnaires is the best to use in clinical practice for patients with COPD on an individual-level, the most commonly used questionnaires should be validated and compared. It is important to assess both the discriminative and the evaluative part of the questionnaires.[33] Since treatment of patients with COPD should be tailored also on the basis of impact of disease, health status should also be monitored prospectively provided that the measurement properties of the questionnaire used are satisfactory, something that has not been studied well as yet.

Health status questionnaires used in this thesis

CCQ

The CCQ consists of 10 items and has 3 domains: symptoms (4 items), mental state (2 items) and functional state (4 items), and a total score (10 items).[27] All scores range from 0-6, a lower score indicating a better health status. The minimal clinically important difference (MCID) of the CCQ is 0.4 points.[34]

CAT

The CAT consists of 8 items and has a total score only. The score ranges from 0-40, a lower score indicating a better health status.[31] The MCID of the CAT is 2 points.[32]

SGRQ

The SGRQ consists of 51 items and has a total score (51 items), and three domain scores: symptoms (8 items), activity (16 items) and impact (26 items).[29] The score ranges from 0-100. The MCID of the SGRQ is 4 points.[35]

Leicester Cough questionnaire (LCQ)

Originally, the LCQ is a cough-specific questionnaires used in patients with chronic productive cough.[36] The LCQ has 19 items and consists of a total (19 items) and 3

domain scores: physical (5 items), psychological (7 items) and social (4 items). The score ranges from 3-21, a higher score corresponds with a better health status. The MCID of the LCQ in patients with chronic cough was 1.3 points.[37]

Minnesota Living with Heart Failure questionnaire (MLHF-Q)

The MLHF-Q is disease-specific questionnaire, used in patients with heart failure. The MLHF-Q consists of 21 items and has a total (21) and 2 domain scores: physical (8 items) and emotional state (5 items). The questionnaire has a 6-point response scale and ranges from 0 to 5. A higher score indicates a poorer health status.[38] The MCID has been estimated at 4.8.[39]

Short Form 36 (SF-36)

The SF-36 is a generic health status questionnaire and has 8 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items).[40-42] All scores are transformed to a range from 0 to 100. A higher score indicates a better health status. The MCID is 4.[43]

Global rating of change (GRC)

The GRC was used to assess self-perceived change in health status on a 15-point scale (-7 a very great deal worse, 0 no change, +7 a very great deal better).[44] The GRC is frequently recommended to be used as anchor for validation studies.[33]

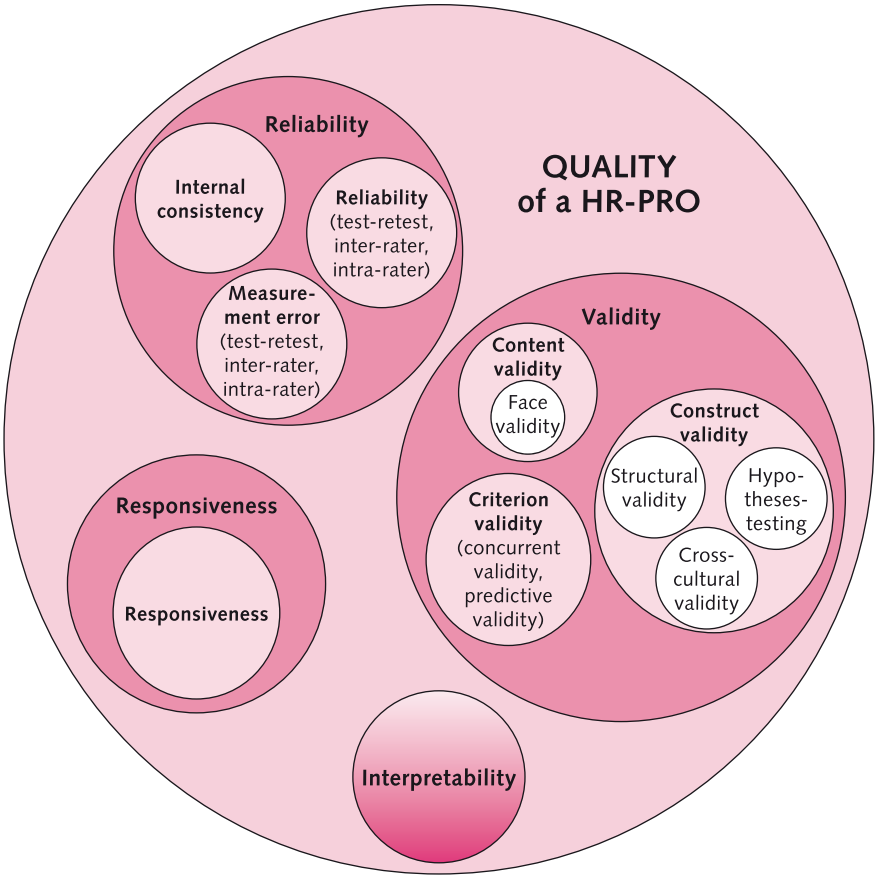
Psychometric properties

To compare and validate in patients with COPD the short and most commonly used questionnaires, the CAT and the CCQ, the following psychometric properties were examined. At first the validity, the degree to which an instrument truly measures the construct it purports to measure, of the questionnaires was established by assessing face validity, content validity and construct validity. Secondly, the reliability, the extent to which scores for stable patients are the same for repeated measurements under several conditions, was assessed by determining test-retest-reliability and agreement. The inter-relatedness between the items of the questionnaires was evaluated with the internal consistency. The last psychometric property that was assessed was change over time, i.e. responsiveness, which is the ability of an instrument to detect change over time in the construct to be measured.[33;45]

A lot of terminology and definitions are used to validate health status questionnaires. We chose to use the taxonomy of the COnsensus based Standards for the selection of health Measurement INstruments (COSMIN), shown in Figure 4.[46] These guidelines have been constructed by consensus of approximately 50 experts with a background of psychometrics, epidemiology, statistics and clinical medicine.[33;47]

The construct that we want to measure in this thesis was the health status in patients with COPD.

FIGURE 4: COSMIN taxonomy of relationships of measurement properties



Abbreviations: COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments; HR-PRO, health related-patient reported outcome.

Reprinted from Journal of *Clinical Epidemiology*, Jul; 63(7): 737-45, L.B. Mokkink et al, The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes, Copyright (2010), with permission from Elsevier.[47]

1.3 Outline and aim of this thesis

The aim of this thesis

The aim of this thesis was two-fold. In the first part (**chapter 2-4**) the most frequently used health status questionnaires are validated and compared to explore which of the questionnaires should be recommended most for use in clinical practice. This part also examines the use of questionnaires in different COPD-populations, i.e. COPD patients with chronic productive cough and patients both with COPD and heart failure. In the second part (**chapter 5-7**) of this thesis we investigate whether the management of patients with COPD can be optimized.

Outline of this thesis

The Leicester Cough Questionnaire (LCQ) is validated in COPD patients with a phenotype chronic productive cough in **chapter two.** Two most commonly used, short questionnaires, the CAT and the CCQ, are validated and compared in daily clinical practice in the Netherlands in **chapter three**. And in the last chapter of the first part, **chapter four**, two commonly used questionnaires; the CCQ and the MLHF questionnaires are validated and compared in patients with combined COPD and chronic heart failure. The latter is done to explore whether COPD specific health status questionnaires can also be used in patients with COPD and comorbidities.

In the second part of this thesis we investigate whether management of COPD can be optimized. In **chapter five** telemedicine, care provided by electronic communication, is examined in stable COPD patients. We hypothesized that the use of telemedicine can serve as an alternative or extension to traditional outpatient visits. In **chapter six** a so-called on-demand-system in COPD patients is assessed. This system allows patients to self-refer when they consider an outpatient visit needed, instead of fixed outpatient appointments initiated by pulmonologists. Theoretically, this system has the potential of better adaptation to the increasing demand on outpatient clinics and might reduce unnecessary outpatient visits and healthcare costs. In **chapter seven** the effect on health status of use of prophylactic macrolide in patients with COPD and chronic productive cough is established. In the last chapter, **chapter eight**, the summary, conclusions and perspectives of this thesis will be presented.

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Part I

Chapter 2

The Validity and Precision of the Leicester Cough Questionnaire in COPD patients with chronic cough.

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Status

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Abstract

Background

A validated instrument to assess the effects of chronic cough on health status in patients with chronic obstructive pulmonary disease (COPD) is currently not available. The Leicester Cough Questionnaire (LCQ) is a cough-specific health status questionnaire which is originally validated for a population of general patients presenting with chronic cough. We examined the psychometric performance of the LCQ in patients with COPD and chronic productive cough.

Methods

Concurrent validity, internal consistency, reproducibility and responsiveness were determined. The St. George's Respiratory Questionnaire (SGRQ) and the Short Form-36 (SF-36) were used as external criteria. Questionnaires were completed at the start of the study. After 2 and 12 weeks the LCQ was repeated, together with a global rating of change.

Results

In total 54 patients were included. Concurrent validity analysis showed significant correlations between corresponding domains of the LCQ and the SGRQ (r_s -0.31 to -0.60). Corresponding domains of the LCQ and the SF-36 showed weaker correlations (rs 0.04 to 0.41). Internal consistency was adequate for two of the three domains (Cronbach's α 0.74 - 0.86). Test-retest reliability in stable patients was high (intraclass correlation coefficients 0.79 - 0.93). The mean difference after two weeks was 0.73 (± 1.75). Responsiveness analysis indicated that the LCQ was able to detect changes after 12 weeks.

Conclusion

The LCQ is a valid, reliable, responsive instrument to measure health status in COPD patients with chronic productive cough.

Trial Registration

ClinicalTrials.gov: NCT01071161

Keywords

LCQ, COPD, validity, cough, health status

Background

COPD is a leading cause of morbidity and mortality all over the world. In 2001 COPD was the fifth cause of death and its relative importance is predicted to increase in future years.[1;2] Detection of airflow limitation is paramount in the GOLD definition of COPD[3;4], but clinically COPD is characterized by chronic and progressive dyspnea, cough and sputum production.[4;5] Prevalence rates of chronic productive cough in the male COPD population are estimated to be 15-44% and 6-17% in females. These rates increase with age and are strongly related to smoking.[6] The high prevalence of cough in COPD may be caused by increased production of mucus, by the inability to produce a sufficiently large expiratory flow leading to ineffective clearing of the mucus, and by impaired mucociliary clearance leading to mucus retention. Also, many patients with COPD have bronchiectasis.[7;8]

Chronic productive cough in COPD patients is associated with severe exacerbations which require hospitalization.[9] These exacerbations have serious effects on health status and quality of life.[10]

Improving health status in COPD patients is a management goal in the GOLD guideline. To measure this, assessment is recommended on regularly basis.[4] Although cough is a frequent symptom in COPD, the impact of cough on health status in these patients is largely unknown.[2] One study found that only a small part (2%) of the variance in the scores of the St. George's Respiratory Questionnaire (SGRQ), a disease specific health status questionnaire, is explained by cough.[2] Several cough-specific health status questionnaires have been developed and validated in the general population presenting with cough but not necessarily with COPD.[11-15] Of these questionnaires only the Leicester Cough Questionnaire (LCQ)[16] is available in Dutch.[17] Thus, well validated cough-specific health status questionnaires for COPD patients are absent, rendering it impossible to evaluate patients health status both individually and in clinical trials.

In this paper we investigated the precision and validity of the LCQ in COPD patients with chronic cough.

Methods

Study design

The study was designed as a prospective validation study. Blinded data were used from a larger clinical trial in which the effects of azithromycin on cough related health status were studied. Patients were randomised between azithromycin and placebo for twelve weeks and started at day 1. The study was registered at Clinical-Trials.gov (NCT01071161) and was approved by the Ethics Committee of the Isala klinieken, Zwolle, Netherlands (NL19886.075.07, local number: 07.0971). All questionnaires were administered during the first visit, the LCQ was repeated after two and twelve weeks.

Subjects

Patients with COPD (GOLD II-IV) who were ≥40 years of age were eligible to participate if they were suffering from chronic productive cough, defined as productive cough for at least three months a year, in two subsequent years. The inclusion period lasted from September 2009 to September 2010. Exclusion criteria were: a prior history of asthma, use of intravenous or oral corticosteroids and/or antibiotics for an exacerbation three weeks before inclusion, suffering from other relevant lung or liver diseases at the discretion of the treating physician, pregnancy or lactation, use of macrolides in the last six weeks prior to inclusion, allergy or intolerance to macrolides, or other study medication started two months prior to inclusion.

Questionnaires

The LCQ is a cough-specific health status questionnaire that is well validated in the general population. It consists of 19 items which are divided over 3 domains: physical, psychological and social. A 7-point Likert scale is used to rate. It assesses the impact of cough over the preceding 2 weeks. The total score ranges from 3-21; a higher score corresponds to a better health status.[16;18;19] We have previously described the validation of the Dutch translation for the general population.[17] The SGRQ is a disease-specific health status questionnaire for asthma and COPD, which assesses the impact of symptoms over the preceding 3 months. It contains 76 items divided in 3 sections: symptoms, activity and impacts. The scores range from 0-100, a low score indicates a good health status.[20;21]

The Short Form Health Survey (SF-36) questionnaire is a self administrated generic health status questionnaire containing 36 items that cover 9 health dimensions. The SF-36 comprises 8 health scales: physical functioning, role limitations physical, bodily pain, general health, vitality, social functioning, role limitations emotional, and mental health. One single item is used to assess any change in health. Each dimension is scaled from 0-100, higher scores represent better health status.[22-26]

A global rating of change (GRC) was used to evaluate self-perceived health change on a 15 point scale (-7 a very great deal worse, 0 no change, +7 a very great deal better).

Validity & Precision

The following concepts were assessed to determine psychometric performance of the LCQ in COPD: concurrent validity, internal consistency, reproducibility, responsiveness and floor or ceiling effects.

Concurrent validity (appropriate correlations between established measures and the new questionnaire) was measured with the SGRQ and SF-36.[16] Ideally, we would have used an additional cough-specific questionnaire. However, such questionnaires have not been specifically developed for, nor tested in COPD patients.[11-15] We used the SGRQ as the reference standard. Internal consistency concerns the degree to which scores of items in a questionnaire correlate homogeneously, and was assessed using data from the LCQ of the first visit.

TABLE 1: Patient characteristics		
n		54
Sex, male, n (%)		40 (74)
Age (years), mean (SD)		68 ± 10
Pack-years, mean (SD)		36 ± 22
Current smoker, n (%)		22 (41)
FEV_1 (litres)*		1.3 ± 0.5
FEV_1 % predicted		47 ± 13
COPD GOLD, n (%)†	II	27 (50)
	III	19 (35)
	IV	8 (15)
Respiratory medication, n (%)	Inhaled corticosteroids	51 (94)
	Short acting bronchodilator‡	2 (4)
	Long acting bronchodilator§	35 (65)
	Both‖	17 (31)

* Forced Expiratory Volume in one second

† Classification by the global initiative for Chronic Obstructive Lung Disease[3]

‡ Short acting bronchodilator: short acting beta-2 agonist and/or short acting anticholinergic

§ Long acting bronchodilator: long acting beta-2 agonist and/or long acting anticholinergic

‖ Both long and short acting beta-2 agonist and/or anticholinergic bronchodilators

TABLE 2: Baseline health status scores		
	mean (SD)	**Range**
LCQ*		
physical	4.2 (± 0.8)	(1.8 - 5.8)
psychological	4.8 (± 1.0)	(2.3 - 6.6)
social	4.6 (± 1.3)	(1.0 - 6.5)
total	13.6 (± 2.8)	(5.9 - 18.1)
SGRQ†		
symptoms	65.3 (± 17.4)	(26.7 - 92.8)
activity	66.2 (± 24.3)	(0 - 100)
impact	39.9 (± 18.9)	(1.6 - 77.3)
total	52.1 (± 18.5)	(5.9 - 81.2)
SF-36‡		
physical functioning	36.1 (± 25.2)	(0 - 90)
role physical	23.1 (± 35.6)	(0 - 100)
pain	61.6 (± 25.6)	(22 - 100)
general health	32.6 (± 19.0)	(0 - 75)
vitality	47.1 (± 18.3)	(15 - 90)
social functioning	65.0 (± 27.1)	(0 - 100)
role emotional	72.0 (± 37.5)	(0 - 100)
mental health	69.6 (± 18.7)	(24 - 100)

* Leicester Cough Questionnaire

† St. George's Respiratory Questionnaire, a disease-specific health status questionnaire

‡ Short form 36, a generic health status questionnaire

TABLE 3: Concurrent validity

	LCQ*			
	Physical	**Psychological**	**Social**	**Total**
SGRQ†				
Symptoms	-0.57 (54; <0.001)	-0.45 (54; 0.001)	-0.51 (53; <0.001)	-0.58 (53; <0.001)
Activity	-0.58 (54; <0.001)	-0.11 (54; 0.42)	-0.39 (53; 0.004)	-0.42 (53; 0.002)
Impact	-0.67 (54; <0.001)	-0.31 (54; 0.023)	-0.60 (53; <0.001)	-0.61 (53; <0.001)
Total	-0.68 (54; <0.001)	-0.28 (54; 0.037)	-0.57 (53; <0.001)	-0.60 (53; <0.001)
SF-36‡				
Physical functioning	0.39 (54; 0.004)	0.06 (54; 0.65)	0.29 (53; 0.039)	0.28 (53; 0.041)
Role physical	0.31 (53; 0.022)	0.05 (53; 0.72)	0.23 (52; 0.099)	0.22 (52; 0.11)
Pain	0.47 (53; <0.001)	0.29 (53; 0.038)	0.47 (52; 0.001)	0.47 (52; <0.001)
General health	0.42 (54; 0.002)	0.25 (54; 0.072)	0.36 (53; 0.008)	0.37 (53; 0.007)
Vitality	0.64 (54; <0.001)	0.24 (54; 0.086)	0.49 (53; <0.001)	0.50 (53; <0.001)
Social functioning	0.41 (54; 0.002)	0.32 (54; 0.017)	0.41 (53; 0.002)	0.43 (53; 0.001)
Role emotional	0.05 (53; 0.70)	0.04 (53; 0.77)	0.13 (52; 0.38)	0.10 (52; 0.48)
Mental health	0.40 (54; 0.003)	0.30 (54; 0.026)	0.37 (53; 0.006)	0.44 (53; 0.001)

Spearman correlation coefficients are presented (n; *p*-value).

* Leicester Cough Questionnaire

† St. George's Respiratory Questionnaire, a disease-specific health status questionnaire

‡ Short form 36, a generic health status questionnaire

TABLE 4: Internal consistency

	Cronbach's alpha coefficient		
LCQ*	**Birring[16]†**	**Huisman[17]†**	**This study‡**
physical	0.79	0.77	0.67
psychological	0.89	0.84	0.75
social	0.85	0.83	0.74
total	0.92	0.93	0.86

* Leicester Cough questionnaire

† patients with chronic cough

‡ patients with COPD and chronic productive cough

TABLE 5: Reliability

	Intraclass correlation coefficient			95%CI*
LCQ†	**Birring[16]‡**	**Huisman[17]‡**	**This study§**	
Physical	0.93	0.86	0.93	0.84;0.97
Psychological	0.90	0.93	0.79	0.51;0.91
Social	0.88	0.93	0.88	0.72;0.95
Total	0.96	0.93	0.92	0.81;0.96

* 95% Confidence Interval for ICC this study

† Leicester Cough Questionnaire

‡ patients with chronic cough

§ patients with COPD and chronic productive cough

Reproducibility is a measure of precision and concerns the degree to which repeated measurements in a stable persons (defined as GRC=-1, 0 and 1 in our study) correspond. Reproducibility can be divided in agreement and reliability.[27] Agreement concerns the closeness of the results of repeated measurements after two weeks and assessment is preferred if the aim is to measure change in health status, whereas reliability denotes the degree to which patients can be distinguished from each other, despite measurement error.[28] Both parameters were obtained by comparing the LCQ scores of week 0 and week 2.

Responsiveness is the ability to detect important within-patient changes, even if they are small; it was determined by comparing the LCQ scores of the first visit with LCQ scores after 12 weeks in patients who perceived a significantly improvement in cough symptoms (arbitrarily chosen as GRC≥4 (moderately better to a very great deal better) in our study.

Furthermore the floor or ceiling effects can be assessed if more than 15% of the patients achieve the lowest or highest possible score, respectively. Absence of floor or ceiling effects indicates a good content validity.[17;27]

Statistical Analyses

The concurrent validity was determined by calculating correlation coefficients between LCQ-scores and scores on SGRQ and SF-36. Depending on the distribution of the variables Pearson correlation coefficients or Spearman rank correlation coefficients were used. We made a priori assumptions of the associations between the LCQ total and domain scores and the corresponding scores of the SGRQ and SF-36, respectively. We expected correlation coefficients ≥0.5 for associations between the LCQ and SGRQ and ≥0.4 between the LCQ and SF-36. Corresponding domains of the LCQ physical domain were the SGRQ activity and symptoms domains, and for the LCQ psychological and social domains the SGRQ impact domain.[20] For the LCQ physical domain, the corresponding domain of the SF-36 were the physical functioning/role physical domains, and for the LCQ psychological domain the SF-36 mental health domain and for the LCQ social domain the SF-36 social functioning domain.[16]

Internal consistency of the LCQ was evaluated using Cronbach's alpha coefficients for the three domains and the total LCQ. Cronbach's alpha coefficients between 0.7 and 0.9 are considered as proof of internal consistency. Agreement over time was assessed by constructing a Bland-Altman plot for the LCQ total score.[29] Reliability was analysed by calculating Intraclass Correlation Coefficients (ICC) for the 3 domains and the total LCQ.[17]

Responsiveness was measured as the area under the receiver operating characteristic (ROC) curve which indicates the probability of correctly identifying subjects who report improvement.[27;30]

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 (SSPS, Chicago, IL, USA).

Results

Patients

Fifty-four patients met the inclusion criteria. All patients were eligible in the cross-sectional analyses (concurrent validity, internal consistency, floor or ceiling effects). Data from 52 patients could be used for reproducibility analysis. Data from 49 patients were used to test responsiveness. Two patients withdrew the informed consent after one week. One patient stopped after 4 weeks because of chronic diarrhoea. Two patients failed to return the questionnaire after 12 weeks. Baseline characteristics are shown in table 1 and 2. Most of the patients were male and current smokers with moderate to severe COPD.

Concurrent Validity

Since most of the distributions were skewed, Spearman rank correlation coefficients were used. The correlation coefficients are summarized in table 3. The concurrent validity showed significant correlations between the corresponding domains (described in the statistical analysis section) of the LCQ and the SGRQ. Only the correlation between the psychological domain of the LCQ and the corresponding impact domain of the SGRQ was low to moderate and did not meet the pre-defined minimal level of 0.50.
Correlation coefficients for the LCQ and most of the corresponding domains of the SF-36 were low, and almost non existent for the psychological domain. Except the correlations between the social domain of the LCQ and the social functioning domain of the SF-36 (r=0.41; p=0.002).

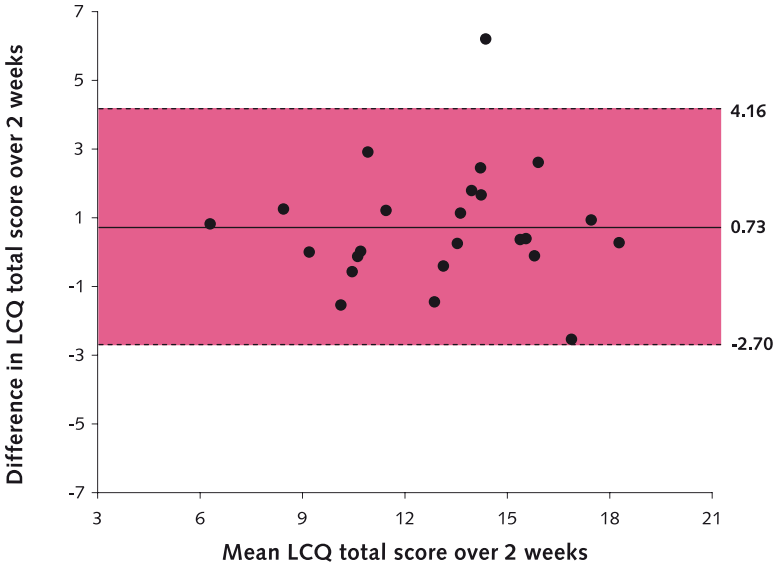
Internal consistency

The internal consistency of the LCQ, shown in table 4 in the column on the right, was adequate (≥0.70) for two of the three domains and the total questionnaire, with Cronbach's alpha coefficients ranging from 0.74 to 0.86. For the physical domain the Cronbach's alpha coefficient was 0.67. The results were comparable with the studies by Birring and Huisman in the more general population presenting with cough but not necessarily with COPD (table 4).[16;17]

Reproducibility

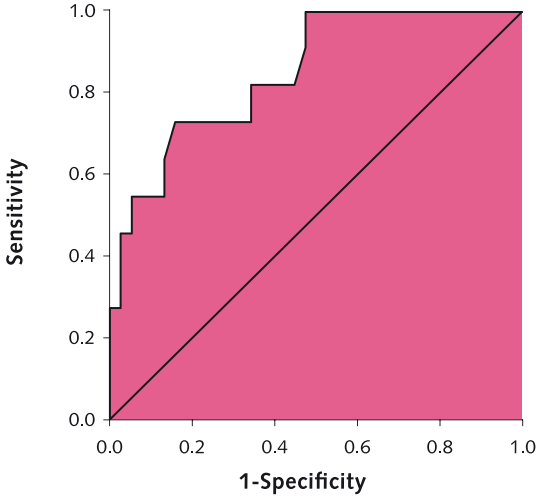
Reproducibility was tested in 24 stable patients. The ICC's for the LCQ are shown in table 5. Except for the psychological domain all repeated measurements were highly correlated, which indicates high test-retest reliability. A Bland-Altman plot of the LCQ total score is shown in Figure 1. The mean difference after two weeks was 0.73 (± 1.75). The upper limit of agreement for the LCQ total score is 4.16 and the lower limit of agreement -2.70.

FIGURE 1: Bland-Altman plot of LCQ total score repeated over 2 weeks in stable patients representing agreement



The mean difference over 2 weeks is represented by the solid line. The dashed lines are the limits of agreement, which represent 2 times the standard deviation of the mean difference.

FIGURE 2: Receiver Operating Characteristic Curve for responsiveness of the LCQ total score in COPD patients with chronic cough (*n*=49)



The Area Under the Curve is 0.85 (95%CI: 0.73; 0.97).

Responsiveness

Eleven of the forty-nine patients perceived a significant improvement in cough (GRC≥4). In these patients the mean change in the total LCQ score after 12 weeks was 4.3 ± 2.5. The Area Under the Curve (AUC) of the ROC was 0.85 (95%CI 0.73; 0.97, $p<0.001$, $n=49$), Figure 2. According to Terwee et al, an AUC of >0.70 is considered to be adequate.[27] Thus, the LCQ was able to detect changes in this specific group of patients.

Floor or ceiling effect

Floor or ceiling effects (the worst or the best possible score) were analysed at baseline, table 2. Only one patient (1.9%) had the worst possible score in the social domain of the LCQ. No best possible scores were found. Thus, floor or ceiling effects were not present, both in the domains and in the total questionnaire.

Discussion

This study is the first to examine the validity and precision of the LCQ specifically in COPD patients with chronic productive cough. It shows that the LCQ in these patients reliably measures the same construct as the original LCQ in patients with chronic cough in the general population. Responsiveness analysis indicated that the change in LCQ total scores after 12 weeks was able to predict which patients reported improved health status and which did not. No floor or ceiling effects were present which assured good content validity.

Good concurrent validity of the LCQ was found in relation to the SGRQ but not with the SF-36. This may be explained by both questionnaires measuring different concepts, but more importantly, this is caused by the nature of these questionnaires: the LCQ measures symptom-specific health status and the SGRQ COPD-specific health status, while the SF-36 measures generic health status. The results regarding concurrent validity were in accordance with Birring's original validation study but slightly lower compared to the Dutch validation of the LCQ.[16]

In general, the LCQ had an acceptable internal consistency, supporting the hypothesis that the associated questionnaire items are related to each other but do not completely overlap in which case the Cronbach's alpha would have a value of 1, and the item (or domain) would be redundant. The exception with poorer internal consistency was the physical domain (Cronbach's alpha coefficient=0.67). Three items contributed most to the lower Cronbach's alpha in the physical domain: loss of energy, hoarseness and smoking (questions 9, 14 and 15). As most patients with COPD have a smoking history and many suffer form loss of energy or hoarseness these three items may be less discriminative in COPD patients than in patients with chronic cough. When these items were removed from this domain, the Cronbach's alpha coefficient increased to almost 0.70.

Previous studies showed comparable Cronbach's alpha coefficients which varied be-

tween 0.77 and 0.91, except for the physical domain.[16;17]

To examine reproducibility, test-retest reliability and agreement were assessed after two weeks in clinically stable patients. Total score and scores on all domains were repeatable with intraclass correlation coefficients above 0.7. So, repeatability of the LCQ in COPD patients with chronic cough was adequate and in accordance with previous results.[16;17]

Agreement was assessed in clinically stable patients after 2 weeks according to the method described by Bland and Altman.[29] We found a mean change in the LCQ total score of 0.73 (± 1.75), similar to the results of Birring (0.73 (± 0.94)) after two weeks.[16] Agreement is regarded as acceptable when the limits of agreement are smaller than the minimal clinical important difference (MCID). In previous studies the MCID for the LCQ total score in patients with chronic cough was estimated between 1.3 (± 2.3) and 2.8 (± 2.0).[31;32] In this study we found limits of agreement above these values, indicating inadequate agreement. However, we realise that this randomised controlled trial was not the ideal setting to measure reproducibility specifically since patients received either active (azithromycin) or placebo medication from the first day. This treatment/placebo difference will have increased noise, resulting in larger limits of agreement and rendering assessment of reproducibility poorer. To draw a more definitive conclusion this analysis should therefore be repeated in clinically stable COPD patients not receiving any (or stable) study medication. The MCID specifically for COPD patients with chronic cough should also be obtained.

The LCQ has been validated and used primarily in patients suffering from chronic cough but not exclusively. Murray et al validated the LCQ in patients with bronchiectasis. They concluded that the questionnaire was able to measure quality of life for assessing existing and new therapies.[19] Both concurrent validity, reliability and responsiveness were comparable with our results. Polley et al undertook a cross-sectional comparison of the LCQ and the Cough specific Quality of life Questionnaire (CQLQ) in patients with either chronic cough, bronchiectasis, COPD or asthma. The group of COPD patients was small (n=18), but had similar baseline LCQ scores as our participants. They demonstrated significant concurrent validity (r=-0.49) for the total score of the LCQ and the CQLQ in COPD patients. Remarkably, we found a better concurrent validity (r=-0.60) when using the SGRQ, which is not a cough-specific questionnaire. Like in our study, the psychological domain in their study showed weaker correlations in COPD patients than in patients with chronic cough. They reasoned that chronic cough is associated with more psychological problems in women than in men. In both studies the majority of patients included were male, in Polley et al 83% and in our study 74%. Possibly the relatively weak correlations can be explained by this gender imbalance. An additional explanation, they suggest, is that in COPD patients physical complaints are more prevalent than in chronic cough patients, in which psychosocial complaints are predominant.[33]

There are some limitations to our study. First it is based on participants in the setting of a randomised double-blind controlled trial. During the analyses of this validity study

it was unknown which participants were treated with antibiotics and which were not. In case of significant treatment effect, this will, as earlier mentioned, have influenced reproducibility. Secondly, to assess internal consistency Cronbach's alpha coefficients as well as factor analysis is recommended. The latter analysis was not done in our study, because another method of item reduction was used during the development of the LCQ.[16] Furthermore, we realise that it is difficult to confirm factor structures in different populations.[34] And last, the SGRQ was used as the reference standard. A recent study showed that the SGRQ measures health status only partly. It concluded that the SGRQ can be used mainly for measuring subjective symptoms and impairments and that other aspects of health status such as physical activity, dyspnoea, fatigue or quality of life in general are covered less. Preferably, different questionnaires should be combined.[35]
Ideally, questionnaires which measure health status should be both discriminative (able to distinguish patients with different degrees of disease severity) and evaluative (able to detect within patients changes following therapy). In this study the emphasis is mostly on the evaluative properties of the LCQ, because the main goal of the study was to validate the LCQ for use in clinical trials. The discriminative properties should be assessed in a future study.
In summary, our study shows that the LCQ can be used in COPD patients to measure cough-related health status. This provides a tool to study the antitussive or mucolytic effects of drugs in patients with COPD and chronic productive cough.

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Chapter 3

Clinical COPD Questionnaire (CCQ) and COPD Assessment Test (CAT) questionnaire; Do we have to choose?

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Abstract

Background

To measure health status, two COPD-specific health status questionnaires, the Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT) are commonly used in clinical practice. Both questionnaires are short, practical, easy to use and administered for use in follow-up in current guidelines.

Objectives

It is unclear which of the questionnaires is superior for use in clinical practice; which questionnaire do we have to choose?

Methods

This prospective study included COPD-patients referred by the general practitioner to the pulmonologist for optimisation of their inhalation medication. Validity, reliability and responsiveness were determined. St. George's Respiratory Questionnaire was used as external criterion. All questionnaires were completed at baseline. CCQ and CAT were administered after 2 and 6 weeks together with a global rating of change.

Results

56 patients were included, with a mean age of 68±9.4 years and a mean FEV_1% predicted of 52±13.1%. The correlation coefficient for construct validity between CAT total score and CCQ total score was 0.83 (p=0.01). Internal consistency showed Cronbach's α coefficients of 0.83 and 0.89 for CAT and CCQ total score. Test-retest reliability in stable patients showed intraclass correlation coefficients of 0.88 for both CCQ and CAT total score. Agreement for both questionnaires was doubtful. Responsiveness was limited with an area under the curve of 68% for both questionnaires.

Conclusions

CAT and CCQ have equivalent measurement properties for validity and reliability. The evaluative value of both questionnaires was limited. The optimal instrument and especially its way of use in daily clinical practice therefore remain to be established.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease and is characterized by persistent airflow limitation that is caused by chronic inflammation, small airway diseases and parenchymal destruction. The prevalence of COPD is expected to increase in the coming decades due to continued exposure of risk factors, like tobacco smoking, air pollution and aging of the world population.[1] COPD-patients experience respiratory symptoms as dyspnoea, cough, phlegm, exercise intolerance but also depression, restriction of social activities.[2] Part of these symptoms benefit from inhaled medications, while other requires other interventions. Given this multilayered plethora of symptoms, the GOLD committee in the recent update of the GOLD guideline[1] has therefore broadened the assessment of severity to include also current impact, to be measured by modified Medical Research Council (mMRC), COPD Assessment Test (CAT) or Clinical COPD Questionnaire (CCQ) the latter two being measurements of health status. Health status clearly provides additional information up and above spirometry, number of exacerbations or mortality.[3] Most specifically, alterations in spirometry are poorly correlated with patients' perception of symptoms or health status.[4] Advantages of health status measurements in clinical practice are making explicit and measurable the patient's experience of symptoms in comparison with the clinician's evaluation of the same problem, which often show a discrepancy. The use of health status questionnaires also leads to a better compliance of COPD-patients because of improvement of patient satisfaction.[2]

To measure health status, two COPD-specific health status questionnaires, the CCQ[5] and the CAT[6] are commonly used. Both questionnaires are short, practical and easy to use in clinical practice. Both, CAT and CCQ, are administered for use in follow-up, as recommended in current guidelines.[7] Recently, two studies[8;9] compared both questionnaires and found similar psychometric properties. The purpose of the use of health status questionnaires in clinical practice is in particular evaluative and only partly discriminative. Two studies[8;9] failed to mention two important psychometric properties, the agreement and the responsiveness, the evaluative part. Furthermore, these two previous studies compared the CAT total and CCQ total score only; the value of the separate domains (symptom, functional and mental domains) of the CCQ in comparison with the CAT total score was not elucidated.

Therefore, it is still unclear which of the questionnaires is superior for use in clinical practice. Thus, the aim of our study was to measure the construct 'health status of COPD-patients in an outpatient setting' and to assess the evaluative value of the CCQ and the CAT and the additional value of the domains and to compare the psychometric properties of both questionnaires.

Material and Methods

Study design

This was a prospective validation study. Patients were recruited from a specialized centre of the department of pulmonology of the Isala hospital in Zwolle in the Netherlands, the asthma-COPD-diagnosis-centre (ACDC). In the ACDC, patients with respiratory symptoms in primary care could be referred to secondary care for screening. All referred patients received a spirometry and were seen by a pulmonologist or a pulmonary nurse practitioner. After a diagnosis of COPD inhaled medication was started or optimized and follow-up was initiated.

Participants

Patients of ≥40 years of age, ≥10 pack-years, a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of <70% and a FEV_1/FVC ratio ≤70 without reversibility, had no medical history of asthma or heart failure, had no earlier spirometry in secondary care and were able to complete questionnaires, were eligible to participate in the study.

HEALTH STATUS QUESTIONNAIRES

CCQ

The CCQ[5] is a COPD-specific questionnaire, consists of 10 items, a total score and 3 domains scores: symptoms, functional and mental state. The scores ranges from 0-6; a lower score indicate better health status. The minimal clinical important difference (MCID) of the CCQ is 0.4 points.[10] CCQ domains were defined during the development and were not confirmed by factor analysis.[5]

CAT

The CAT[6] is also a COPD-specific questionnaire and has 8 items. The CAT has no domains, only a total score ranges from 0-40; lower score indicating better health status. The MCID of the CAT is 2 points.[11]

Factor-analysis for the CAT was not determined however, since item reduction was performed with Rash analysis.[6;12]

St. George's respiratory questionnaire (SGRQ)

The SGRQ[13] is a disease-specific health status questionnaire for asthma and COPD. It contains 51 items divided in 3 domains: symptoms, activity and impacts. The scores ranges from 0-100, a lower score indicates better health status. Since the SGRQ is a well-evaluated and widely used questionnaire[13-16] among COPD-patients it was used as external criterion to assess construct validity. The MCID of the SGRQ is 4.[17]

Global Rating of Change (GRC)

The GRC[18] was used to evaluate self-perceived health change on a 15 point scale (-7

TABLE 1: Patient characteristics

n		56
Sex, male, n(%)		33 (59)
Age (years), mean (SD)		68 (9.4)
Pack-years, median (range)		30 (10-86)
Current smoker, n(%)		17 (30.4)
FEV_1 (%predicted)*, mean (SD)		52.4 (13.1)
GOLD, n(%)	2	29 (51.8)
	3	27 (48.2)
	4	0 (0)
Inhaled medication primary care, n(%)		
	Short-acting	20 (35.7)
	Long-acting	27 (48.2)
	ICS	22 (39.3)
Inhaled medication after optimalization, n(%)		
	Short-acting	22 (39.3)
	Long-acting	48 (85.7)
	ICS	40 (71.4)
SGRQ total score, median (range)		36.9 (4.2-82.9)
CCQ total score, median (range)		1.6 (0.1-5.2)
CAT total score, median (range)		15.5 (5-36)

CCQ=Clinical COPD Questionnaire, CAT=COPD Assessment Test, SGRQ=St. George's Respiratory Questionnaire, FEV_1=Forced Expiratory Volume in one second, Short-acting=beta2-mimetica and anti-cholinergicum, Longacting=beta2-mimeticum and anti-cholinergicum, ICS=combination of longacting beta2-mimetica with corticosteroids or inhalation corticosteroids alone. COPD classification by post-bronchodilator spirometry according to GOLD guidelines[7]

a very great deal worse, 0 no change, +7 a very great deal better). The GRC was used as anchor to determine in reliability, in stable patients, and responsiveness, in patients with a marked change (GRC>3).

Methods

At baseline, demographics, medical history, and post-bronchodilator spirometry were recorded.

The study was approved by the local medical Committee of Ethics of the Isala hospital in Zwolle of the Netherlands, and patients gave written informed consent.

The CAT, CCQ and SGRQ[13] were sent to patients by mail completed at home and returned by mail at baseline. This procedure was repeated for the CAT en CCQ after 2 and 6 weeks.

Internal consitency and construct validity were assessed using the baseline CAT, CCQ and SGRQ scores. Reliability was determined for the CAT and CCQ in stable patients after 2 weeks (defined as GRC=-1, 0 and 1 in this study[19]). To assess responsiveness the CAT and CCQ were administered at baseline and after 6 weeks in changed patients (chosen as GRC≤-3 or GRC≥3[19] (moderately better/worse to a very great deal better/worse) in our study).

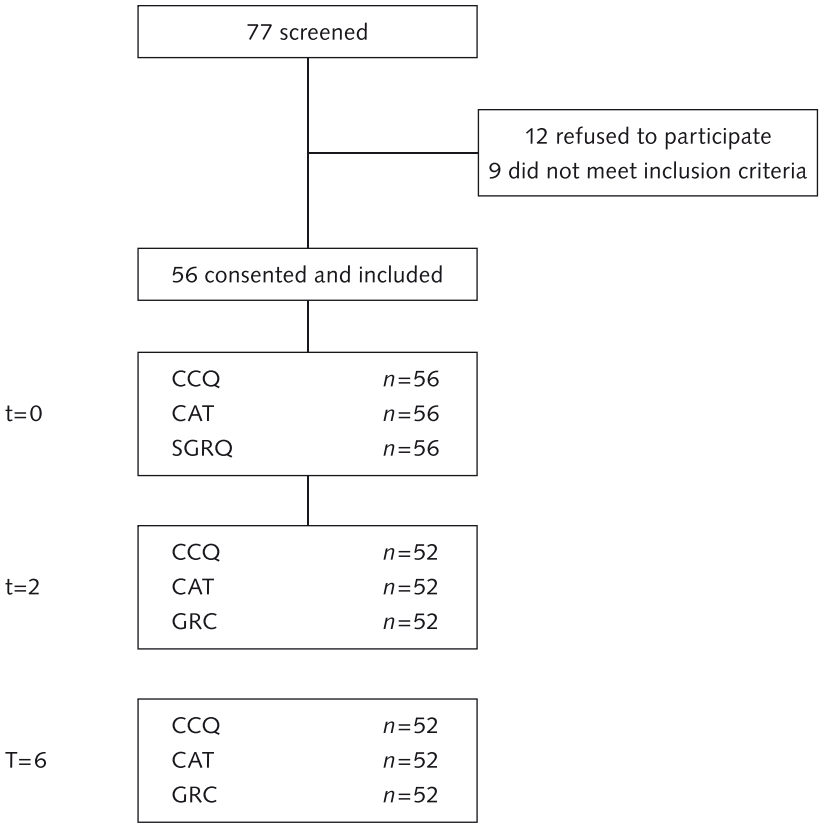
Analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM corporation, Armonk, NY, USA). Baseline characteristics are presented as mean (standard deviation) unless otherwise stated.

The definitions of the clinimetrics statistics were based on the 'consensus based standards for the selection of health measurement instruments' (COSMIN) study.[20;21]

First, two of the five authors assessed face validity, the degree to which the items of the CAT and CCQ indeed look as an adequate reflection of the construct to be measured, namely 'health status in COPD patients'. To assess content validity of the CAT and CCQ these four questions were answered, i.e. *'Do all items of the questionnaires refer to relevant aspects of the construct?' 'Are all items relevant for the study population?' Are all items relevant for the purpose of the application of the instrument?' 'Do all items together comprehensively reflect the construct to be measured?'* To determine construct validity, the degree to which the scores of the CCQ, CAT and SGRQ are consistent with hypotheses based on the assumption that both questionnaires validly measures health status in COPD patients, Spearman rank correlation coefficients were used, because most of the distributions were skewed. Correlations of ≥0.5 were considered as good, correlations between 0.3-0.5 moderate and correlations of <0.3 as poor.[22] We predefined corresponding domains of the questionnaires and hypotheses of construct validity. For the CAT total score and the CCQ total and domain scores we expected correlations of ≥0.5. For the CAT total score and the SGRQ total and domain scores we also expected correlations of ≥0.5. Corresponding domains of the CCQ and the SGRQ were predefined as: CCQ symptom and SGRQ symptom, CCQ mental and

FIGURE 1: Flow Chart



SGRQ impact, CCQ functional and SGRQ activity and CCQ total and SGRQ total with al domain scores, correlations of ≥0.5 were expected. Correlations of <0.1 were expected for FEV_1 with CAT total and CCQ total and domain scores. Construct validity is acceptable as ≥75% of the hypotheses correspond.[21]

Internal consistency, the degree of inter-relatedness among the items, of the CCQ and CAT were evaluated by calculating Cronbach's alpha coefficient. Internal consistency between 0.7 and 0.9 was considered as adequate.[21;23] Test-retest-reliability, the degree that both questionnaires can distinguish stable patients from each other, despite measurement error, was assessed with Intraclass Correlation Coefficients (ICC) based on the two-way random effect model and the standard error of measurement (SEM) was used to indicate absolute measurement error in stable patients after 2 weeks. Reliability should preferably reach ICC values of ≥0.7.[23] Agreement, the degree that repeated measurements give the same results, was assessed with a Bland-Altman plot for the CAT total score and CCQ total and domain scores. Agreement is acceptable when the limits of agreement are smaller than the MCID.[23;24]

Responsiveness, the ability to detect change over time of health status in COPD-patients, was determined for CAT en CCQ total scores after 6 weeks, in patients who experienced improvement or deterioration. To determine responsiveness the area under the receiver operating characteristic (ROC) curve was used. An adequate area under the curve (AUC) was set at least 0.70.[21;23] Sensitivity and specificity were calculated.

Floor and ceiling effects were assessed. When less than 15% of the patients achieve the highest or lowest possible score respectively, floor and ceiling effects were called absent and the questionnaire adequate.[21;24]

Results

In total 56 patients were included from the 15th March 2011 till the 13th of July 2013, as shown in Figure 1. Baseline characteristics are presented in Table 1. The mean age of the patients was 68±9.4 years; the mean FEV_1% predicted was 52.4±13.1. General practitioners referred 30 (53.6%) patients with suspected COPD; the other 26 (46.4%) patients had a non-spirometry-confirmed diagnosis of COPD by the general practitioner. Of the 56 patients, 8 (14.3%) patients had an exacerbation during their first outpatient visit.

VALIDITY

Face validity

The items of both questionnaires, the CCQ and the CAT, have to reflect the construct 'health status' of patients with COPD. Health status is defined as the effect of a person's health on the ability to perform and enjoy the activities of daily life. Health status encompasses functional state, ability to perform tasks of daily living, and health

TABLE 2: Construct validity (*n*=56)

Construct validity				
	SGRQ total	SGRQ symptom	SGRQ impact	SGRQ activity
CCQ total	**0.83 (0.01)**	**0.54 (<0.0001)**	**0.75 (<0.0001)**	**0.75 (<0.0001)**
CCQ symptom	**0.65 (<0.0001)**	**0.61 (<0.0001)**	0.60 (<0.0001)	0.52 (<0.0001)
CCQ mental	**0.66 (<0.0001)**	0.51 (<0.0001)	**0.63 (<0.0001)**	0.53 (<0.0001)
CCQ functional	**0.78 (<0.0001)**	0.40 (0.002)	0.66 (<0.0001)	**0.80 (<0.0001)**
CAT total	**0.84 (0.01)**	**0.67 (<0.0001)**	**0.78 (<0.0001)**	**0.75 (0.0001)**
	CCQ total	CCQ symptom	CCQ mental	CCQ functional
CAT total	**0.84 (<0.001)**	**0.75 (<0.001)**	**0.60 (<0.001)**	**0.74 (<0.001)**
	CCQ total	CCQ symptom	CCQ mental	CCQ functional
FEV_1 %pred	**0.02 (0.86)**	**-0.007 (0.96)**	**0.003 (0.86)**	**0.007 (0.64)**
	CAT total			
FEV_1 %pred	**0.10 (0.44)**			

CCQ=Clinical COPD Questionnaire, CAT=COPD Assessment Test, SGRQ=St. George's Respiratory Questionnaire, FEV_1=Forced Expiratory Volume in one second. Correlations of corresponding domains are bolded. Hypotheses for correlations of construct validity were: <0.30 poor correlations, 0.30-0.50 moderate correlations, >0.50 good correlations.

TABLE 3: Internal consistency

	Our study (*n*=55)	**Original validation study**[5] (*n*=20)
CCQ total	0.89	0.91
CCQ symptom	0.82	0.78
CCQ mental	0.72	0.80
CCQ functional	0.88	0.89
	Our study (*n*=55)	**Original validation study**[6] (*n*=1490)
CAT total	0.83	0.88

CCQ= Clinical COPD Questionnaire, CAT= COPD Assessment Test

Cronbach's alpha coefficient between 0.70 and 0.95 is considered as good internal consistency.

related quality of life (HRQL), the subjective experience of a person of the impact of the health status on the quality of life.[3]
The CAT and the CCQ are both COPD-specific questionnaires and assess the effect that particular pulmonary symptoms, i.e. dyspnoea, cough and sputum, have on a patient's life.[25] Both questionnaires, CAT and CCQ exist of items that reflect these facets of health status.

Content validity
To assess the relevance and comprehensiveness of items of the CAT and CCQ to measure health status in COPD patients these four questions were examined. 1. *'Do all items of CCQ and CAT refer to relevant aspects of health status in COPD-patients?'* and 2. *'Are all items relevant for COPD-patients?'* The CCQ was developed and firstly validated in 2003[5], the CAT questionnaire in 2009.[6] To ensure that all relevant items to assess health status were included in the CCQ, focus group discussions with COPD-patients were conducted, other COPD questionnaires were reviewed, guidelines were identified and clinicians involved in treatment of COPD were consulted.[5;6] A limitation of both questionnaires is that factor-analysis was not used for development. 3. *'Are all items relevant for the purpose of the application of the CAT and CCQ?'* Ideally, a disease-specific questionnaire should be discriminative and evaluative. Several studies[8;9;26] have analysed the discriminative part of the questionnaires which was adequate, however the evaluative properties of both questionnaires, agreement and responsiveness, were never fully assessed. 4. *'Do all items together comprehensively reflect health status in COPD-patients?'* Based on previous validation studies[5;6;8;9] of the CAT and CCQ, we can assume that both questionnaires reflect health status in COPD-patients.

Construct validity
All predefined corresponding domains in the section 'statistical analyses met the expected hypothesized correlations of ≥0.5, depicted in Table 2. The CAT total score and CCQ total and domain scores were both closely and significantly related to each other. As expected, CCQ total and domain scores and CAT total score did not correlate with FEV_1% predicted. All corresponding domains met the predefined hypotheses.

RELIABILITY

Internal consistency
Table 3 presents internal consistency of the CCQ total and domain scores and the CAT total score. The internal consistencies of the CCQ total and CAT total scores were 0.89 and 0.83, respectively. Internal consistency was comparable with other validation studies, shown in Table 3.

Test-retest reliability
Test-retest reliability was tested in 23 patients that remained stable after 2 weeks,

TABLE 4: Test-retest-reliability

	Our study (*n*=23)		**Other validation studies**[8;27]	
	ICC (95%CI)	SEM	ICC (95%CI)	SEM
CCQ total	0.88 (0.75;0.95)	0.86	0.95 (0.92;0.96)[8]	0.21
CCQ symptom	0.86 (0.72;0.94)	1.21	0.74 (NA)[27]	NA
CCQ mental	0.64 (0.32;0.83)	0.74	0.83 (NA)[27]	NA
CCQ functional	0.80 (0.59;0.91)	0.10	0.86 (NA)[27]	NA
	Our study (*n*=23)		**Other validation study**[8]	
CAT total	0.88 (0.75;0.95)	6.51	0.94 (0.92;0.96)[8]	1.92

CCQ= Clinical COPD Questionnaire, CAT= COPD Assessment Test, 95%CI=95%Confidence Interval,
ICC= Intraclass correlation coefficient (ICC≥ 0.70 indicates good test-retest reliability),
SEM=Standard Error of Measurement

TABLE 5: Floor and ceiling effect for CCQ and CAT

	Our study (*n*=56)			**Other validation study**[27] (*n*=111)		
	Mean (SD)	Floor (%)	Ceiling (%)	Mean (SD)	Floor (%)	Ceiling (%)
CCQ total	1.87 (1.06)	0	0	2.33 (1.03)	0	0
CCQ symptom	2.32 (1.35)	1.8	0	2.57 (1.17)	1.8	1.8
CCQ mental	0.92 (1.15)	39.3	0	2.44 (1.75)	14.4	3.6
CCQ functional	1.89 (1.23)	0	0	2.03 (1.22)	3.6	0.9
	Our study (*n*=56)			**Other validation study**[31] (*n*=301)		
CAT total	16.25 (7.54)	0	0	15.43 (7.84)	0	0

based on the anchor, GRC -1, 0, 1. With the exception of CCQ mental score, CCQ total and the other domain scores and CAT total score have an ICC >0.70, shown in Table 4. The SEM on individual level of the CCQ total and domain scores was larger than the MCID (0.40) and the SEM of the CAT total score was also larger than the estimated MCID (2), depicted in Table 4. The SEM on group level for the CCQ total score was 0.18 and the SEM for the symptom-, mental- and functional domain was 0.25, 0.15 and 0.02 respectively. The SEM on group level for the CAT total score was 1.36. The SEM on group level for the CAT total score was 0.57.

Agreement

Bland-Altman plots of the CAT total and CCQ total score for 23 stable patients are shown in Figure 2. The mean difference after 2 weeks of the CCQ total score was 0.03±0.1 and the mean difference of CAT total score -0.6±0.7. The CCQ total score had an upper limit of agreement of 0.89 and a lower limit of agreement of -0.83. The upper limit of agreement of the CAT total score was 5.7 and the lower limit of agreement -6.9.

MEASUREMENT OF CHANGE

Responsiveness

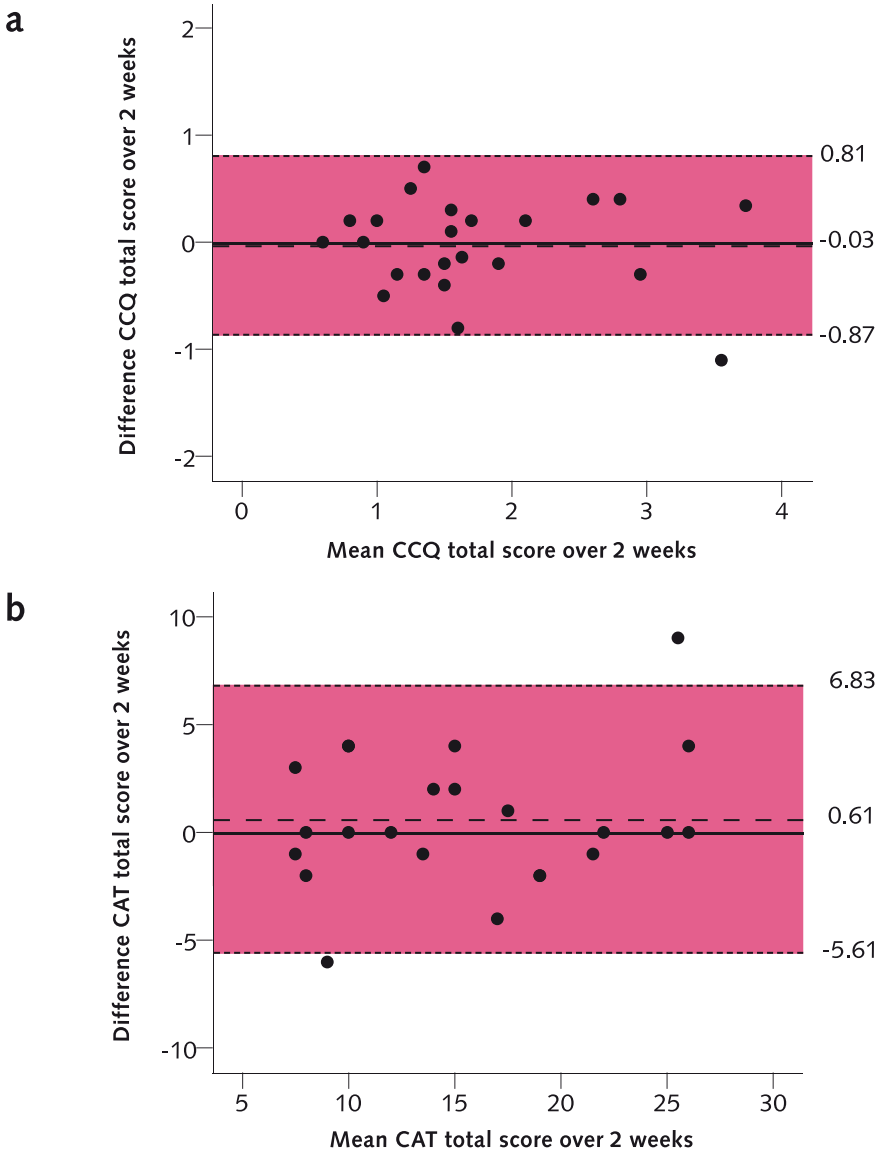
22 patients perceived a moderate improvement or deterioration of health change (GRC≥3 or GRC≤-3) after 6 weeks, the mean change of the CCQ total score was 0.36±0.14 (95%CI 0.07;0.65, p=0.02) and of the CAT total score 3.1±1.3 (95%CI 0.5;5.6, p=0.02). Figure 3 shows the AUC of the ROC curve of the CCQ total score, 68% (95%CI 0.54;0.83, p=0.03), and the CAT total score, 68% (95%CI 0.53;0.83, p=0.03). The CCQ total score had a sensitivity of 36.4% and a specificity of 76.7%. The sensitivity and specificity of CAT total score were 50.0% and 70.0% respectively.

INTERPRETABILITY

Floor and Ceiling effects

Floor and ceiling effects were analyzed at baseline, Table 5. In the CAT floor and ceiling effects were not present. In the CCQ mental domain 22 patients (39.3%) and one patient (1.8%) of the CCQ symptom domain had the best possible score.

FIGURE 2: Agreement over time in stable COPD-patients of CAT total score and CCQ total score



CCQ= Clinical COPD Questionnaire, CAT= COPD Assessment Test, GRC=Global Rating of Change

The agreement of the CCQ total score (2a) and the agreement of the CAT total score (2b) over 2 weeks in stable COPD patients (GRC=-1, 0 and 1). The bolded dashed line represents the mean difference over 2 weeks of the CCQ and the CAT total scores. The small dashed lines are the limits of agreement, 1.96* standard deviation of the mean difference. (*n*=23)

Discussion

In this is study we compared the psychometric properties, i.e. the discriminative and evaluative value, of the CAT and the CCQ in COPD patients to decide which questionnaire is preferable to use in clinical practice for follow-up of health status after start or change of inhalation medication. Our findings showed that the psychometric properties, validity, reliability, responsiveness and floor and ceiling effects of the CCQ and the CAT were equivalent.

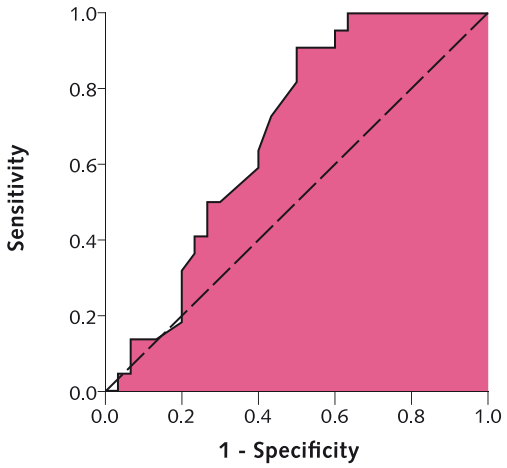
Construct validity, internal consistency and test-retest-reliability are important psychometric properties for questionnaires with a discriminative value. For both questionnaires, the CCQ and the CAT, the discriminative part was adequate, which is similar to previous validation studies.[5;6;8;9;26;27] However, disease-specific health status questionnaires are also used in clinical practice for follow-up of COPD-patients after a switch or optimisation of medication and therefore should also be evaluative. The evaluative part of patients was assessed with agreement, the degree to differentiate between stable patients and unstable patients, and responsiveness, the degree of questionnaires to detect changes in patients over time. Unfortunately, the evaluative value of both questionnaires was limited in our study. We will discuss all measurement properties separately.

Construct validity was adequate for both the CAT and CCQ. Both questionnaires met the predefined hypotheses of this study. The latter means that both questionnaires truly measure health status in COPD patients. Ideally, when a long time-consuming disease-specific health status questionnaire has to be replaced by a shorter disease-specific questionnaire, it is important to be sure that both questionnaires measure the same construct. So, both questionnaires should be highly correlated. Maybe, our predefined hypotheses were to mild and should be stricter, for instance correlations of ≥0.7 would be considered as good instead of correlations ≥0.5. However, the predefined hypotheses were based on previous literature.[5;6] Correlations of previous studies between the CCQ total score and the SGRQ total score were, 0.71[5], 0.77[8], 0.75[9], and 0.80[6], 0.65[8], 0.73[9] between the CAT total score and the SGRQ total score. Our study found comparable correlations for construct validity in comparison with these previous studies.

The CCQ and CAT had both a good internal consistency, indicating that the items of the domains of the questionnaires are related to each other. Internal consistency with a Cronbach's alpha above 0.95 suggests that items within one domain greatly overlap each other and that one of the items should be removed. Cronbach's alpha coefficients of the CCQ total and domain scores varied between 0.72-0.89 and of the CAT total score the Cronbach's alpha coefficient was 0.83. To assess test-retest-reliability ICC's and SEMs were examined in stable patients. The ICC of the CAT total score was high, 0.88. The ICC's for the CCQ total score and domain scores (0.80-0.88) were comparable except for the CCQ mental score (ICC 0.64). This implies that the CAT and the

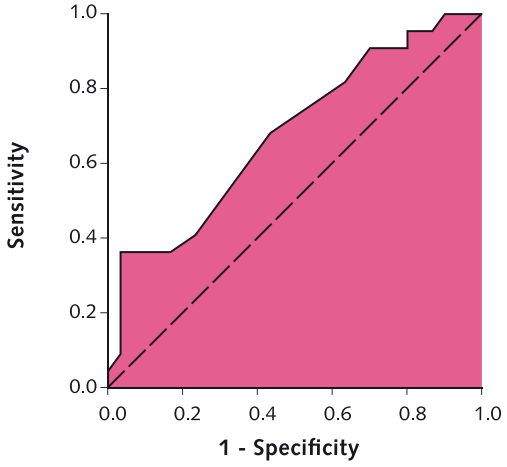
FIGURE 3: Receiver Operating Characteristic (ROC) curve for responsiveness of the CCQ total score and CAT total score in changed COPD patients. (*n*=52)

a



		GRC			
		changed	not changed	total	
CCQ	MCID ≥0.4	8	7	15	
	MCID ≤0.4	14	23	37	Sensitivity: 36.4%
	total	22	30	52	Specificity: 76.7%

b



		GRC			
		changed	not changed	total	
CAT	MCID ≥2	11	9	20	
	MCID ≤2	11	21	32	Sensitivity: 50.0%
	total	22	30	52	Specificity: 70.0%

CCQ= Clinical COPD Questionnaire, CAT= COPD Assessment Test

The solid line in figure 3a represents the curve of the CCQ and the solid line in figure 3b represents the CAT curve. The dashed line represents the reference line in both figures 3a and b.

CCQ total, symptom and functional score are able to distinguish patients from each other despite measurement error; these findings are also comparable with previous studies[5;6;8], as shown in Table 4. The test-retest reliability of the CCQ mental score was moderate. The items of the CCQ mental domain include two questions; *'Concerned about getting a cold or your breathing getting worse?'* and *'Depressed (down) because of your breathing problems?'* Of the 56 patients 22 (39.3%) patients had the best possible score and thus the same score at baseline for this domain and therefore the questionnaire was unable to distinguish between these patients. There are some barriers for assessing anxiety and depression in COPD-patients, like the fear of stigmatization, or masking mood disorders by physical symptoms.[28] Patients could be tempted to express depressive feelings in physical symptoms like shortness of breath, cough or phlegm production. It is possible that this influences the answers on the questions of the CCQ mental domain.

The test-retest reliability is a relative measure and the degree of variation between the subjects can affect the ICC, the SEM is an absolute value and is not affected by a heterogeneous population. Therefore it is complementary to interpret the ICC with the SEM.[29] The SEMs of the CCQ total and domain scores on individual level were larger than the MCID of 0.4 in our study and varied between 0.74 and 1.21. Except for the CCQ functional domain, SEM of 0.10. The SEM of the CAT was 6.51 and was also larger than the MICD of 2. This suggests that the CAT and the CCQ total, symptom and mental score were not able to distinguish a relevant change from measurement error on an individual level. However, the SEMs on group level for the CCQ total score and for the symptom-, mental- and functional domain were 0.18, 0.25, 0.15 and 0.02 respectively. The SEM on group level for the CAT total score was 1.36. This indicates that both questionnaires can indeed distinguish a relevant change from measurement error on a group level, for instance in clinical research. In literature, two studies have addressed the SEM as well, these were 0.29[26] and 0.21[8] for the CCQ total score and 1.92[8] for the CAT total score. In one study[26] the distribution-based-method was used instead of the preferred anchor-based method to determine the SEM of the CCQ total score, and could therefore not be compared with our study. The other study[8] assessed the SEM of the CAT total score and the CCQ total score anchor-based and on group level and was therefore comparable with our study. SEMs of the CAT total score and CCQ total score were even better in our study.

Agreement was determined in stable patients and was depicted by Bland-Altman-plots. The limits of agreement of both, the CCQ total score and the CAT total score, were larger than the MCID of both questionnaires on individual level, the upper limit of agreement was 0.89 and the lower limit of agreement was -0.83 for the CCQ total score and 5.7 and -6.9 for the CAT total score, respectively. Unfortunately, none of the other previous validation studies assessed agreement over time previously. Thus we were not able to compare our findings with other literature. The limits of agreement on group level were for the CCQ total score 0.19 and -0.17 and for the CAT total score 1.19 and -1.44. These findings suggest that both questionnaires could not differentiate

stable patients from changed patients on individual level but actually can on group level. This implies that the evaluative value of both questionnaires for COPD-patients on individual level is limited. The evaluative value on group level is adequate for both questionnaires.
Responsiveness was assessed in patients whose health changed a moderately to a great deal, regardless of the direction of change. Both questionnaires had an AUC of 68%, which is just below the desirable value of 70%. This means that both questionnaires can detect changes in patients moderately to acceptably. However, both questionnaires were not able to detect a clinical relevant change very well since the specificity and sensitivity were both low. Responsiveness was not assessed with the criterion approach before for the CAT and the CCQ total score with a ROC curve, which is the preferred method according to the COSMIN guidelines.[21] Therefore we were not able to compare our results with previous studies. One previous study[26] showed a ROC curve of the CAT. Unfortunately, in this study responsiveness was assessed only for patients whose health had improved; deterioration was not taken into account. Another difference between our study and this previous study was the lack of an anchor or extern criterion, as we used the GRC in our study. Thus the ROC curves of this previous study could not be compared with our study.
The moderate evaluative value of both questionnaires could partly be due to a 'response shift phenomenon'. Response shift is defined as a change in the meaning of a patient's self-evaluation of a construct.[30] In this study patients were included who were referred from primary care to secondary care because of increasing respiratory symptoms despite treatment by the general practitioner. After optimisation of inhalation medication at secondary care, patients expected their symptoms to diminish. However, during treatment a patient adapts to their increased symptom level to deal with the circumstances and will experience their symptoms as less disabling then at start of the study. This 'response shift phenomenon' could influence the evaluative value of questionnaires, underestimating change.

This study has some limitations. The first limitation is the small sample size of 56 participants, though the COSMIN guidelines [21;23] state that a sample size of 50 participants is sufficient. However, since only 23 patients remained stable after 2 weeks assessment, the test-retest reliability and agreement must be interpreted with caution. Secondly, the CCQ and CAT were developed without factor analysis. Preferably, factor-analysis should be done in this validation study. However, this study was not designed to perform factor-analysis. To perform factor-analysis a sample size of at least 100 participants is needed.[21] Subsequently, it is not possible to perform factor-analysis because of the small sample size. Another limitation is that the GRC≥3 and GRC≤-3 are to some degree chosen arbitrarily to assess responsiveness, though this cut-off point was chosen from other literature[19] and can possibly under- or overestimate responsiveness. The last limitation is that the MCID was also adapted from previous literature[5;12] and was not re-assessed in the patient population of this current study. The quoted MCID of the

CCQ was determined in stable COPD-patients, the MCID of the CAT is established in COPD-patients after pulmonary rehabilitation; this could influence the interpretation of the agreement and the SEM. Unfortunately, our sample size was too small to determine the MCID of both questionnaires.

In conclusion, the CCQ and CAT questionnaires have similar psychometric properties in our study population of COPD-patients. The discriminative value of both questionnaires was adequate. However, the evaluative value of both questionnaires was limited on an individual level and acceptable on group level. This means that both questionnaires are valid and reliable to use in clinical research and randomized trials (group level use). However, the value of the CAT and CCQ in follow-up of health status in individual COPD-patients in clinical practice remains to be established.

Authorship

All authors should have made substantial contributions to all of the following: JWB, FFB and SU contributed to the conception and design of the study. FFB and AWV contributed to the acquisition of data. SU, AWV and FFB contributed to analysis and interpretation of data. All authors contributed to drafting and revising the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

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Chapter 4

Health status in patients with coexistent COPD and heart failure, a validation and comparison between the CCQ and the MLHF-Q.

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Status

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Abstract

Introduction

Chronic Obstructive Pulmonary Disease (COPD) and heart failure (HF) are both common diseases that coexist frequently. Patients have worse stable state health-status compared to patients with one of the diseases. In many outpatient clinics, health-status is monitored routinely; for COPD-patients with the Clinical COPD Questionnaire (CCQ) and for HF-patients with the Minnesota Living with Heart Failure Questionnaire (MLHF-Q). This study validated and compared which questionnaire, the CCQ or the MLHF-Q, is suited best for patients with coexistent COPD and HF.

Methods

Patients with both COPD and HF who were ≥40 years old were included. Construct validity, internal consistency, test-retest-reliability, agreement) were determined. The Short-Form-36 was used as external criterion. All questionnaires were completed at baseline. The CCQ and MLHF-Q were repeated after 2 weeks together with a global rating of change.

Results

In total 58 patients were included, 50 patients completed the study. Construct validity was acceptable. Internal consistency was adequate for CCQ and MLHF-Q total and domain scores, Cronbach's alpha's ≥0.70. Reliability was adequate for MLHF-Q and CCQ total and domain scores, intraclass correlation coefficients (ICC's) 0.70-0.90, except for the CCQ symptom score, ICC 0.42. The standard error of measurement (SEM) on group level was smaller than the minimal clinical important difference (MCID) of both questionnaires. However the SEM on individual level was larger than the MCID. Agreement was acceptable on group level and limited on individual level.

Conclusion

CCQ and MLHF-Q were both valid and reliable questionnaires to assess health-status in patients with co-existent COPD and HF on group level, and hence for research. However, in clinical practice, on individual level, characteristics of both questionnaires were not as good. There is room for a questionnaire with good evaluative properties on the individual level, preferably tested in a setting of patients with COPD, or HF or both.

Keywords

Clinical COPD Questionnaire, Minnesota Living with Heart Failure Questionnaire, chronic obstructive pulmonary disease, heart failure

Introduction

Chronic obstructive pulmonary disease (COPD) is a major worldwide cause of morbidity and mortality and its prevalence is predicted to increase over the following decades.[1] COPD is an inflammatory disease with extra-pulmonary manifestations, among others an increased prevalence of cardiovascular diseases in comparison with the general population.[2] 9-41% of the COPD-patients have heart failure (HF).[3] Both systemic conditions have certain pathophysiologic characteristics in common, i.e. the shared risk factor of smoking leading to low-grade systemic inflammation, which in turn accelerates progression of atherosclerosis in both diseases.[4] COPD and HF also have overlapping clinical manifestations, like dyspnea, fatigue and exercise intolerance.[5;6] Managing patients with combined COPD and HF is a challenge because it is difficult to determine whether signs and symptoms are caused by COPD, HF, or both. This can lead to delays in adequate treatment, to more severe exacerbations, and to more frequent hospital admissions.[7] Patients hospitalized with an exacerbation of COPD and HF have more hospital days, more re-admissions, and higher mortality compared to COPD-patients without HF. [8] COPD patients with combined disease also have more frequent exacerbations which leads to worse health status.[9] Furthermore patients with coexistent COPD and HF have a worse health status in stable-state than patients with COPD only.[10] Improving health status is a treatment goal in the follow up of COPD patients.[11] Thus, it is important to monitor health status routinely in the outpatient clinic. Unfortunately, many patients have more than one chronic condition. This makes it difficult to use a single disease-specific health status questionnaire. In addition, measuring health status using several questionnaires may be troublesome to the patient. For COPD-patients the most frequently used questionnaire in the Netherlands is the Clinical COPD Questionnaire (CCQ).[12] For HF-patients the Minnesota Living with Heart Failure Questionnaire (MLHF-Q) is most frequently used.[13] Both health status questionnaires, the CCQ and the MLHF-Q, are disease-specific questionnaires. So, patients with coexistent COPD and HF theoretically have to complete both questionnaires, which is time consuming and unpractical in the outpatient clinic. One questionnaire to assess health status for patients with both diseases, COPD and HF, would be ideal. Unfortunately, no health status questionnaire has been constructed for patients with coexistent COPD and HF. Therefore, the aim of this study was to compare which existing questionnaire, the CCQ or the MLHF-Q, is suited best for patients with coexistent COPD and HF.

Methods

Study design

This single-center prospective validation study was carried out in the Isala, a large teaching hospital in Zwolle, the Netherlands. Stable patients with both HF and COPD were contacted by telephone and invited to participate in the study and signed an

informed consent. Approval of the local ethics committee was received (local number 11.10127).

Patients

Patients with COPD GOLD stage ≥2 (defined as a post-bronchodilator of FEV_1 <80% and a ratio of FEV_1 to forced vital capacity of <70%), HF (defined clinically as a syndrome in which patients have typical signs and symptoms of HF and a reduced left ventricular ejection function or diastolic dysfunction[14]), New York Heart Association (NYHA) functional class ≥2, who were 40 to 85 years old, had a smoking history ≥5 pack years and provided written informed consent were included. Patients who were not able to complete questionnaires on their own were excluded.

Data collection

At baseline demographic characteristics, comorbidity (Charlson Comorbidity Index), post-bronchodilator spirometry, pro-b-type natriuretic peptide (pro-BNP) and the NYHA classification for heart failure were recorded. Construct validity, internal consistency and floor and ceiling effects were determined by administrating the CCQ, MLHF-Q and the Short Form 36 (SF-36) at baseline. To assess reliability and responsiveness all questionnaires together with the Global Rating of Change (GRC) were administrated at week 2 and week 12. Questionnaires were sent to patients by mail, were completed at home and were returned by mail.

QUESTIONNAIRES

CCQ

The CCQ[12] is a 10-item COPD-specific questionnaire with a total-, symptom-, functional status- and mental status domains. A higher score indicates a worse health status. The minimal clinical important difference (MCID) of the CCQ total score is 0.4.[15] The CCQ was developed without factor-analysis because a discrepancy was found between factor-analysis and expert opinion. After deliberation, clinicians and expert in the field of COPD management decided to forego the factor-analysis and to compose the domains themselves.[12]

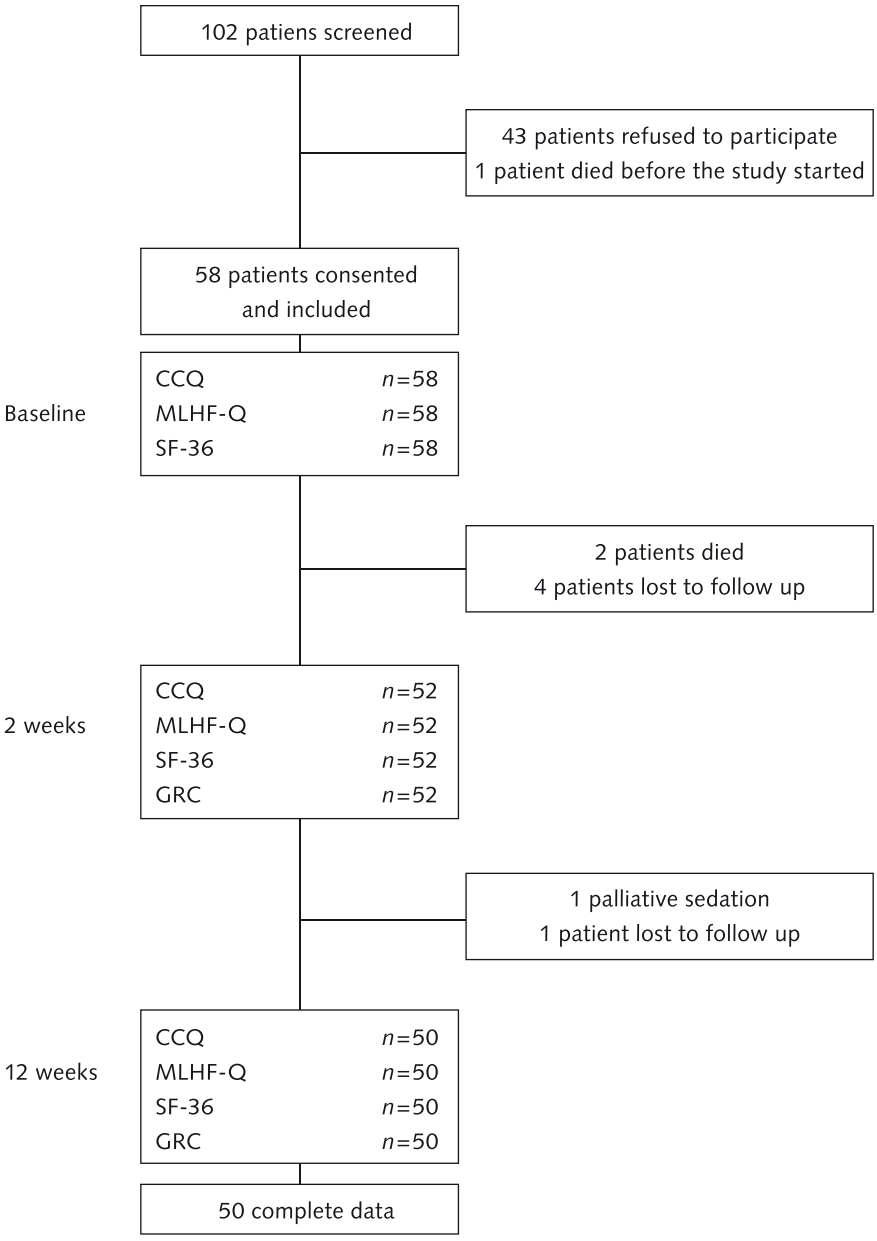
MLHF-Q

The MLHF-Q is HF-specific questionnaire that consists of 21 items with a 6-point response scale from 0 to 5, leading to a total score and two domain scores, i.e., physical and emotional state. A higher score indicates worse health status.[13] The MCID was estimated at 4.8.[16] The MLHF-Q was developed with factor analysis.[13]

SF-36

The SF-36 is a generic health status questionnaire with 8 domains, i.e., physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emo-

FIGURE 1: Flow chart showing the recruitment and retention of the study participants.



Note: In total 58 patients were included in the study, and 50 patients completed the study.

Abbreviations: CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; SF-36, Short-Form 36; GRC, Global Rating of Change.

tional, and mental health.[17-19] All scores are transformed to a range from 0 to 100, higher scores indicating better health status.

GRC

The GRC was used to assess self-perceived change in health, *'To what extent have you're pulmonary and/or cardiac symptoms changed in the past weeks?'*, on a 15-point scale (-7 a very great deal worse, 0 no change, +7 a very great deal better).[20]

Statistical analysis

Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (New York, IBM, USA). Baseline characteristics are presented as mean (standard deviation) unless otherwise stated. In this study the clinimetrics statistics definitions of the 'consensus based standards for the selection of health measurement instruments' (COSMIN) study were followed.[21;22] First, one of the authors assessed face validity, the degree to which the items of the CCQ and MLHF-Q indeed look as an adequate reflection of the construct to be measured, namely 'health status in patients with both, COPD and HF'. To assesses content validity[22] the relevance and comprehensiveness of items of the CCQ and MLHF-Q were viewed and the subsequent four questions were answered, i.e. *'Do all items of the questionnaires refer to relevant aspects of the construct?' 'Are all items relevant for the study population?' 'Are all items relevant for the purpose of the application of the instrument?' 'Do all items together comprehensively reflect the construct to be measured?'* To determine construct validity Spearman rank correlation coefficients of the CCQ, MLHF-Q and the SF-36 were used, because most of the distributions were skewed. The SF-36 was used as external criterion to assess construct validity. We predefined the hypotheses concerning the construct validity between corresponding domains: correlations <0.30 were considered as poor, correlations between 0.30-0.50 moderate and ≥0.50 were considered as strong.[22;23] Corresponding domains were defined as: CCQ total and MLHF-Q total score with all SF-36 domains, we expected the CCQ functional and MLHF-Q physical domains to correspond with the SF-36 domains physical functioning, social functioning, physical and vitality; CCQ mental and MLHF-Q emotional domain with SF-36 domain mental health, social functioning and role emotional; CCQ symptom domain with SF-36 domain pain and vitality. Correlations of <0.1 were expected for FEV_1 with MLHF-Q and CCQ total and domain scores. Construct validity was labeled acceptable when ≥75% of the predefined hypotheses of the corresponding domains agreed.[22] Internal consistency of the CCQ, MLHF-Q and SF-36 were assessed with Cronbach's alpha coefficients; these were deemed adequate between 0.7 and 0.9.[24] Reliability, comprising test-retest reliability and agreement, was evaluated in stable patients after 2 weeks (defined here as GRC=-1, 0 and 1). Test-retest reliability was assessed with Intraclass Correlation Coefficients (ICCs) based on the two-way random effect model and the standard error of measurement (SEM), test-retest-reliability was assumed sufficient when ICC was ≥0.7.[24] Agreement was assessed with a Bland-Altman plot for

TABLE 1: Patient characteristics	
n	58
Sex, male, n (%)	43 (74.1)
Age (years), mean (SD)	73 (6)
Pack years, median (range)	37.5 (5-102)
Current smoker, n (%)	17 (29.3)
Oxygen therapy, n (%)	11 (19)
BMI, mean (SD)	27 (5)
FEV_1 (post-bronchodilator % predicted), mean (SD)	51 (15)
GOLD, n (%)	
2	29 (50)
3	16 (27.6)
4	13 (22.4)
Pro-BNP (pg/mL), a median (range)	3,180 (59-31,390)
NYHA, n (%)	
2	41 (70.7)
3	14 (24.1)
4	3 (5.2)
Charlson Comorbidity Index, n (%)	
2	12 (20.7)
3	24 (41.4)
≥4	22 (37.9)
CCQ total score, mean (SD)	2.7 (1.1)
MLHF-Q, mean (SD)	43 (22)
SF-36, general health, mean (SD)	31 (18)

Notes: an=57. COPD classification by post-bronchodilator spirometry according to GOLD guidelines.

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; pro-BNP, pro-B-type natriuretic peptide; NYHA, New York Heart Association; CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; SF-36, Short-Form 36; SD, standard deviation.

the CCQ and MLHF-Q total score. Agreement was defined acceptable when the limits of agreement were smaller than the MCID.[24-26] Responsiveness would be determined with the receiver operating characteristic (ROC) curve and the area under the curve (AUC), an adequate AUC was declared when at least 0.70.[22;24] Floor and ceiling effects were assessed. When less than 15% of the patients achieve the highest or lowest possible score respectively, floor and ceiling effects were labeled absent and the test adequate.[22;25]

Results

From 25 October 2011 to 06 September 2013, 58 patients were recruited and 50 patients completed the study, as shown in Figure 1. Demographic and clinical patient characteristics are presented in Table 1. All patients had COPD and HF; other common comorbidities were myocardial infarction (31, 53.4%), diabetes mellitus (12, 20.7%) and peripheral vascular disease (17, 29.3%).

VALIDITY

Face validity

The CCQ and the MLHF-Q are both disease-specific questionnaires, separately designed for COPD and HF, respectively. For use in patients with both morbidities, the items of both questionnaires have to reflect the construct 'health status of patients with both COPD and HF'. Health status in patients with COPD and HF will partly derive from the severity of symptoms, i.e. dyspnea, edema, orthopnea, cough and phlegm. When the questionnaires are compared, the question *'Did your HF prevent you from living as you wanted during the past month by causing swelling in your ankles or legs?'* is missing in the CCQ and the questions *'How much of the time did you cough?'* and *'How much of the time did you produce phlegm?'* were missing in the MLHF-Q. Except for the question about 'ankle oedema' all other questions of the MLHF-Q were comparable with the questions of the CCQ.

Content validity

1. *'Do all items of CCQ and MLHF-Q refer to relevant aspects of health status in patients with COPD and HF?'* Originally, the CCQ is developed and validated in COPD-patients.[12] The MLHF-Q is developed and validated in patients with HF.[13] Since symptoms of COPD-patients and HF-patients show considerable overlap, most of the items of both questionnaires reflect health status for both diseases COPD and for HF.
2. *'Are all items relevant for patients with COPD and HF?'* The CCQ lacks an item about ankle edema[12], and the MLHF-Q lacks items about cough and phlegm.[13] All other items are similar for both questionnaires.
3. *'Are all items relevant for the purpose of the application of the CCQ and MLHF-Q?'*

TABLE 2: Construct validity (n=58)

	CCQ			
	Total	**Functional**	**Mental**	**Symptom**
SF-36				
General health	-0.57 (<0.001)	-0.53 (<0.001)	-0.30 (0.02)	-0.51 (<0.001)
Role physical	-0.32 (0.01)	-0.25 (0.06)	-0.21 (0.11)	-0.26 (0.05)
Pain	-0.44 (0.001)	-0.36 (0.006)	-0.36 (0.006)	-0.31 (0.02)
Physical functioning	-0.63 (<0.001)	-0.77 (<0.001)	-0.44 (0.001)	-0.34 (0.008)
Vitality	-0.65 (<0.001)	-0.50 (<0.001)	-0.60 (<0.001)	-0.53 (<0.001)
Social functioning	-0.62 (<0.001)	-0.60 (<0.001)	-0.59 (<0.001)	-0.38 (0.003)
Role emotional	-0.30 (0.02)	-0.23 (0.09)	-0.33 (0.01)	-0.22 (0.10)
Mental health	-0.50 (<0.001)	-0.27 (0.04)	-0.62 (<0.001)	-0.38 (0.004)
	MLHF-Q			
	Total	**Physical**	**Emotional**	
SF-36				
General health	-0.50 (<0.001)	-0.48 (<0.001)	-0.38 (0.004)	
Role physical	-0.37 (0.005)	-0.29 (0.03)	-0.34 (0.008)	
Pain	-0.40 (0.002)	-0.37 (0.004)	-0.36 (0.006)	
Physical functioning	-0.51 (<0.001)	-0.63 (<0.001)	-0.29 (0.03)	
Vitality	-0.64 (<0.001)	-0.61 (<0.001)	-0.53 (<0.001)	
Social functioning	-0.61 (<0.001)	-0.62 (<0.001)	-0.60 (<0.001)	
Role emotional	-0.33 (0.01)	-0.27 (0.04)	-0.27 (0.05)	
Mental health	-0.53 (<0.001)	-0.46 (<0.001)	-0.60 (<0.001)	

Notes: Construct validity is presented with Spearman rank correlations (p-value). Correlations of the corresponding domains of ≥0.5 are adequate according to the hypothesis described in the statistical section.

Abbreviations: CCQ, Clinical COPD Questionnaire; SF-36, Short Form 36; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire.

Ideally, a disease-specific questionnaire for patients with both COPD and HF should be developed which has good discriminative and evaluative properties. However, both questionnaires[12;13] are largely equal and theoretically the authors consider therefore that both questionnaires perhaps can be used in patients with COPD and HF.

4. *'Do all items together comprehensively reflect health status in patients with COPD and HF?'* Based on previous validation studies[12;27;28] the CCQ reflects health status in COPD-patients but is also validated in other patient populations as patients with laryngotracheal stenosis. The MLHF-Q reflects health status in HF patients[13], patients with atrial fibrillation[29] and patients with heart valve surgery.[30] Comprehensive evaluation of health status in patients with both COPD and HF has not been assessed yet for either questionnaire.

Construct validity

The correlation coefficients between the corresponding domains of the CCQ and the MLHF-Q with the external criterion, the SF-36, are shown in Table 2. Most of the corresponding domains between the SF-36 and the CCQ and MLHF-Q show moderate to strong correlations, except for the SF-36 role emotional domain and the corresponding MLHF-Q emotional domain (-0.27) and the SF-36 role physical and the corresponding MLHF-Q physical domain (-0.29). Convergent validity is depicted in Table 3. As hypothesized, all corresponding domains of the CCQ and the MLHF-Q had strong correlations (≥0.50). Conversely, correlations between the CCQ and MLHF-Q questionnaires and FEV_1%predicted were indeed low, although some did slightly surpass the 0.1 boundary, Table 3.

Predefined hypothesis for the corresponding domains of the CCQ, MLHF-Q, SF-36 and for FEV_1%predicted agreed in 75% of the cases.

RELIABILITY

Internal consistency

All Cronbach's alpha's were >0,7 implying satisfactory internal consistency for the CCQ and MLHF-Q total and domain scores and most of the SF-36 domain scores, except for the domains general health (0.63) and social (0.69, see Table 4).

Test-retest reliability

The ICC was tested in 33 patients that remained stable after 2 weeks and was adequate (≥0.7) for all questionnaires, the CCQ, MLHF-Q and SF-36, indicating good test-retest reliability (Table 5). The only exceptions that had lower ICCs were: the CCQ symptom score (0.42 (0.11;0.66)), SF-36 physical functioning (0.64 (0.32;0.82) and SF-36 role emotional (0.24 (-0.13;0.53)).

The SEM's of the total and domain scores of all questionnaires were larger than the MCID on the individual level, except for the MLHF-Q emotional domain (SEM 2.02).

Table 3 Construct validity: convergent and divergent validity (*n*=58)

Convergent validity[a]	**MLHF-Q total**	**MLHF-Q physical**	**MLHF-Q emotional**	
CCQ total	0.84 (<0.001)	0.82 (<0.001)	0.57 (<0.001)	
CCQ symptom	0.61 (<0.001)	0.54 (<0.001)	0.43 (<0.001)	
CCQ functional	0.67 (<0.001)	0.72 (<0.001)	0.35 (0.007)	
CCQ mental	0.69 (<0.001)	0.68 (<0.001)	0.65 (<0.001)	
Divergent validity[b]	**CCQ total**	**CCQ symptom**	**CCQ functional**	**CCQ mental**
FEV_1 % predicted	-0.17 (0.20)	-0.16 (0.23)	-0.17 (0.20)	0.03 (0.85)
	MLHF-Q total	**MLHF-Q physical**	**MLHF-Q emotional**	
FEV_1 % predicted	0.04 (0.76)	0.04 (0.74)	0.10 (0.46)	

Notes: a. Adequate convergent validity is present if Spearman rank correlations of the corresponding domains are ≥0.5 according to the hypothesis described in the statistical section; b. Spearman rank correlations of divergent validity were expected to be ≥0.1.

Abbreviations: CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; FEV_1, forced expiratory volume in one second.

TABLE 4: Internal consistency (*n*=58)

	Cronbach's α
CCQ	
Total	0.87
Mental	0.80
Symptom	0.75
Functional	0.86
MLHF-Q	
Total	0.91
Emotional	0.90
Physical	0.86
SF-36	
General health	0.63
Mental health	0.83
Role emotional	0.86
Role physical	0.91
Physical functioning	0.88
Social functioning	0.69
Vitality	0.80
Pain	0.92

Notes: Internal consistency is assessed with the Cronbach's α coefficient, a correlation between 0.70 and 0.95 is considered as good internal consistency.

Abbreviations: CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; SF-36, Short Form 36.

Agreement

Bland-Altman-plots of the CCQ total score and MLHF-Q total score, for the 33 patients that remained stable after 2 weeks are shown in Figure 2. The mean difference after 2 weeks was -0.26±0.14 for the CCQ total score and -3.64±2.15 for the MLHF-Q total score. The upper and lower limits of agreement were 1.35 and -1.87 for the CCQ total score. The MLHF-Q had an upper limit of agreement of 20.52 and a lower limit of agreement of -27.80.

MEASUREMENT OF CHANGE

Responsiveness

Patients in this study were in a stable phase of their diseases, i.e., HF and COPD. After inclusion, patients received no change in intervention and were not expected to improve much. Therefore responsiveness could not be assessed in this study.

INTERPRETABILITY

Floor and ceiling effects

Floor effects (lowest score) were present in the CCQ mental domain 36.2% and in the MLHF-Q emotional domain 20.7%. The SF-36 showed floor effects for the domains role emotional (25.9%) and physical functioning (75.9%) and ceiling effects (highest score) for the domains role emotional (50%) and pain (36.2%), shown in Table 6.

Discussion

This is the first study that compared and validated the CCQ and MLHF-Q in patients with coexistent COPD and HF. The discriminative part of the psychometric properties, i.e. validity, internal consistency and test-retest-reliability, were comparable for the CCQ and MLHF-Q. The only exception was the CCQ symptom score, in which weaker correlations were found for the test-re-test-reliability and construct validity. The evaluative part, i.e., the agreement of the CCQ and MLHF-Q, was similarly limited in both. The psychometric properties of both questionnaires will be discussed separately. Because the CCQ and MLHF-Q have not been validated before in patients with both COPD and HF, we cannot compare our findings directly with similar validation studies. Therefore, to give some perspective and to quantify our findings we will compare our study with validation studies in other patient populations.

Construct validity was assessed between the external criterion, i.e., the SF-36, and both questionnaires, i.e., the CCQ and MLHF-Q. Most of the correlations between the corresponding domains of the SF-36 and MLHF-Q were moderate to strong. Other validation studies[29;30], in patients with atrial fibrillation and patients undergoing heart

TABLE 5: Test-retest reliability (n=33)

	ICC (95% CI)	SEM
CCQ		
Total	0.70 (0.48; 0.84)	0.60
Mental	0.75 (0.55; 0.87)	0.67
Symptom	0.42 (0.10; 0.66)	0.89
Functional	0.79 (0.63; 0.89)	0.69
MLHF-Q		
Total	0.85 (0.71; 0.92)	8.96
Emotional	0.90 (0.80; 0.95)	2.02
Physical	0.79 (0.62; 0.89)	5.17
SF-36		
General health	0.74 (0.54; 0.86)	9.35
Mental health	0.79 (0.61; 0.89)	8.74
Role emotional	0.24 (-0.13; 0.65)	36.00
Role physical	0.90 (0.80; 0.95)	8.70
Physical functioning	0.64 (0.32; 0.82)	25.75
Social functioning	0.80 (0.64; 0.90)	12.12
Vitality	0.76 (0.57; 0.88)	11.54
Pain	0.82 (0.67; 0.91)	12.19

Notes: Test-retest-reliability is presented with the ICC and 95% CI. ICC ≥0.70 gives a positive rating for test-retest reliability. Only stable patients (Global Rating of Change -1, 0, 1).

Abbreviations: CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; SF-36, Short-Form 36; SEM, standard error of measurement; ICC, intraclass correlation coefficient; CI, confidence interval.

valve surgery found similar correlations between the SF-36 and MLHF-Q. Corresponding domains of the CCQ and SF-36 achieved moderate to strong correlations as well, and were comparable with most of the correlations that were found in the original validation study.[12] The exception to this notion is the CCQ symptom domain, which seems to have lower correlations with SF-36 in comparison to the original validation study in patients with COPD only.[12] This might signify that the CCQ symptom domain is not a reflection of the most important symptoms of patients with combined COPD and HF. The symptoms in COPD and HF overlap partially; however some symptoms are different, like orthopnea or edema.[31] The CCQ symptom domain consists of 4 items: *'Short of breath at rest?' 'Short of breath doing physical activities?' 'Did you cough?' 'Did you produce phlegm?'* These questions reflect symptom-related health status for patients with COPD alone. Symptom-related health status for patients with both, COPD and HF, is probably more complex.

The test-retest reliability of the CCQ symptom domain was also limited, with an ICC of 0.42 (0.10;0.66). Previous studies in other populations showed higher ICC's of the CCQ symptom domain; one study[27] in patients with COPD in primary care found an ICC of 0.74 and another study[28] in adults with laryngotracheal stenosis found an ICC of 0.94. We do not have an explanation for this, but have considered whether the low ICC in our study could be due to the fact that patients with both COPD and HF are a more homogeneous population then expected. In that case, the variability of the scores on the CCQ symptom domain between patients is low and within patients are equally present, leading to a low ICC and hampering its use as a discriminative tool in patients with both COPD and HF.

The MLHF-Q physical domain consists of 8 items with 6 items containing questions about the functional state and 2 items about symptom-related health status, i.e. *'Did your heart failure prevent you from living as you wanted during the last month by making you short of breath?' 'Did your heart failure prevent you from living as you wanted during the last month by making you tired, fatigued, or low on energy?'*[13] The MLHF-Q physical domain has an adequate discriminative value in patients with COPD and HF, an ICC of 0.79 (0.62;0.89). Perhaps this is due to the combination of functional state and symptoms-related questions about health status in the MLHF-Q physical domain. The discriminative value in patients with COPD and HF is adequate as well, with an ICC of 0.79 (0.63;0.89).

The degree of interrelatedness between the items of the domains of the CCQ and the MLHF-Q, internal consistency, were adequate, all Cronbach's alpha coefficients were ≥0.70, and were comparable with previous validation studies[12;13;30] in patients with COPD, heart valve surgery or HF.

The SEM of the CCQ and MLHF-Q total and domain scores on the individual level was larger than the MCID of both questionnaires. This suggests that neither questionnaire could differentiate between a clinical relevant change and measurement error in our study. Two studies have addressed the SEM of the CCQ total score before and found SEMs of 0.29[32] and 0.21.[33] However, these SEMs were determined in COPD-patients

TABLE 6: Floor and ceiling effects (*n*=58)

	Mean (SD)	Floor (%)	Ceiling (%)
CCQ			
Total	2.7 (1.1)	1.7	0
Mental	1.3 (1.4)	36.2	0
Symptom	3.0 (1.3)	1.7	1.7
Functional	3.2 (1.4)	1.7	0
MLHF-Q			
Total	43.3 (22.5)	5.2	0
E motional	7.2 (6.5)	20.7	0
Physical	22.3 (10.9)	5.2	0
SF-36			
General health	31 (18.1)	3.4	0
Mental health	72.4 (19.0)	0	5.2
Role emotional	60.3 (43.5)	25.9	50
Role physical	32.1 (25.2)	12.1	0
Physical functioning	15.1 (31.0)	75.9	8.6
Social functioning	60.3 (27.4)	3.4	19
Vitality	44.7 (31.0)	0	0
Pain	66.2 (32.0)	1.7	36.2

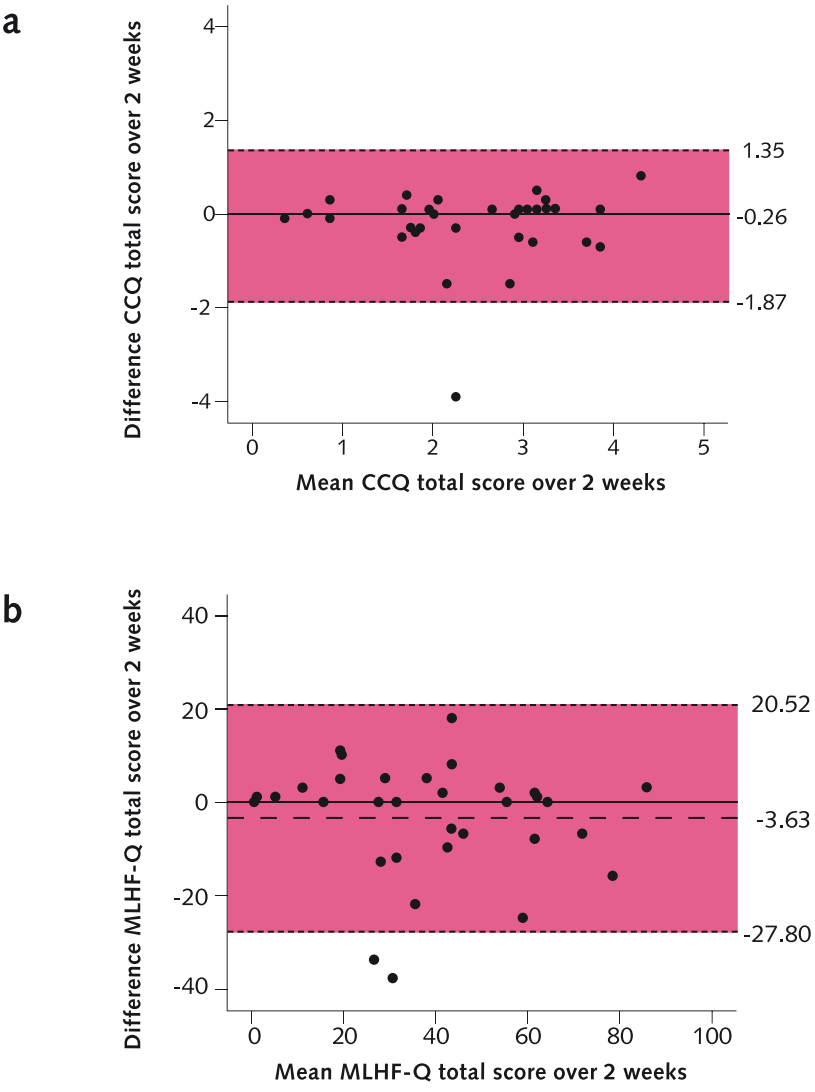
Abbreviations: CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; SF-36, Short-Form 36; SD, standard deviation.

without HF. In our study, a SEM of 0.60 was found for the CCQ total score. The SEM can ben calculated on the group level and on the individual level (per patient). The SEM on the individual level can be interpreted and used in clinical practice in the outpatient clinic. The SEM on the group level can be interpreted and used in groups, i.e., clinical research. The SEMs for the CCQ total, symptom, functional and mental score were 0.10, 0.15, 0.12 and 0.11. The latter SEM values are all smaller than the MCID of the CCQ, 0.4 points. Thus, on the group level the CCQ is able to differentiate a real change from measurement error. The SEMs for the MLHF-Q total, emotional and physical score on the group level were 1.56, 0.35 and 0.90 respectively. The MCID of the MLHF-Q is 4.8. Also the MLHF-Q was able to differentiate clinically relevant change from measurement error in patients with COPD and HF on the group level.
Similar results were found for the agreement. Both questionnaires had large limits of agreement on the individual level, i.e., 1.35 and -1.87 for the CCQ total score and 20.52 and -27.80 for the MLHF-Q total score. On the group level the limits of agreement were 0.23 and -0.32 for the CCQ total score and 3.5 and -4.84 for the MLHF-Q. On the group level, the limits of agreement are smaller or comparable with the MCID of both questionnaires, indicating that a clinically relevant change of health status can be distinguished from measurement error.

This study has some limitations that are worth discussing. One limitation is that the responsiveness, i.e., the ability of the CCQ and MLHF-Q to detect changes in health status over time, could not be assessed in this study because patients received no change in intervention. Therefore, no conclusion can be drawn regarding patients who improved or deteriorated versus those who remained stable. Most of the patients remained stable because no intervention was given. Another limitation is the use of the SF-36, a generic health status questionnaire, as the reference standard; ideally a disease-specific health status questionnaire for patients with COPD and HF would be used. Unfortunately, there is no such questionnaire for these patients. We chose the generic SF-36 because it is validated for both, COPD and HF.[34;35] The last limitation is the MCIDs used for the CCQ and MLHF-Q. These MCID's were determined for patients with either COPD or HF, but not in patients with combined disease. This could underestimate or overestimate the interpretation of the agreement, because agreement was acceptabe when the limits of agreement were smaller than the MCID.

In conclusion, both questionnaires, the CCQ and MLHF-Q are valid and reliable for patients with both COPD and HF on the group level, for instance in clinical research or validation studies. However, the CCQ symptom domain does not reflect all symptoms of patients with coexistent COPD and HF, limiting its usefulness in this setting. On the individual level, i.e., in clinical practice, the CCQ and MLHF-Q are not able to differentiate a real clinically relevant change from measurement error in patients with COPD and HF in this study. Ideally, a new questionnaire should be developed, whereby a more complete reflection of health status can be measured in patients with both COPD and HF.

FIGURE 2: Agreement over time of CCQ total score and MLHF-Q total score in stable COPD patients.



(A) Agreement of the CCQ total score and **(B)** agreement of the MLHF-Q total score over 2 weeks in stable COPD patients (GRC -1, 0, 1).

Notes: The bold flat line represents the mean difference over 2 weeks for the CCQ and MLHF-Q total scores. The dashed lines are the limits of agreement, 1.96× standard deviation. (*n*=33).

Abbreviations: COPD, chronic obstructive pulmonary disease; CCQ, Clinical COPD Questionnaire; MLHF-Q, Minnesota for Living with Heart Failure Questionnaire; GRC, Global Rating of Change.

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Disclosure

The authors report no conflicts of interest in this work.

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Part II

Chapter 5

Telemedicine, the effect of nurse-initiated telephone follow up, on health status and healthcare utilization in COPD patients. A randomized trial.

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Summary at a glance

Telemedicine has the potential to improve continuity of care, increase efficiency of outpatient management and prevent deterioration of health status in COPD patients. However, the effectiveness of telemedicine is still under debate. This study demonstrated that telemedicine alone, without any form of education, pulmonary rehabilitation or training, had no benefits for COPD patients at all.

Abstract

Background and objective

Telemedicine, care provided by electronic communication, may serve as an alternative or extension to traditional outpatient visits. This pilot study determined the effects of telemedicine on health-care utilization and health status of chronic obstructive pulmonary disease (COPD) patients.

Methods

One hundred and one patients were randomized, 52 patients received telemedicine care and 49 had traditional outpatient visits. The primary outcome was COPD-specific health status, measured with the Clinical COPD Questionnaire (CCQ). Secondary outcomes included St. George's Respiratory Questionnaire (SGRQ) and the Short Form-36 (SF-36) and resource use in primary and secondary care.

Results

The mean age of the participants was 68 ± 9 years and the mean per cent of predicted forced expiratory volume in 1 s was 40.4 ± 12.5. The CCQ total score deteriorated by 0.14 ± 0.13 in the telemedicine group, and improved by -0.03 ± 0.14 in the control group (difference 0.17 ± 0.19, 95% confidence interval (CI): -0.21-0.55, $p=0.38$). The CCQ symptom domain showed a significant and clinically relevant difference in favour of the control group, 0.52 ± 0.24 (95% CI: 0.04-0.10, $p=0.03$). Similar results were found for the SGRQ, whereas results for SF-36 were inconsistent. Patients in the control group had significantly fewer visits to the pulmonologist in comparison to patients in the telemedicine group ($p=0.05$). The same trend, although not significant, was found for exacerbations after 6 months.

Conclusions

This telemedicine model of initiated phone calls by a health-care provider had a negative effect on health status and resource use in primary and secondary care, in comparison with usual care and therefore cannot be recommended in COPDpatients in its current form.

Key words

chronic obstructive pulmonary disease, Clinical Chronic Obstructive Pulmonary Disease Questionnaire, healthcare utilization, health status, telemedicine.

Abbreviations

ANCOVA, analysis of covariance; CCQ, Clinical Chronic Obstructive Pulmonary Disease Questionnaire; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MCID, minimal clinical important difference; SF-36, Short Form-36; SGRQ, St. George's Respiratory Questionnaire.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and mortality worldwide, and unfortunately, its prevalence is still increasing.[1;2] Expected increase in prevalence puts pressure on the efficiency of outpatient management. Currently, outpatient visits are initiated by pulmonologists, but unpredictable alternation of stable and instable periods of COPD[3] make it difficult to determine when an outpatient visit is needed. Delay in treatment for COPD patients with an exacerbation may result in hospitalization or death[4] or, generally, may lead to a deterioration of health status[5] and therefore timely contacts are important. Information technology may be applied to monitor the health status of patients. Telemedicine, care provided by electronic communication, may serve as an alternative or extension to traditional outpatient visits. It could improve continuity of care, and increase efficiency of outpatient management, and therefore it has a potential to relieve the burden of COPD in the health-care system. Additionally, it could be a way to prevent deterioration of health status compared with traditionally planned outpatient visits.

Several studies[6-8] investigated telemedicine in COPD patients or other chronic diseases; however, the effect of telemedicine on healthcare utilization and health status is still debatable. One large recent randomized trial[9] concluded that telemedicine had a positive effect in patients diagnosed with COPD, diabetes mellitus and heart failure, leading to significantly less hospital admissions ($p=0.017$) and less mortality ($p<0.001$) in the telemedicine group compared with the control group. Despite high expectations of telemedicine, systematic reviews[6;10] still showed insufficient evidence of benefit for telemedicine interventions specifically in COPD patients, perhaps, because of the heterogeneity of current studies. The interventions were heterogeneous in the telemedicine modes they employed: telephone calls[11-13], videoconference[14-16] and internet.[17-19] Other studies[11;14;18;20] incorporated rehabilitation programmes, which makes it difficult to assign the results to the telemedicine intervention or the rehabilitation intervention. A common limitation in previous studies[11;12;15;17] was a high percentage of loss to follow up, which was probably caused by the unreliability of the technology and characteristics of the study population (many older COPD patients have difficulty in using the advanced communication devices). Therefore, we chose a very reliable telemedicine intervention in this study in which the patients were contacted by telephone, initiated by a specialized nurse.

We hypothesized that telemedicine consisting of provider-initiated telephone contacts in addition to traditional outpatient management would reduce health-care utilization in comparison to usual care and increase the health status of COPD patients by timely detection of incipient exacerbations.

Methods

Study design

This pilot study with a follow up of 6 months was designed as a single-centre prospective randomized controlled trial, carried out in Isala in Zwolle, the Netherlands. Randomization was performed with a computer minimization programme[21] to achieve balanced groups for: gender, age (<65 years or ≥65 years), predicted forced expiratory volume in 1 s (FEV_1<35% or ≥35%) and body mass index (<21 or ≥21 kg/m^2). Approval of the local ethics committee had been obtained (local number 02.0960).

Intervention

Telemedicine – A medical call centre that only employed registered nurses was contracted to make phone calls to the patients. Patients randomized to the telemedicine group had a regular outpatient visit by the pulmonologist at baseline and after 6 months. Additionally, patients were contacted every 2 weeks by phone, by the same nurse from the call centre for 6 months. This structured phone call consisted of a brief introductory conversation followed by administration of a short validated health status questionnaire, Clinical COPD Questionnaire (CCQ).[22] Total scores of the CCQ were recorded in a database and if change with the previous CCQ total score exceeded the minimal clinical important difference (MCID) of 0.4 points,[23] pulmonologists were notified immediately to contact the patient. The pulmonologist then inquired about signs and symptoms of an exacerbation. An exacerbation was defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that necessitates treatment with prednisolone, antibiotics or a combination of both.[24] Depending on this inquiry, the pulmonologist decided how to proceed further: treatment for an exacerbation, visit to the outpatient clinic or visit to the general practitioner.

Control – Patients in the control group had a regular outpatient visit at baseline and after 6 months by the pulmonologist. Interim outpatient visits were planned at 2 and 4 months with a pulmonary nurse practitioner.

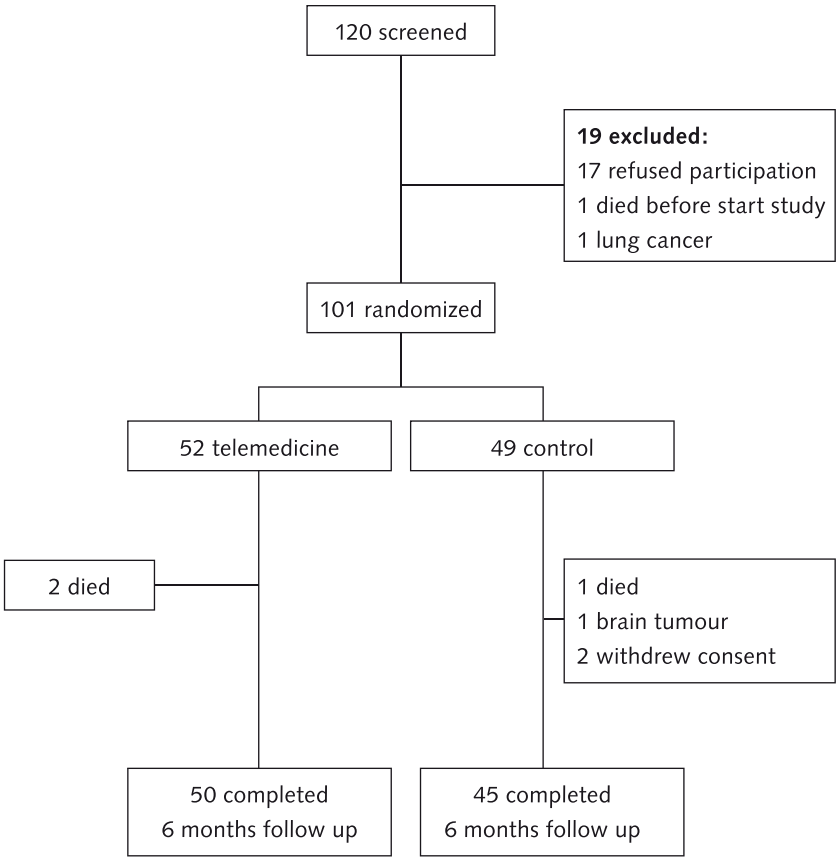
Participants

Eligible patients had a smoking history of >10 packyears, had a diagnosis of severe COPD, defined as a post-bronchodilator of FEV_1 <50% and a ratio of FEV_1 to forced vital capacity of <70%, and provided written informed consent. Exclusion criteria were a prior history of asthma, unable to answer the phone and a life expectancy of <6 months.

Procedures

During the first outpatient visit, data on baseline post-bronchodilator spirometry and smoking status were collected and patients were asked to complete the CCQ,[22] St. George's Respiratory Questionnaire (SGRQ)[25] and the Short Form-36 (SF-36).[26]

FIGURE 1: Consort flow chart



Patients of the telemedicine group were contacted by phone every 2 weeks during which the CCQ was conducted for 6 months. At 6 months in both the telemedicine and the control group, all questionnaires were sent to the patient and were returned by mail.
Data on primary care visits for COPD and exacerbations of the patients at 3 and 6 months were collected during the biweekly phone calls. The computer system of the hospital was used to collect the number of outpatient visits to the pulmonologist, general practitioner, number of hospitalizations and number of exacerbations in secondary care.

Endpoints

The primary endpoint was change in CCQ total and domain scores after 6 months. CCQ total score and the domain scores vary from 0 to 6, with a lower score signifying better health status. The MCID is 0.4.[23] Secondary endpoints were change in SGRQ scores (range from 0 to 100; a low score indicates a good health status; the MCID is 4),[27] and SF-36 scores (range from 0 to 100; higher scores represent better health status; the MCID is 4) after 6 months.[28] Health-care utilization was assessed as number of hospitalizations for COPD, number of outpatient visits to the pulmonologist, number of COPD exacerbations and number of visits to the general practitioner for COPD.

Statistical analyses

Since this study was designed as a pilot study, no formal sample size calculation was performed.
Descriptive statistics depict baseline characteristics of both groups. Primary and secondary analyses were done according to the intention-to-treat principle. Normal distributions of outcomes were checked using histograms. Differences between the two groups in the mean change in scores after 6 months for CCQ total and domain scores, SGRQ total and domain scores and SF-36 were tested using analysis of covariance (ANCOVA), adjusting for baseline values.[29] Interaction terms between treatment group and baseline value were checked. Between-group comparisons of proportions were performed using chi-square tests. Differences between groups in median values were tested using the independent samples median test. *P*-values <0.05 were considered significant and *p*-values between 0.05 and 0.1 as borderline significant. Analyses were performed using SPSS Statistics version 19.0 (IBM corporation, Armonk, NY, USA).

Results

Participants

Recruitment started 29 April 2003 and ended 11 June 2003, and the last patient finished after 6 months of follow up, thus winter season was included. A consort flow chart (Figure 1) shows that 120 patients were eligible for study entry and 101

TABLE 1: Patient characteristics

		Telemedicine (n=52)	Control (n=49)
Age (years)	mean (SD)	68 ± 9	68 ± 9
Male gender	n (%)	34 (65.4)	34 (69.4)
BMI (kg/m2)	mean (SD)	26.5 ± 4.0	25.8 ± 4.4
FEV_1 %predicted	mean (SD)	40.0 ± 13.5	40.9 ± 11.5
Oxygen use at home	n (%)	9 (17.3)	6 (12.2)
Hospitalization in past 12 months	n (%)	23 (44.2)	17 (34.7)
Inhalation medication	n (%)		
	Short-acting	30 (57.7)	32 (65.3)
	Long-acting	48 (92.3)	39 (79.6)
	Corticosteroids	49 (94.2)	45 (91.8)
CCQ scores	mean (SD)		
	Total	2.4 ± 0.9	2.0 ± 1.1
	Symptoms	2.7 ± 1.3	2.1 ± 1.5
	Functional state	2.8 ± 1.1	2.5 ± 1.3
	Mental state	0.8 ± 1.1	0.7 ± 1.1

BMI, body mass index; CCQ, Clinical COPD Questionnaire; FEV_1, forced expiratory volume in 1 s.

TABLE 2: Change and difference at 6 months in CCQ scores†

CCQ	Telemedicine (n=48)	Control (n=45)	Difference	95% CI	p-value
Total	0.14 ± 0.13	-0.03 ± 0.14	0.17 ± 0.19	-0.21; 0.55	0.38
Symptoms	0.17 ± 0.17	-0.35 ± 0.17	0.52 ± 0.24	0.04; 0.10	0.03
Functional	0.29 ± 0.17	0.28 ± 0.17	0.01 ± 0.24	-0.47; 0.50	0.96
Mental	-0.07 ± 0.13	-0.001 ± 0.14	-0.07 ± 0.19	-0.45; 0.31	0.71

† All scores are presented as mean with standard error and were adjusted for baseline. A lower CCQ score signifies better health status.

CCQ, Clinical COPD Questionnaire; 95% CI, 95% confidence interval.

patients were randomized. Baseline characteristics were similar for both groups, except for worse CCQ total and symptom score, and a tendency for more home oxygen and hospitalizations all in the telemedicine group (Table 1).

Primary outcome

The telemedicine group showed an increase in CCQ total score and symptom score after 6 months of 0.14 ± 0.13 and 0.17 ± 0.17 respectively, indicating a deterioration of health status. By contrast, the control group showed decreases of -0.03 ± 0.14 and -0.35 ± 0.17 in CCQ total and symptom score respectively, indicating an improvement of health status. The mean difference between the telemedicine and the control group for CCQ symptom score was statistically significant in favour of the control group (0.52 ± 0.24, 95% confidence interval (CI): 0.04-0.10, p=0.03,Table 2); the difference also met the MCID. In both groups, the CCQ functional state score declined to a similar degree and changes in CCQ mental state score were negligibly small. The 3-month data were not different from the 6-month results (data not shown).

SGRQ outcome

Similar to the primary outcome, SGRQ symptom score increased, by 6.1 ± 2.6 in the telemedicine group and decreased by 2.8 ± 2.8 in the control group, indicating a deterioration of health status in the telemedicine group and an improvement in health status control group, respectively. The mean difference of 8.9 ± 3.8 (95% CI: 1.4-16.4, p=0.02) was in favour of the control group and also met the MCID. Total and other domain scores showed a deterioration of health status for both groups, though the deterioration was less in the control group and differences between groups were not significant (see Table 3).

SF-36 outcome

No significant differences between both treatment groups were found in the changes in any of SF-36 domain scores after 6 months. Nevertheless, and although not significant, the difference between both treatment groups met the MCID in favour of the control group for the domains: physical functioning, role physical and social functioning.

Resource use in primary and secondary care

During 6-month follow up, patients in the control group visited the pulmonologist significantly less in comparison to patients in the telemedicine group (p=0.05, Table 4). The same trend, although not significant, was found for the median number of patients with an exacerbation COPD, median number of hospitalization and median days in hospital after 6 months. Number of visits to the general practitioner for COPD only was similar for both groups. The number of patients with at least one exacerbation in the telemedicine group was 31 (59.6%) in comparison with 23 (46.9%) in the control group (p=0.20).

TABLE 3: Change and difference of the SGRQ and SF-36 scores at 6 months†

SGRQ	Telemedicine (*n*=50)	Control (*n*=44)	Difference	95% CI	*p*-value
Total score	6.7 ± 1.8	4.3 ± 1.9	2.4 ± 2.6	-2.7; 7.5	0.36
Symptoms	6.1 ± 2.6	-2.8 ± 2.8	8.9 ± 3.8	1.4; 16.4	0.02
Activity	10.6 ± 2.5	6.7 ± 2.7	3.9 ± 3.7	-3.5; 11.4	0.29
Impact	4.4 ± 1.8	3.3 ± 1.9	1.1 ± 2.6	-4.0; 6.3	0.66
SF-36	Telemedicine (*n*=50)	Control (*n*=44)			
General health	-4.4 ± 2.6	-2.7 ± 2.8	-1.7 ± 3.9	-9.4; 5.9	0.66
Physical functioning	-9.9 ± 2.5	-3.1 ± 2.7	-6.8 ± 3.7	-14.1; 0.5	0.07
Bodily pain	6.0 ± 3.5	-2.2 ± 3.8	8.2 ± 5.2	-2.1; 18.5	0.12
Vitality	-0.7 ± 2.5	0.4 ± 2.7	-1.1 ± 3.7	-8.4; 6.3	0.78
Role physical	-7.5 ± 5.6	6.9 ± 6.0	-14.4 ± 8.3	-30.8; 2.0	0.09
Role emotional	1.7 ± 5.1	-1.1 ± 5.5	2.8 ± 7.5	-12.2; 17.7	0.72
Social functioning	-6.7 ± 3.8	-0.05 ± 4.1	-6.7 ± 5.7	-17.9; 4.6	0.24
Mental health	-0.8 ± 2.3	0.8 ± 2.4	-1.6 ± 3.4	-8.3; 5.1	0.64

† All scores are presented as mean with standard error and were adjusted for baseline values. A lower SGRQ score signifies better health status. Higher SF-36 scores represent better health status.

95% CI, 95% confidence interval; SGRQ, Saint George's Respiratory Questionnaire; SF-36, Short-Form 36.

TABLE 4: Resource use in primary and secondary care for COPD only at 6 months†

	Telemedicine (*n*=52)	Control (*n*=49)	*p*-value
Primary care			
Visits general practitioner	2 (0-12)	2 (0-14)	0.81
Secondary care			
Visits pulmonologist	2 (0-6)	1 (0-6)	0.05
Hospitalizations‡	1 (0-9)	0 (0-6)	0.27
Hospital days	4 (0-129)	0 (0-96)	0.21
Total			
Exacerbations§	1 (0-3)	0 (0-3)	0.33

† All outcomes are presented per patient as median with range. *P*-values are calculated with the independent-samples median test.

‡ Hospitalizations: median number of patients with a hospitalization.

§ Exacerbations: median number of patients with an exacerbation COPD.

Discussion

This pilot study showed that this telemedicine model, of care provided by electronic communication, in stable COPD patients did not result in improvement of health status. On the contrary, the control group showed a significant and clinically relevant improvement of CCQ symptom domain score after 6 months whereas the telemedicine group deteriorated. We also observed more health-care utilization in the telemedicine group, since significantly more patients of the telemedicine group visited the pulmonologist in comparison with the control group. So, our telemedicine model appeared not effective in the management of COPD patients.

Several aspects of the telemedicine model used in this study are worth discussing such as the difference of our study with other telemedicine studies and the perspectives of the patient. From these, possible approaches to improve the effectiveness of a telemedicine intervention can be distilled.

One of the differences between our study and others were the provider-initiated, biweekly phone calls. These were not guided or initiated by the complaints, symptoms or physical impairment of the patient as in some other studies.[30;31] The fixed time interval may have interfered with picking up sufficient or early signals of impending deterioration. In addition, we did not intend to guide patients in day-to-day management of their own disease. Perhaps feedback based on measured pulse rates, blood pressure, oxygenation, temperature or even standardized symptoms, followed by intrinsic and extrinsic feedback, would have led to improvement of functioning as has been suggested.[30]

In fact, many telemedicine studies[11;13-20;32-36] in patients with COPD, heart failure and diabetes mellitus have investigated telemedicine in combination with an educational component or pulmonary rehabilitation programme. Due to these training programmes, patients became aware of their symptoms and learned how to cope with them.[37] This educational component could have influenced the interpretation of the results of these telemedicine studies.[11;13-20;32;33] It is therefore difficult to distinguish the effect of training and education from the effect of telemedicine alone. This hypothesis is supported by one recent telemedicine study (i.e. Pinnock et al.).[38] In this study, both intervention and control group received the same clinical care and self-management advice. The only difference between the intervention and the control group was the telemonitoring service. This study[38] showed no effect of telemedicine either in number and in duration of an exacerbation COPD and health status, similar to our study. Combining prior studies,[11;13-20;32;33] ours and the study by Pinnock et al., the educational component appears pivotal in driving a successful telemedicine model.

Our study was not hampered by selection bias. In our study, little loss to follow up was present whereas in other telemedicine studies,[11;17;20;33] 60% or more of patients were excluded either before or during the study. Probably, one of the causes of the high loss to follow up was the inability of COPD patients to use the telemedicine devices. If a telemedicine application is not accepted by its users, for example COPD patients, it can

never be implemented successfully in everyday care.[30] In our study, the telephone was used, thus exclusion due to the inability to use a device was not present.
Secondly, it has been reported in COPD patients that symptoms such as dyspnoea, cough or sputum were described in terms of acceptance of the situation as a way of life. Only during an exacerbation COPD patients classified themselves as really ill.[39] In our study, we called those patients every 2 weeks and confronted them with their illness, limitations and symptoms. This may have caused patients to become more aware of their illness, upsetting their natural coping and acceptance of their disease which may have led to a deterioration of health status.[40]
We are not the only group unable to document positive results; deterioration, though not significantly, or no improvement of health status was also found in four other telemedicine studies.[16;20;33;41] Health status in these studies was assessed with the SF-36 and/or the CCQ, like our study. Three of these studies[16;20] used a device at home to monitor symptoms and vital parameters of the patient and one study[33] used a computer at home with videoconferencing. Two studies[16;41] offer no explanation for the deterioration of health status. The two other studies[20;33] suggested that the main reason of no improvement in health status in both groups was probably that the participants were already optimized because patients were included directly after pulmonary rehabilitation. The negative results from the four studies[16;20;33;41] may hint that telemedicine in these forms is not at all the holy grail for all patients with a chronic disease.
One of the limitations of our study was the small sample size, which is inherent to a pilot study. Usually, however, small sample size yields inconclusive results, instead of significant in this case negative results. In other words, statically spoken, our results were perhaps unexpected but sufficiently robust. Other limitations of our study were two imbalances in baseline characteristics. The patients participating in the telemedicine arm reported a lower health status and had been more frequently admitted to the hospital in the preceding year compared with the control group. ANCOVA was used to adjust for these baseline imbalances.
In conclusion, this study found that a telemedicine model initiated by phone calls by health-care providers had a negative effect on health status and resource use in primary and secondary care, in comparison with usual care. Thus this study, with a limited loss to follow up, demonstrated that telemedicine alone, without any form of education, pulmonary rehabilitation or training had no benefits for COPD patients at all. Our study contributes to a mixed picture of the applicability of telemedicine in COPD.

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Chapter 6

The effect of an outpatient care on-demand-system on health status and costs in patients with COPD. A randomized trial.

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Status

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Abstract

Background

Traditionally, outpatient visits for COPD are fixed, pre-planned by the pulmonologist. This is not a patient centered method, nor, in times of increasing COPD prevalence and resource constraints, perhaps the optimal method.

Objectives

This pilot study, determined the effect of an on-demand-system, patient initiated outpatient visits, on health status, COPD-related healthcare resource-use and costs.

Methods

Patients were randomized between on-demand-system (n=49) and usual care (n=51), with a 2-year follow-up. Primary, health status was assessed with Clinical COPD Questionnaire (CCQ). Secondary endpoints were: St. George's Respiratory Questionnaire (SGRQ), Short Form-36 (SF-36) scores, visits to general practitioners (GP), pulmonologists, and pulmonary nurse practitioners (PNP), exacerbations and total treatment costs from healthcare providers and healthcare insurance perspectives.

Results

Participants had a mean FEV_1 of 1.3 ± 0.4 liters and were 69 ± 9 years. CCQ total scores deteriorated in both groups, with no significant difference between them. CCQ symptom domain did show a significant and clinically relevant difference in favor of the on-demandgroup, -0.4 ± 0.21, CI95% -0.87; -0.02, p=0.04. Similar tendency was found for the SGRQ whereas results for SF-36 were inconsistent. Patients in the on-demand-group visited GP significantly less (p=0.01), but PNP significantly more, p=0.003. Visits to pulmonologists and exacerbations were equally frequent in both groups. Mean total costs per patient were lower in the on-demand-group in comparison with usual care, difference of €-518 (-1993; 788) from healthcare provider and €-458 (-2700; 1652) insurance perspective.

Conclusions

The on-demand-system was comparable with usual care, had a cost-saving tendency, and can be instituted with confidence in the COPD outpatient care setting.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major chronic diseases worldwide. Its prevalence is increasing over time, putting pressure on outpatient clinics.[1-3] Traditionally, outpatient visits are pre-planned by the pulmonologist and often occur when patients are stable and thus when little action is required. However, COPD has varying unpredictable episodes of deteriorations and frank acute exacerbations.[2] If urgent attention is needed, it is frequently a struggle in the current system to respond to this request because the outpatient clinic is fully booked. Delay in treatment for an exacerbation COPD may result in hospitalization or death[4], and lead to a deterioration of health status[5]. While improving health status is precisely an important goal in the treatment of patients with COPD.[6] In the Netherlands, COPD-exacerbations account for approximately 34% of the total respiratory-related healthcare costs.[7]

Better adaptation to increasing demand on outpatient clinics can be achieved by allowing patients to self-refer when they consider an outpatient visit needed, a so called on-demand-system, instead of fixed outpatient appointments initiated by pulmonologists.[8] This system might reduce unnecessary outpatient visits and healthcare costs.

In the last years several studies[9-12] have investigated the on-demand-system in patients with chronic inflammatory diseases, i.e. inflammatory bowel disease (IBD) and rheumatoid arthritis (RA). These studies compared ondemand visits with rapid specialist access in times of need with routinely booked appointments. One study[11] in IBD patients reported that open access is preferred by patients because the system increased the degree of control in their lives to make the decision of receiving medical care. Two studies[10;12], 1 in IBD and 1 in RA patients, showed fewer outpatient appointments in the open access group. Both studies found no differences in health status between the 2 groups, as measured with the Short Form-36 (SF-36). SF-36 is a generic health status questionnaire, which allows comparison between different diseases, though a disease-specific questionnaire could be of more clinical value. No data exist on the effectiveness of an ondemand- system to the outpatient clinic in patients with COPD. Therefore we designed a pilot study to compare an on-demand-system with routinely booked appointments. Our primary hypothesis was that the on-demand-system improves disease-specific health status in patients with COPD after 24 months. Secondary hypotheses were that the on-demand-system also leads to improvement of generic health status, reduction of resource use in primary and secondary care, and reduction of healthcare treatment costs from the healthcare provider's and the healthcare insurer's perspective.

Materials and methods

Study design

This pilot study was a single-center prospective randomized controlled trial, carried out in a large teaching hospital in Zwolle, the Netherlands. Randomization was performed with a computer minimization program[13] to achieve balanced groups for: gender, age (<70 years or ≥70 years), and predicted forced expiratory volume in 1 s (FEV_1<40% or ≥40%). Approval of the local ethics committee was received (NL 14887.075.06, local number 07.0325). The study was registered in Clinicaltrial.gov (NCT00556816).

Participants

Eligible patients were ≥40 years, COPD GOLD stage ≥2 (defined as post bronchodilator of FEV_1<80% and a ratio of FEV_1 to forced vital capacity of <70%), smoking history >10 pack-years, and provided written informed consent. Exclusion criteria were prior history of asthma; drugs or alcohol abuse; incapability of completing questionnaires.

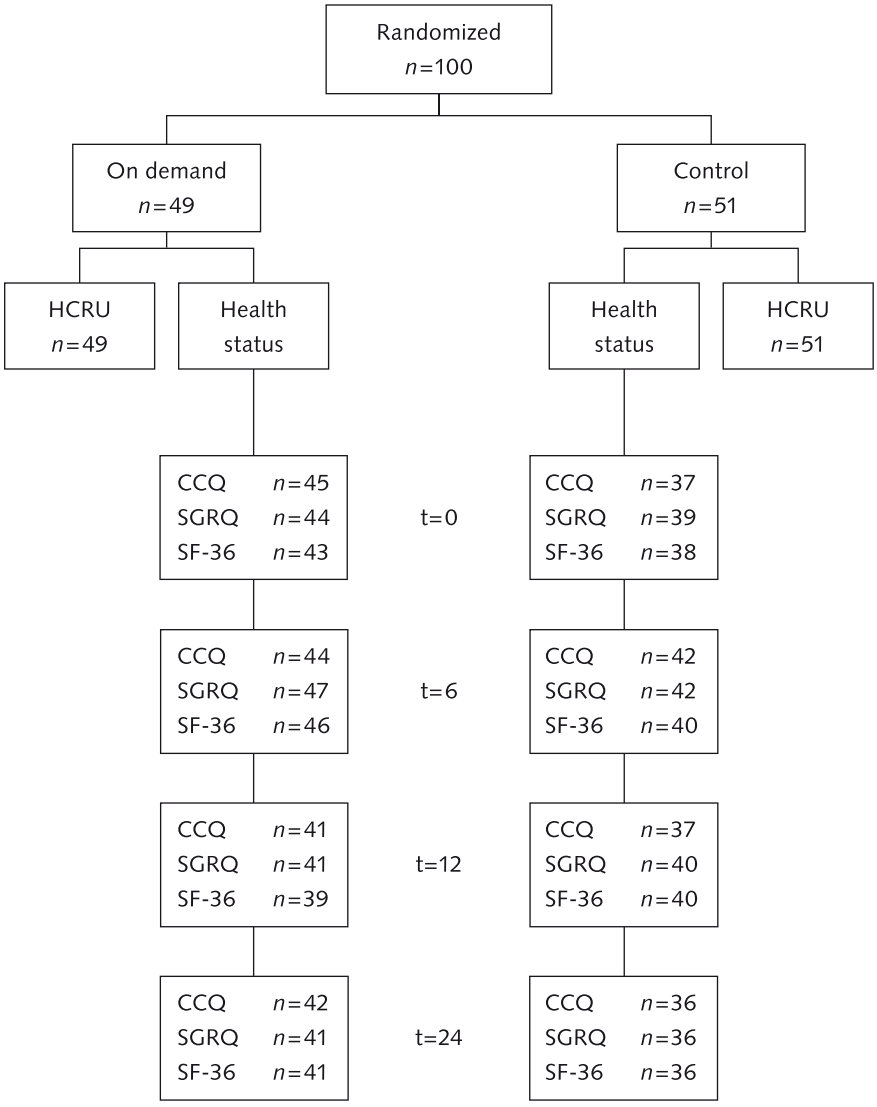
Interventions

On-demand group – Patients randomized to the on-demand group had one fixed appointment a year. The patient initiated other outpatient visits. Patients were instructed to call the pulmonary NPs when they experienced an increase of symptoms, like dyspnea, cough, sputum, haemoptysis or thoracic pain. The pulmonary NP followed the on demand-protocol, specifically designed for this study, as shown in the Supplement. If a patient contacted the pulmonary NP, first a history was taken by phone to assess the urgency. When according to the protocol the urgency was low, an outpatient visit was planned the next day to the pulmonary NP. When urgency was deemed, advice of a pulmonologist was asked and an outpatient visit to the pulmonologist was planned as soon as possible, preferably within hours.

Control group – Patients in the control group continued with traditional outpatient visits to the pulmonologist or the pulmonary NP, initiated by the pulmonologist. The frequency of visits was also left at the discretion of the pulmonologist.

Procedures – At baseline post-bronchodilator spirometry and smoking history were collected. At 6, 12, and 24 months, patients completed Clinical COPD Questionnaire (CCQ)[14], St. George's Respiratory Questionnaire (SGRQ)[15] and SF-36. [16] Questionnaires were sent to patients and were returned by mail. At the end of the study GPs and pharmacists were contacted to collect healthcare resource use in primary care: GP visits and exacerbations. Hospital's computer system was used to collect healthcare resource use in secondary care: visits to pulmonologists, pulmonary NPs and exacerbations. An exacerbation was defined as a sustained worsening of the patient's condition, from stable state and beyond normal day-to-day variations, that necessitates treatment with prednisolon, antibiotics or a combination of both.[17]

FIGURE 1: Consort Flowchart



HCRU: Healthcare resource use, CCQ: Clinical COPD Questionnaire, SGRQ: St. George's Respiratory Questionnaire, SF-36: Short-Form-36, t=time in months.

Endpoints

Primary endpoints were mean change in CCQ total and domain scores (range from 0 to 6, with a lower score signifying better health status, minimal clinical important difference (MCID) of CCQ total score is 0.4).[18] Secondary endpoints were: SGRQ scores (range from 0 to 100, a low score indicates a good health status, MCID of SGRQ total score is 4)[19], SF-36 scores (range from 0 to 100, higher scores represent better health status, MCID of SF-36 scores is 4)[20], time to first exacerbation COPD, number of patients with at least one exacerbation COPD in primary and secondary care, number of visits to pulmonologists and pulmonary NPs, and number of GP visits for COPD.

Costs were calculated from two perspectives: healthcare provider and healthcare insurance. Direct healthcare costs were determined retrospectively for a 2-year followup period and included: visits to GPs, pulmonologists, pulmonary NPs, number of visits to the emergency department, number and length of hospital admissions.

The costs per unit for healthcare resource use variables for the healthcare provider perspective were used from Dutch manual for costing studies[21] and were transformed from euros 2009 to euros 2013 using the consumer price indexes from StatLine, electronic databank of Statistics Netherlands. The costs per unit healthcare resource use for the healthcare insurance perspective were extracted from the Diagnosis Treatment Combination (DBC) of 2013 of our hospital.

Analysis

Since this study was designed as a pilot study, sample size was not determined. Baseline characteristics were determined with descriptive statistics. Analyses were done according to the intention-to-treat-principle. Normal distributions were checked using histograms. Differences between groups and mean change scores after 24 months of CCQ, SGRQ and SF- 36 were tested using analysis of covariance (ANCOVA), adjusting for baseline values.[22] Interaction terms between treatment group and baseline values were checked. Repeated measurement analysis of variance (MANOVA) was carried out in cases of whom complete CCQ total score data on 6, 12 and 24 months were present. A log-rank test was used to test differences in time to first exacerbation between study groups, which were graphically presented by Kaplan-Meier-curves. Between-group comparisons of proportions were performed using Chi-squared tests. Differences between groups in median values were tested using the independent-samples median test.

Total costs were calculated as the sum of the healthcare resource use costs per patient. Bootstrapping of data was used to calculate the uncertainty around the estimates of costs.[23] All statistical analyses were performed on each of 1000 bootstrap replications and 95% confidence intervals (CI) were determined for mean differences in costs were obtained by nonparametric bootstrapping. *P*-values <0.05 were considered significant. Analyses were performed using SPSS-Statistics version 19.0 (IBM corporation, Armonk, NY, USA).

TABLE 1: Patient characteristics

	On-demand (*n*=49)	Control (*n*=51)
Age (years), mean (SD)	69±9	69±9
Male sex, n (%)	36 (73.5)	38 (74.5)
FEV_1 (L), post bronchodilator, mean (SD)	1.25±0.43	1.33±0.46
FEV_1 %predicted, post bronchodilator, mean (SD)	45.5±11.6	47.0±13.5
FEV_1/FVC post bronchodilator, ratio (%), mean (SD)	40.7±10.0	40.8±11.3
BMI (kg/m2), mean (SD)	26.8±4.7	27.2±5.6
Pack-years, median (range)	40.0 (2-117)	39.5 (2-124)
CCQ scores, mean (SD)		
Total	2.1±0.9	2.2±1.0
Symptoms	2.4±0.9	2.4±1.0
Functional state	2.3±1.3	2.5±1.3
Mental state	1.0±1.0	1.0±1.1

BMI=body mass index; CCQ=Clinical COPD Questionnaire; FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity; SD=standard deviation.

Pack-years was missing for one patient in the control group, *n*=50. For CCQ total and domain scores: On demand, *n*=44, Control, *n*=37.

TABLE 2: Change from baseline and differences at 24 months in CCQ

CCQ	On-demand (n)	Control (n)	Difference	95%CI	*p*-value
Total	0.33±0.11 (40)	0.53±0.13 (29)	-0.20±0.17	-0.55; 0.14	0.24
Symptoms	0.14±0.14 (40)	0.58±0.16 (29)	-0.44±0.21	-0.87;-0.023	0.04
Functional state	0.59±0.16 (40)	0.57±0.18 (29)	0.02±0.24	-0.46; 0.50	0.93
Mental state	0.13±0.12 (40)	0.34±0.14 (29)	-0.21±0.19	-0.58; 0.17	0.28

CCQ=Clinical COPD Questionnaire; CI=Confidence Interval.

All scores are presented as mean with standard error and were adjusted for baseline.

Results

Participants

Recruitment started Oct. 10, 2007 and ended Oct.12, 2009, the last patient finished after 24 months of follow-up. A flowchart, Fig. 1, showed that 100 patients were randomized. Baseline characteristics were similar for both groups, Table 1.

Primary outcome

Both groups showed an increase in CCQ total score after 24 months, indicating a decline in health status. CCQ symptom domain showed a significantly smaller deterioration in health status in favor of the on-demand-group, which also met the MCID, Table 2.

SGRQ, SF-36 and healthcare resource use

Similar to the CCQ, the SGRQ also deteriorated in both groups, Table 3. Difference in the SGRQ symptom domain showed a smaller deterioration, in favor of the on-demandgroup and met the MCID.

There were no statistically significant differences between both groups in any of the SF-36 domains over 2 years, Table 3. Nevertheless, some domains showed differences between the groups that reached the MCID but were too variable to be significant: bodily pain, role emotional, and mental health.

The time path of deterioration in health status was comparable in both groups during the 2 years follow-up for the CCQ ($p=0.86$), SGRQ ($p=0.81$) and SF-36 ($p=0.88$), as depicted in Fig. 2.

The GP was visited significantly less frequently for COPD in the on-demand-group ($p=0.01$), as illustrated in Table 4. The percentage of patients in the on-demand-group that had no visit to the GP for COPD in the 2 years was 20.4% in comparison with 13.7% in the control group ($p=0.37$). In the on-demand-group 57.1% of the patients had an exacerbation treated by the GP in comparison with 64.7% in the control group in 2 years, $p=0.23$. In secondary care the number of patients with at least one exacerbation were comparable for the on-demand-group and the control group, 19 (38.8%) versus 16 (31.4%) respectively ($p=0.44$).

The number of visits to the pulmonary NP increased significantly in the on-demand compared to the control group, $p=0.003$. Visits to the pulmonologist, exacerbations and hospitalizations were similar in both groups.

The median time to the first exacerbation COPD, in both primary and secondary care, was 307 ± 61.6 days (95%CI 186.3; 427.7) in the on-demand-group compared with 335 ± 60.2 days (95%CI 217.0; 453.0) in the control group ($p=0.40$ log-rank test), Fig. 3. The total number of exacerbations, treated either by GP or in the hospital, was very similar in both groups (47 in the on-demand-group versus 49 in the control group).

Healthcare resource use and costs are presented in Table 5. Total costs were lower in the on-demand-group in comparison with the control group both from the healthcare

TABLE 3: Change from baseline and differences at 24 months in SGRQ and SF-36

SGRQ	On-demand (n)	Control (n)	Difference	95% CI	*p*-value
Total score	5.0±2.2 (38)	6.4±2.4 (30)	-1.4±3.3	-7.9; 5.1	0.67
Symptoms	2.6±3.0 (38)	10.3±3.4 (30)	-7.7±4.6	-16.8; 1.4	0.10
Activity	4.2±2.5 (38)	2.8±2.8 (30)	1.4±0.7	-6.1; 8.8	0.72
Impact	6.6±2.7 (38)	6.6±3.0 (30)	0.0±4.1	-8.1; 8.2	0.99
SF-36	On-demand (n)	Control (n)	Difference	95% CI	*p*-value
General health	-5.2±2.1 (37)	-4.8±2.3 (30)	-0.4±3.1	-6.7; 5.8	0.89
Physical functioning	-7.5±2.4 (38)	-6.1±2.7 (29)	-1.4±3.6	-8.7; 5.7	0.68
Bodily pain	-1.8±3.3 (38)	2.9±3.8 (29)	-4.7±5.0	-14.6; 5.3	0.36
Vitality	-3.2±2.3 (38)	-4.3±2.6 (30)	1.1±3.5	-6.0; 8.2	0.75
Role physical	-4.8± 5.6 (35)	-6.8±6.4 (27)	2.0±8.5	-15; 19	0.81
Role emotional	-2.0±6.9 (34)	-13.6±7.8 (27)	11.6±0.3	-9.2; 32.4	0.27
Social functioning	-7.1±3.3 (39)	-7.5±3.7 (30)	0.4±5.0	-9.6; 10.4	0.94
Mental health	-0.3±2.4 (38)	-4.4±2.7 (30)	4.1±3.6	-3.1; 11.4	0.26

CI=Confidence Interval; SGRQ=St. George's Respiratory Questionnaire; SF-36=Short Form-36.

All scores are presented as mean with standard error and were adjusted for baseline values.

Table 4 Resource use in primary and secondary care over 2 years

		On-demand (*n*=49)	Control (*n*=51)	*p*-value
Primary care				
Visits	GP	4 (0-32)	5 (0-20)	0.01
Exacerbations		0 (0-4)	0 (0-4)	0.32
Secondary care				
Outpatient visits				
	Total	4 (1-22)	4 (0-13)	0.97
	Pulmonologist	3 (0-17)	3 (0-13)	0.82
	Pulmonary NP	1 (0-14)	0 (0-4)	0.003
Exacerbations		1 (0-15)	2 (0-8)	0.57
Hospital days		0 (0-24)	0 (0-36)	0.73

GP=general practitioner (*n*=48 in the On-demand group); Pulmonary NP=Pulmonary nurse practitioner.

All scores are presented as median with range. *P*-value is calculated with the independent-samples median test. Exacerbations: median number of patients with at least one exacerbation COPD.

provider and healthcare insurance perspective, although this did not reach statistical significance. The mean savings were €518 (95%CI -1993; 788) and €458 (95% CI -2700; 1652) per patient respectively. As expected, the costs of the pulmonary NP were significantly higher in the on-demand-group for both perspectives.

Discussion

This pilot study evaluated the effect of an on-demandsystem outpatient-scheduling scheme in patients with COPD on health status and resource use of primary and secondary care. In both groups health status deteriorated over 2 years. Deterioration in disease-specific health status total and domain scores was invariably smaller in the on-demand-group, but the differences were not significant. The exception was the symptom domain of both CCQ and SGRQ, showing significant and borderline significant mean differences over 2 years, respectively, in favor of the ondemand- group. These mean differences also met the MCID[18;19], indicating a clinically relevant effect.

Statistically significantly fewer patients with COPD in the on-demand-group visited the GP in comparison with the control group. In secondary care number of visits to pulmonologists was similar in both groups, while number of visits to the pulmonary NP significantly increased in the ondemand- group. Thus, increasing access to NPs in secondary care might reduce the workload in primary care. Numbers of exacerbations were comparable in both groups. Total costs, although not statistically significant, were lower in the on-demand-group, from both healthcare provider and healthcare insurance perspective.

As per protocol, patients in the on-demand-group were still routinely scheduled to visit the outpatient clinic once a year. It seems logical that skipping this appointment would lower the number of visits to the outpatient clinic. Since we did not test this, we cannot negate that even less fixed visits could lead to inadvertent health status loss, this should be tested in a next study.

An explanation of the clinically relevant difference in the symptom domain scores of CCQ and SGRQ in favor of the on-demand-group could be that patients in the on-demandgroup were more in control. If patients with COPD experience increasing symptoms, which is a stressful situation, they try to reduce or tolerate this with cognitive and behavioral efforts.[24] In the on-demand-group they could directly contact the pulmonary NP when needed. In this way patients were allowed to talk about their complaints and worries, and therefore ensure efforts to manage this situation. This could also have positively affected mental health which is supported by our findings of the mean difference in favor of the on demand group in the SF-36 domains role emotional and mental health.

Worsening symptoms of patients with COPD were noticed earlier. Probably, that was the reason that the median number of days to the first exacerbation COPD was slightly shorter in the on-demand-group. Many studies of self-management of COPD have

Table 5 Treatment costs per patient (in euros, 2013)

		Unit costs	On-demand (*n*=49)	Control (*n*=51)	Difference €
Healthcare provider		**Euros 2013**			
Outpatient visits	GP	30.00	139 (193)	173 (148)	-34 (-96; 37)
	Pulmonologist	68.00	257 (203)	270 (182)	-13 (-85; 67)
	Pulmonary NP	37.00	53 (86)	20 (38)	33 (10; 62)
Inpatient visits	Emergency room	161.00	82 (124)	108 (190)	-26 (-89; 37)
	Pulmonary ward, per day	465.00	1272 (2342)	1750 (3722)	-478 (-1857; 742)
Total costs healthcare provider			1803 (2617)	2321 (3967)	-518 (-1993; 788)
Healthcare insurance		**Tariff 2013**			
Outpatient visits	GP	8.78	41 (57)	51 (43)	-10 (-30; 12)
	Pulmonologist	274.55	1031 (813)	1082 (729)	-51 (-362; 240)
	Pulmonary NP	274.55	387 (634)	145 (282)	242 (59; 437)
Inpatient visits	Emergency room	1865.53	952 (1431)	1244 (2197)	-292 (-1076; 435)
	Pulmonary ward	Reimbursement	1583 (2788)	1930 (3741)	-347 (-1731; 986)
Total costs healthcare insurance			3994 (4669)	4452 (6100)	-458 (-2700; 1652)

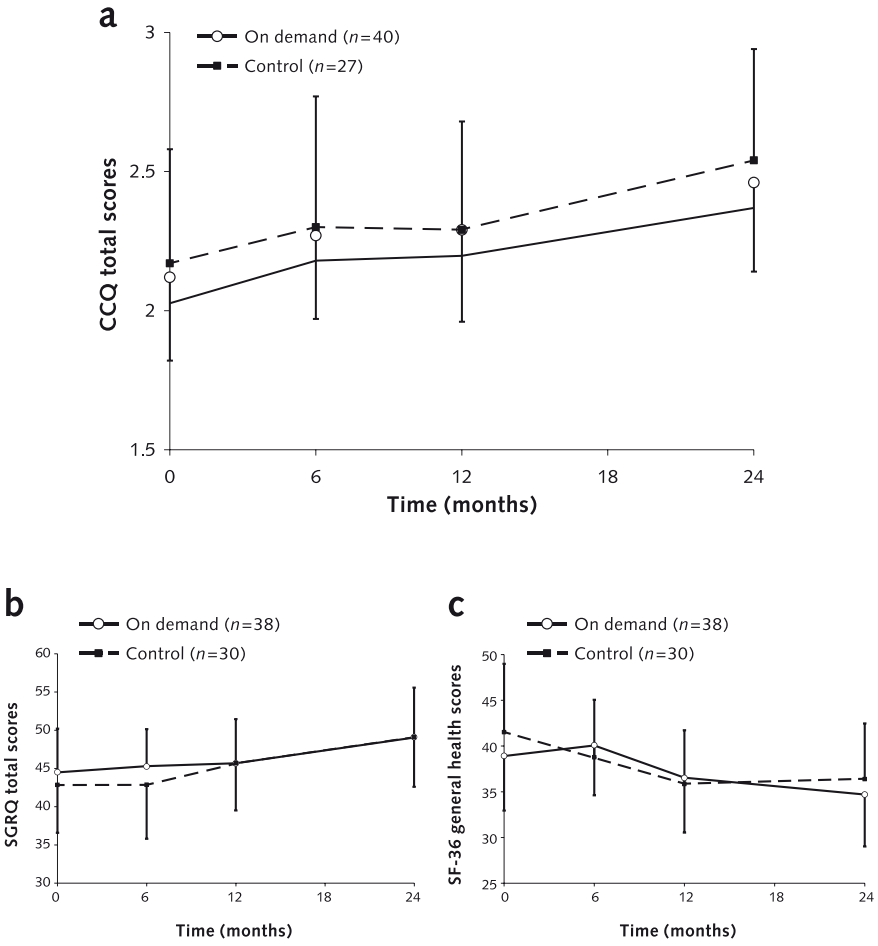
GP=General practitioner (*n*=48 in the On-demand group), Pulmonary NP=Pulmonary Nurse practitioner.

Data are presented as mean (standard deviation).

Reimbursements in the Netherlands are categorized, based on the number of hospitalization days:

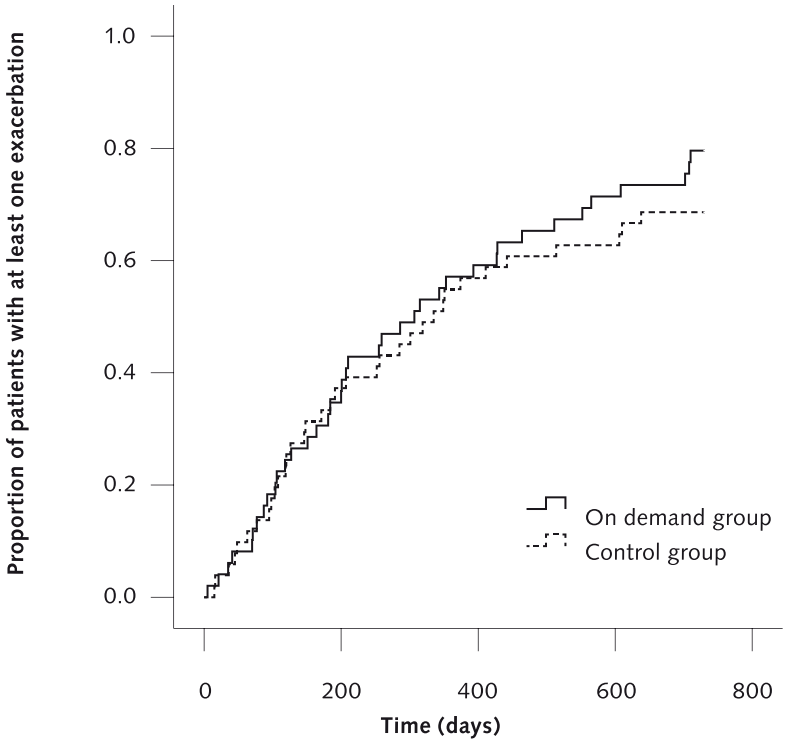
1-4 days: €1865.53, 5-14 days: €3890.80, 15-28 days: €8183.31.

FIGURE 2: Response over time for CCQ, SGRQ and SF-36



Response over time for CCQ, SGRQ and SF-36. Showing time course in the on-demand and the control group, of the Clinical COPD Questionnaire (CCQ) total scores (a), the St. George's Respiratory Questionnaire (SGRQ) total scores (b) and the Short Form-36 (SF-36) general health scores (c). Error bars indicate 95% confidence intervals.

FIGURE 3: Time to first exacerbation COPD



Kaplan Meier curves showing the proportion of patients with at least one exacerbation COPD, in primary and secondary care, against time in days in the on-demand and the control group.

found higher total numbers of exacerbations in the self-management group, but usually of the milder sort and accompanied by beneficial effects on other parameters.[25;26] Costs of severe exacerbations were 7 times as high as milder exacerbations; these costs were almost entirely (for 86%), due to hospitalized days.[7]

The on-demand group showed a cost-saving trend from both the healthcare provider and the healthcare insurance perspective, in comparison with the control group. The reduction in total costs for both perspectives was not significant, however this pilot study was not designed for costanalysis.

Recent studies[9-12] compared the on-demand system in other diseases, i.e. RA or IBD, but not COPD. Two studies[10;12] used SF-36 to assess health status. In both studies no significant difference was found between the groups, similar to our study. One study[12] had resource use of primary and secondary care as endpoint and therefore was comparable with our study. Unlike our study, the on-demand-group showed significantly fewer outpatient visits in comparison to the control group, 4.12 ± 3.41 versus 4.64 ± 2.38 respectively (p=0.002). However, during follow-up patients were transferred back to GP and had no routine appointments in the hospital anymore. Specialists were only contacted when rapid access was needed. In our study patients in the on-demand-group were seen in secondary care once a year per protocol and medical care was not transferred back to GPs. Patients could contact the pulmonary NP by phone if medical care was deemed necessary. Probably this explains the different findings regarding resource use of secondary care between the studies.

A recent study[27] evaluated the cooperation between pulmonary NP and general practitioner for COPD patients in primary care. In this study, disease specific health status showed no significant or clinically relevant difference but an improvement was seen in quality of care and patient knowledge of COPD. A small study[28] of chronic illness, i.e. COPD, led by the pulmonary NP in secondary care showed that patients preferred this care above the usual care. No randomized controlled trials have been published yet evaluating cooperation of the pulmonary nurse and the pulmonologist in the outpatient clinic. Probably, management of patients with COPD with minor symptoms by the pulmonary NP instead of the pulmonologist could also reduce healthcare costs.

One limitation was the design of a pilot study. We choose for a pilot study because the on-demand-system had not been investigated in patients with COPD before. Results of this study are therefore exploratory and give the opportunity for future studies to compute proper sample sizes. Another limitation was the missing data at baseline and the loss to follow-up in the control group to assess health status. The last limitation is that 2 patients did not meet the inclusion criteria of smoking history of >10 pack-years. However, a proportion of patients with COPD never smoked.[29]

Conclusions

In conclusion, this study found that the on-demand-system is comparable in terms of health status and resource use in primary and secondary care, with fixed outpatient visits pre-planned by the pulmonologist and therefore applicable in patients with COPD. A cost-saving tendency was found in favor of the on-demand-group from both healthcare provider and healthcare insurance perspective. Interestingly, the tendency for cost-savings for the on-demand-system in secondary care was not reached by increasing pressure on primary care: it even reduced the burden of COPD in primary care. We suggest that an on-demand-system by patients with COPD is safe and could convey advantages in health status, perhaps increasing self-efficacy skills, this needs to be tested in a larger randomized controlled trial for which power calculations can now be made. Additionally, cost-effectiveness can then be studied in more detail.

Authorship

All authors should have made substantial contributions to all of the following: JWB, DLCV and SU contributed to the conception and design of the study. DLCV, FFB and AMH contributed to the acquisition of data. SU and FFB contributed to analysis and interpretation of data. All authors contributed to drafting and revising the article or revising it critically for important intellectual content. All authors approved the final version of the manuscript to be submitted.

Conflict of interest

All authors confirm that they have no relevant competing financial interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.05.011.

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Appendix
Protocol pulmonary nurse practitioner

1.1 Introduction

This protocol provides a guideline how to act medically when a patient contacts the outpatient clinic. Not all possible situations can be described in a single protocol, though we expect all pulmonary nurse practitioners involved in this study to comply with the nursing ethics.

- If a patient contacts the outpatient clinic, always record name, date of birth and phone number and ask if it is possible to call back within 1.5 hour.
- Ask the medical secretary to search for the medical file and patient's case report form of the study.

1.2 The phone call (anamnesis)

The history provides not only information about current symptoms, but also about the perception and emotions of the patient. Because in a phone call non-verbal information is lacking, properly questionning is important. Let the patient tell his story first (app. 2 minutes) and try to verify actual complaints or problems. Use open-ended questions at the beginning and more specific questions at the end. It is important to figure out the exact reason why the patient is contacting the outpatient clinic.

1.3 Symptom assessment

Dyspnoea

- Acute Dyspnoea: Acute dyspnoea with local pain related to breathing can be associated with a pulmonary embolism or pneumothorax, a patient should be asked to come to the emergency room as soon as possible. Ask what the patient has already done to reduce dyspnoea eg. taken additional medication.
- Dyspnoe on exertion: Try to obtain the degree of dyspnoe. To objectively assess dyspnoea the Modified Medical Research Coucil scale (MMRC) and the Borg-scale were used.
- Orthopnoea: Orthopnoea can indicate heart failure. A myocardial infarction in medical history is a risk factor for heart failure.

Cough

- Productive cough: If the patient has a productive cough, ask for the sputum volume and color. Additionally, ask wether any triggering factors are present. Productive purulent (yellow or green) sputum can be associated with an exacerbation COPD and in case of hemopthysis patient should always be assessed in the outpatient clinic. It is important to be extra alert if previous exacerbations had requiered hospitalization.
- Non-productive cough: In case of non-productive cough, sinusitis, laryngitis and angiotensine converting enzyme (ACE) inhibitors should be considered.
- Unexplained cough can be caused by Gastro-Esophageal Reflux Disease (GERD). Typical symptoms are heartburn, regurgitation, chest pain.

Other

Other symptoms to be alert of: palpitations, angina symptoms, fatigue, oedema, paraesthesia around the mouth.

1.4 Low urgency protocol

The urgency for an outpatient visit is deemed low when the patient has none of following symptoms: fever, cough, purulent sputum, decompensatio cordis. An outpatient visit to the pulmonary nurse practitioner is then planned on the next day. The patient was asked to take along the medication list.

1.5 High urgency protocol

If an exacerbation is suspected, the urgency is deemed high and the high urgency protocol should be followed. The patient should be examined the same day. The patient's medication has to be checked first. Medical history is obtained again. Which is followed by physical examination: general impression, cyanosis, fever, weight, tension, saturation and pulse rate.

Treatment is started with inhaled ipratropium 0.5mg + salbutamol 2.5mg / 2.5ml is started directly. Improvement of dyspnoea must occur within half an hour, and in case of no improvement the pulmonologist should be consulted. The pulmonologist then decides wether the patient should be seen in the emergency room or at the outpatient clinic. If deemed necessary blood gas analysis, chest x-ray and electrocardiogram should be obtained.

Chapter 7

Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial.

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Status

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Abstract

Background

Macrolides reduce exacerbations in patients with COPD. Their effects on health status has not been assessed as primary outcome and is less clear. This study assessed the effects of prophylactic azithromycin on cough-specific health status in COPD-patients with chronic productive cough.

Methods

In this randomised controlled trial 84 patients met the eligibility criteria: age of ≥40 years, COPD GOLD stage ≥2 and chronic productive cough. The intervention-group (n=42) received azithromycin 250 mg 3 times a week and the control-group (n=42) received a placebo. Primary outcome was cough-specific health status at 12 weeks, measured with the Leicester Cough Questionnaire (LCQ). Secondary outcomes included generic and COPD-specific health status and exacerbations. Changes in adverse events and microbiology were monitored.

Results

Mean age of participants was 68 ± 10 years and mean FEV_1 was 1.36 ± 0.47 L. The improvement in LCQ total score at 12 weeks was significantly greater with azithromycin (difference 1.3 ± 0.5, 95% CI 0.3;2.3, p=0.01) and met the minimal clinically important difference. Similar results were found for the domain scores, and COPD-specific and generic health status questionnaires. Other secondary endpoints were non-significant. No imbalances in adverse events were found.

Conclusions

Prophylactic azithromycin improved cough-specific health status in COPD-patients with chronic productive cough to a clinically relevant degree.

Trial registration

ClinicalTrials.gov NCT01071161

Keywords

COPD, Health status, Azithromycin, LCQ, Cough

Background

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death[1], with an estimated worldwide prevalence of up to 10.1%[2] and it is expected to increase over the coming decades.[3] Important and common symptoms in patients with COPD are chronic cough and sputum production, or chronic bronchitis.[4] Additionally, approximately up to 50% of patients with moderate to severe COPD have bronchiectasis at least to some degree and this is associated with a poorer prognosis.[5;6] Chronic cough and sputum production are caused by inflammation due to smoking or inhaled other irritants.[7] Mucus hypersecretion by itself facilitates bacterial proliferation and colonization which in turn contributes to chronic inflammation.[8;9] Chronic obstructive bronchitis, i.e. COPD, is associated with progressive lung function loss, more frequent exacerbations, and hospitalisations.[8] The latter lead to a deterioration of health status.[10] Improving health status is an important goal in the treatment of COPD patients.[3] Inhaled glucocorticoids, long-acting beta2-agonists, and long-acting anticholinergics have all been shown to reduce exacerbation frequency in COPD, but despite these therapies, the average frequency of acute exacerbations still remains approximately 1.4 each year.[11] An addition to the usual therapy is long-term macrolide use, of which the mechanism of action is attributed to the immunomodulatory effects as well as to diverse actions that suppress microbial virulence factors beyond their antibacterial effects.[12-14] In several studies[15-21] macrolides have been demonstrated to reduce the frequency of COPD exacerbations of which four studies[16;18;19;21] examined disease specific and generic health status as a secondary outcome only. None of these studies addressed cough-specific health status specifically. We were interested in cough because it is very relevant to patients' daily life and chronic cough and sputum production are also risk factors for worse outcomes in COPD patients.[22] The impact on cough-specific health status in these patients is largely unknown. The Leicester Cough Questionnaire (LCQ) is a cough-specific health status questionnaire which is originally validated for a population of general patients presenting with chronic cough.[23] Recently, the LCQ was validated to measure cough-specific health status in patients with COPD and chronic bronchitis.[24]

Hence, the primary hypothesis was that prophylactic azithromycin improves cough-specific health status in patients with COPD and chronic productive cough. Important secondary hypotheses were that it also leads to improvements in generic and COPD-specific health status.

Methods

Study design

The study was designed as a single-centre parallel group randomised double-blind placebo controlled trial. It was carried out in the Isala klinieken, a large teaching hos-

pital in Zwolle, the Netherlands. Approval of the local ethics committee was received (NL19886.075.07, local number: 07.0971) and the study was registered at ClinicalTrials.gov (NCT01071161). All participants provided written informed consent.

Participants

Eligible patients were ≥ 40 years, had a clinical diagnosis of COPD GOLD stage ≥2 (defined as a post bronchodilator of forced expiratory volume in 1 second (FEV_1) <80% and a ratio of FEV_1 to forced vital capacity of <70%), and were suffering from chronic productive cough, defined as cough for at least the last 12 weeks, in two subsequent years. Exclusion criteria were a prior history of asthma; use of intravenous or oral corticosteroids and/or antibiotics for an exacerbation three weeks before inclusion; other relevant lung or liver diseases at the discretion of the treating physician; pregnancy or lactation; use of macrolides in the last six weeks prior to inclusion; allergy or intolerance to macrolides; or use of other investigational medication started two months prior to inclusion.

Long term treatment with aerosolized antibiotics, inhaled corticosteroids, and/or bronchodilators was permitted during the trial, provided that it was kept constant.

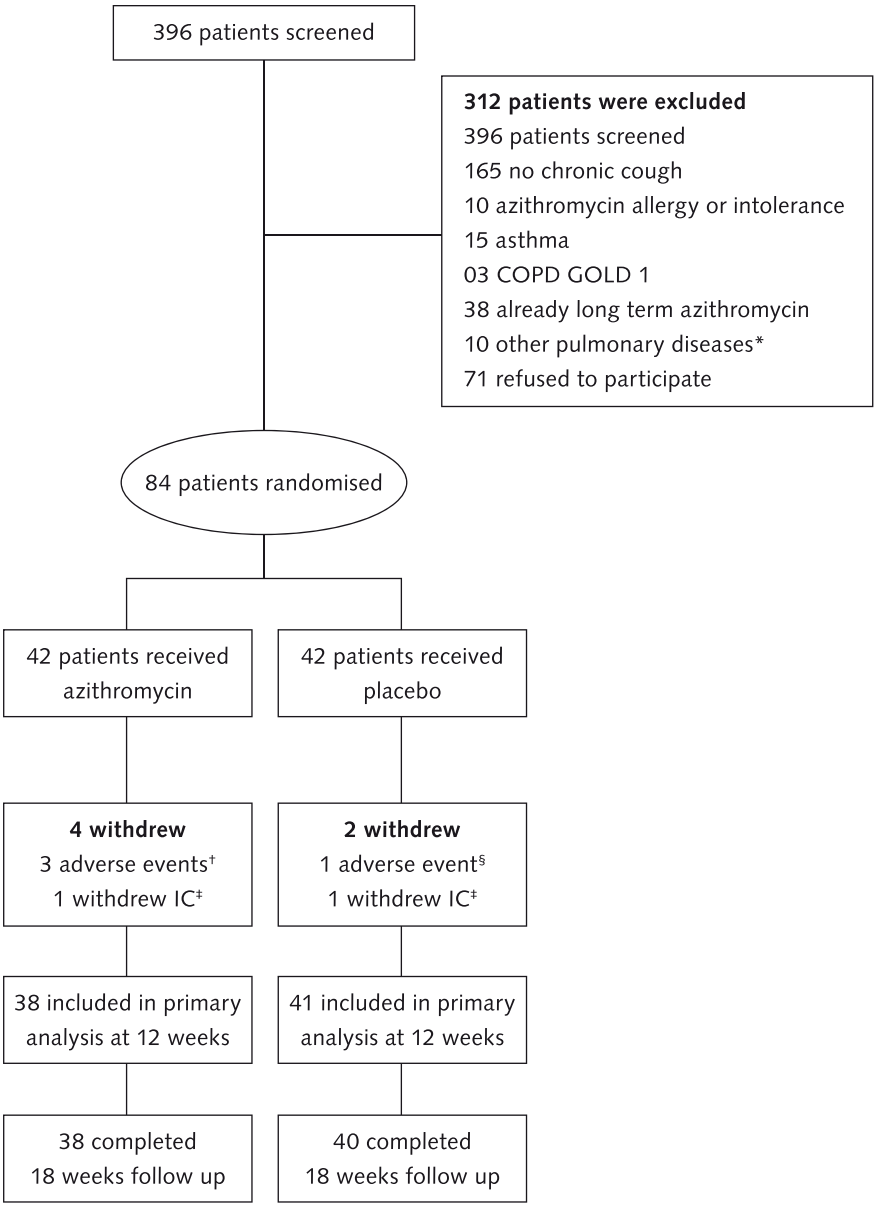
Randomisation and blinding

Patients were randomly assigned, without stratification, to receive azithromycin 250 mg three times a week or an identical appearing placebo for 12 weeks. Randomisation codes were generated using a computer allocation program, with a 1:1 ratio and a permutated block size of 4. Investigators, research nurses, and participants were masked to treatment allocation until final analyses of the data were performed.

Procedures

Patients were instructed to take the study medication weekly on Monday, Wednesday, and Friday. Study medication was prepared by Central Hospital Pharmacy, The Hague, the Netherlands and was distributed by our hospital pharmacy. During the first outpatient visit, baseline spirometry, smoking status, pulmonary medication, and laboratory blood values (aspartate transaminase (ASAT), alanine aminotransferase (ALAT), and C-reactive protein (CRP)), and a spontaneous sputum sample for culture of respiratory pathogens were collected. Patients were asked to complete the LCQ[23;24], SGRQ[25], and SF-36[26], to assess cough-specific, disease-specific (COPD), and generic health status, respectively. At two, six, nine, and eighteen weeks, telephone calls were scheduled to collect data on adverse events, concomitant medication, and to ask the patient to complete the LCQ and return it by mail. At 12 weeks a second outpatient visit was planned at which spirometry was done and blood laboratory values, and a spontaneous sputum sample were collected. Also, the LCQ, SGRQ, and SF-36 were repeated. Adherence was assessed by counting the unused pills. All participants were analysed for bronchiectasis by high resolution CT-thorax at baseline. Criteria for the diagnosis of bronchiectasis were lack of tapering, visibility of bronchi within 1 cm of the pleura and bronchial

FIGURE 1: Consort Flowchart



5 patients with lung cancer, 4 patients with idiopathic interstitial lung disease, 1 patient with bronchiectasis

† 2 patients with diarrhoea and 1 with disturbance of taste. ‡ informed consent.

§ patient with disturbance of taste. Withdrew after 12 weeks.

dilatation (bronchial diameter larger than that of the accompanying pulmonary artery while avoiding slices close to bronchial bifurcations).[6]

Endpoints

The primary endpoints were mean LCQ total and domain scores at 12 weeks. The LCQ total scores vary from 3 to 21 and the domain scores vary from 1 to 7, with a higher score signifying better health status, the MCID is 1.3.[23;24] The secondary endpoints at 12 weeks were: St. George's Respiratory Questionnaire (SGRQ) total score (range from 0-100, a low score indicates a good health status, the MCID is 4[25;27]), Short Form 36 (SF-36) score (range from 0-100, higher scores represent better health status, the MCID is 4[26;28;29]), post-bronchodilator spirometry (FEV_1, FEV_1%predicted), blood values, and microbiology. Other endpoints included time to first exacerbation of COPD, defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that necessitates treatment with prednisolone, antibiotics or a combination of both[30], as well as exacerbation and hospitalization rates for COPD, and adverse events, during 18 weeks.

Sample size considerations

Sample size calculation was based on LCQ total scores. At the time of designing the study no MCID estimate of the LCQ was available. Therefore, a difference between the study groups in mean LCQ total score of at least 1.5 (SD=2.0) points at 12 weeks was chosen. To be able to demonstrate this difference with a power of 90% and a two-sided α level of 0.05, 42 patients were needed in each group (taking into account a drop-out rate of 10%).

Statistical analyses

Primary and secondary analyses were done according to the intention-to-treat principle. Missing LCQ data at 12 weeks were imputed using the last observation carried forward, from 9 weeks, when possible. Normal distributions of outcomes were checked using histograms. Baseline characteristics, microbiology outcomes, and blood values at baseline and at 12 weeks were examined with descriptive statistics. Differences in primary and continuous secondary outcomes (i.e. SGRQ scores, SF-36 scores, and spirometry) were tested using ANCOVA, adjusting for baseline values. Interaction terms between treatment group and baseline value were checked to explore whether the extent of treatment response varied dependent on the value of the baseline value. A log-rank test was used to test differences in time to first exacerbation between study groups which were graphically presented by Kaplan-Meier curves. Between-group comparisons of proportions were performed using Chi-squared tests. *P*-values <0.05 were considered significant. Analyses were performed using SPSS-Statistics version 19.0 (IBM corporation, Armonk, NY, USA).

Table 1: Patient characteristics

		Azithromycin	Placebo
		(*n*=42)	(*n*=42)
Age (years), mean (SD)		67 (9)	68 (10)
Male sex, n (%)		31 (74)	32 (76)
FEV_1 (L), mean (SD)		1.41 (0.52)	1.32 (0.42)
FEV_1 %predicted, mean (SD)		49.8 (16.4)	47.4 (12.9)
FEV_1/FVC ratio (%),mean (SD)		42.2 (11.9)	43.2 (11.7)
BMI (kg/m^2), mean (SD)		27.2 (4.3)	25.7 (5.8)
Pack years, median (range)		30.5 (3-110)	30.0 (1-69)
Current smoker, n (%)		14 (33)	15 (36)
Blood values	CRP (mg/L), median (range)	6.5 (0-46)	4.0 (0-25)
	ASAT (U/L)* mean (SD)	24.2 (6.5)	26.4 (9.8)
	ALAT (U/L)* mean (SD)	24.4 (8.0)	24.4 (13.7)
LCQ scores, mean (SD)	Total	14.5 (2.3)	13.4 (3.3)
	Physical	4.3 (0.7)	4.2 (1.0)
	Psychological	5.1 (1.0)	4.7 (1.1)
	Social	5.0 (1.1)	4.5 (1.5)
Bronchiectasis, n (%)		18 (42.9)	16 (38.1)
Inhaled medication, n (%)	Long acting $beta_2$ agonists	34 (81.0)	35 (83.3)
	Long acting anticholinergics	27 (64.3)	24 (57.1)
	Corticosteroids	41 (98.0)	35 (83.0)
Number of exacerbations in previous year, median (range)		1 (0-8)	1 (0-13)

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; BMI, body mass index; CRP, C-reactive protein; ASAT, aspartate transaminase; ALAT, alanine aminotransferase; LCQ, Leicester Cough Questionnaire.

Total scores range from 3-21 and domain scores from 1-7. Higher scores signify better health status.

* In ASAT and ALAT *n*=41.

Table 2 Change in LCQ scores after 12 weeks adjusted for baseline values

	Azithromycin (*n*=38)	Placebo (*n*=41)	Difference	95% CI	*p*-value
Total	2.2 ± 0.4	0.9 ± 0.3	1.3 ± 0.5	0.3;2.3	0.01
Physical	0.6 ± 0.1	0.2 ± 0.1	0.4 ± 0.2	0.1;0.8	0.01
Psychological	0.8 ± 0.1	0.3 ± 0.1	0.5 ± 0.2	0.2;0.9	0.006
Social	0.8 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.01;0.9	0.046

All scores are presented as mean with standard error.

LCQ, Leicester Cough Questionnaire. Higher scores signify better health status.

A change of 1.3 points is regarded as minimal clinically important.

Results

Participants

Recruitment started Sept. 15, 2009 and ended Oct. 14, 2011, and the last patient finished after 18 weeks of follow up. In total 84 patients were randomised. Screening, randomisation, follow up, and losses after randomisation are shown in a consort flow chart, Figure 1. Baseline characteristics were similar between the groups, except for a small difference in proportion of patients using inhaled corticosteroids and the LCQ total score, Table 1. Adherence with study medication was high during the study. On average, 85% and 92% of the patients used all weekly dosages in the azithromycin and placebo groups, respectively ($p=0.48$ for difference).

Primary outcome

A significantly greater mean increase in LCQ total score after 12 weeks was found in the azithromycin group compared with placebo, 1.3 ± 0.5 (95% CI 0.3; 2.3, $p=0.01$). Significant differences were also found for the different domain scores of the LCQ, Table 2.

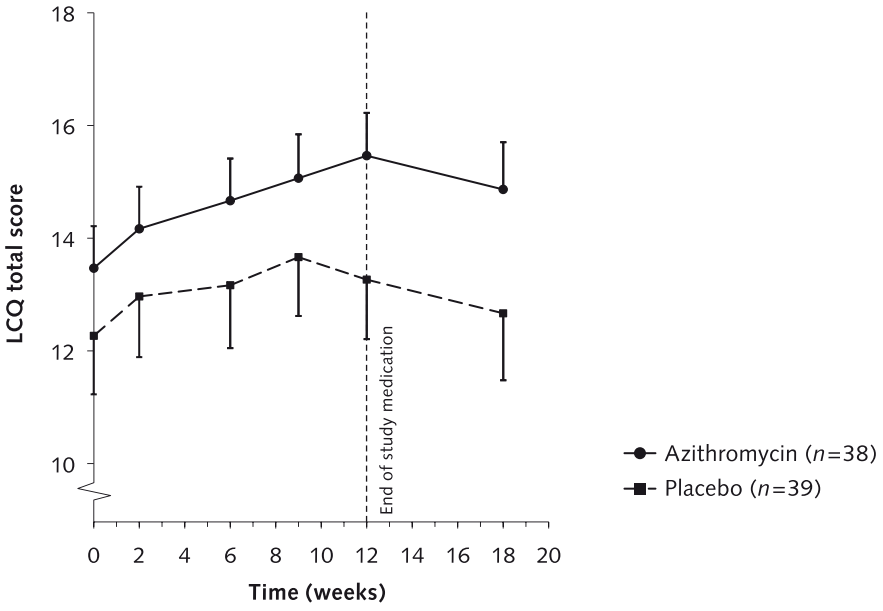
Repeated measurements analysis over the full treatment period also showed that the mean differences between groups for the LCQ total score were significant ($p=0.01$), in favour of the azithromycin group (Figure 2). According to the study protocol prophylactic azithromycin was stopped at 12 weeks which resulted in a decrease of the LCQ total score in the azithromycin group, whereas in the control group this decrease already started at 9 weeks.

As described in the methods, the interaction term between study group and baseline value was checked in the ANCOVA analysis. In all models including LCQ total and domain scores, significant interaction was present. In other words, treatment responses varied dependent on the value of the baseline LCQ total score. To investigate the impact of interaction the study population was divided according to the median of baseline LCQ total score which was 14.1, since no meaningful cut-off values have so far been proposed in literature. The improvement with azithromycin compared to placebo in total LCQ score in the complete population proved to be due almost entirely to the patients with a low LCQ total score (<14.1). The difference over 12 weeks for the azithromycin group with a low LCQ total score at baseline was 2.6 ± 0.8 (95% CI 1.0;4.2, $p=0.002$) and for the azithromycin group with a high LCQ total score at baseline (≥14.1) was 0.1 ± 0.6 (95% CI -1.1;1.2, $p=0.90$).

Secondary outcomes

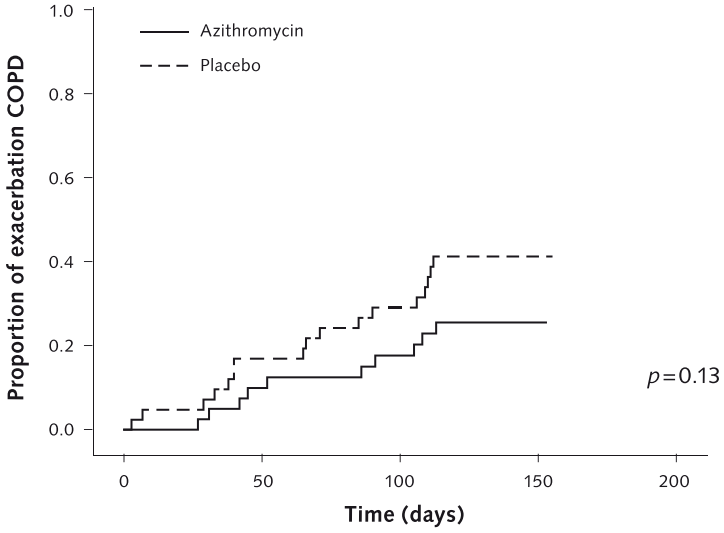
SGRQ and SF-36 — The improvement in SGRQ total score over 12 weeks was greater with azithromycin than with placebo: mean difference was -7.4 ± 2.5 (95% CI -12.5; -2.5 $p=0.004$). The improvements in the SGRQ domain scores symptoms and impact were also significant, Table 3. Similar to the primary outcome the improvements in SGRQ scores also proved to be due almost entirely to the patients with a low LCQ total

FIGURE 2: Change over time in LCQ total score



Repeated measures of the Leicester Cough Questionnaire (LCQ) total scores at 0, 2, 6, 9, 12 and 18 weeks between the azithromycin (n=38) and placebo (n=39) group. Error bars indicate 95% confidence intervals.

FIGURE 3: Time to first exacerbation COPD



Kaplan Meier curves showing the proportion of patients with a first exacerbation against time in days for the azithromycin (n=42) and placebo (n=42) group.

baseline score (<14.1). The difference of the SGRQ total score after 12 weeks in patients with a low LCQ total baseline score was -13.8 ± 4.1 (95% CI -22;-5.5 p=0.002) in favour of the azithromycin group. On the contrary, the difference of the SGRQ total score for patients with a high LCQ baseline score was -1.6 ± 2.9 (95% CI -7.5;4.4 p=0.59). Significant mean differences at 12 weeks in favour of the azithromycin group were found in the SF-36 scores: general health, role physical, social functioning, and mental health, see Table 3. Comparable with the primary and the SGRQ findings, patients with a low LCQ baseline score showed a greater difference after 12 weeks in the SF-36 domain general health (14.1 ± 5.0 (95% CI 4.0;24.3 p=0.01)) in favour of the azithromycin group than patients with a high LCQ baseline score (2.4 ± 4.2 (95% CI -6.2;11.0 p=0.57)). Analysis of the other SF- 36 domain scores follows the same tendency, except for role physical.

Exacerbations – A COPD exacerbation occurred in 10 (23.8%) patients in the azithromycin group and 17 (40.5%) in the placebo group, p=0.10.

Because less than 25% of the patients in the azithromycin group had an exacerbation in 18 weeks the 20th percentile time to the first exacerbation was calculated, which was 105 ± 30 days in participants receiving azithromycin compared with 66 ± 21 days in the placebo group (p=0.13; log-rank test), Figure 3.

Four (9.5%) patients in the azithromycin group and 5 (11.9%) patients in the placebo group were hospitalized for COPD.

Analogous to the other outcomes there was a trend towards a lower exacerbation frequency in the patients with a low LCQ baseline total score which received azithromycin.

Spirometry, blood, sputum and adverse events – There were neither statistically significant nor clinically relevant differences in FEV_1.

ASAT and ALAT were similar in both groups at baseline with no relevant changes in either group after 12 weeks. Furthermore, no individual changes above normal values in ASAT and ALAT were found.

A reduction of respiratory pathogens was seen in the azithromycin group after 12 weeks, Table 4.

Adverse events were comparable in both groups (Table 5). In the azithromycin group three patients with adverse events stopped using study medication, two patients had diarrhoea, and one patient had disturbance of taste. In the placebo group one patient stopped study medication because of disturbance of taste.

Discussion

Our study is the first randomised placebo controlled trial to evaluate the effect of prophylactic azithromycin on cough-specific health status (LCQ) in COPD patients with chronic bronchitis. Cough-specific health status, as well as disease specific (SGRQ), and generic (SF-36) health status improved statistically significantly with azithromycin compared to placebo, with improvements equal to or exceeding the MCID. Moreover,

TABLE 3: Change in SGRQ and SF-36 scores after 12 weeks adjusted for baseline values

	Azithromycin	Placebo	Difference	95% CI	*p*-value
SGRQ	(*n*=37)	(*n*=37)			
Total score	-6.6 ± 1.8	0.9 ±1.8	-7.5 ± 2.5	-12.5;-2.5	0.004
Symptoms	-9.2 ± 3.0	0.1 ± 3.0	-9.1 ± 4.2	-17.6;-.07	0.034
Activity	-4.1 ± 2.3	0.2 ± 2.3	-4.3 ± 3.2	-10.7;2.1	0.18
Impact	-7.3 ± 2.0	1.6 ± 2.0	-8.9 ± 2.8	-14.5;-3.3	0.002
SF-36	(*n*=37)	(*n*=37)			
General health*	4.5 ± 2.4	-3.8 ± 2.4	8.3 ± 3.4	1.6;15	0.016
Physical functioning	5.5 ± 2.2	0.7 ± 2.3*	4.8 ± 3.2	-1.5;11.1	0.13
Bodily pain	5.6 ± 3.3	-0.9 ± 3.3	6.5 ± 4.7	-2.9;15.9	0.17
Vitality*	4.0 ± 2.4	-2.0 ± 2.4	6.0 ± 3.4	-0.8;12.9	0.08
Role physical	16.2 ± 5.4	-1.1 ± 5.4	17.3 ± 7.6	2.2;32.5	0.025
Role emotional	-0.4 ± 5.6	-6.3 ± 5.6	5.9 ± 7.9	-9.8;21.7	0.46
Social functioning	4.4 ± 3.1	-8.5 ± 3.1	12.9 ± 4.4	4.0;21.7	0.005
Mental health*	2.2 ± 1.9	-3.5 ± 1.9	5.7 ± 2.7	0.4;11.0	0.037

All scores are presented as mean with standard error.

SGRQ, St. George's respiratory questionnaire. Scores range from 0-100. A low score indicates a good health status, the minimal important difference is 4; SF-36, Short-form 36. Scores range from 0-100, higher scores represent better health status. The minimal important difference is 4.

**n*=36.

TABLE 4: Microbiology

	Azithromycin		Placebo	
	Baseline	12 weeks	Baseline	12 weeks
Microbiology, n (%)	(*n*=40)	(*n*=30)	(*n*=41)	(*n*=31)
Streptococcus pneumoniae	5 (11.9)	0 (0)	3 (7.1)	2 (4.8)
Haemophilus influenzae	11 (27.5)	4 (13.3)*	7 (17.1)	10 (32.3)
Moraxella catarrhalis	5 (12.5)	0 (0)	5 (12.2)	3 (9.7)
Pseudomonas aeruginosa	0 (0)	1 (3.3)	2 (4.9)	3 (9.7)
Staphylococcus aureus	1 (2.5)	0 (0)	1 (2.4)*	0 (0)

*one patient with azithromycin resistant bacteria.

TABLE 5: Adverse events in 12 weeks

Adverse events	Azithromycin	Placebo	*p*-value
Gastro-intestinal*, n (%)	5 (11.9)	6 (14.3)	0.75
Upper respiratory†, n (%)	7 (16.7)	8 (19.0)	0.78
Cardiovascular‡, n (%)	2 (4.8)	1 (2.4)	0.56
Other§, n (%)	3 (7.1)	5 (11.9)	0.71

*gastro-intestinal adverse events were diarrhoea, nausea and ulcus ventriculi.

†Upper respiratory adverse events were common cold, dyspnoea and cough.

‡Cardiovascular adverse events: myocardial infarction, supraventricular tachycardia, heart failure.

§Other include: pruritis, headache, disturbance of taste, malaise, atralgia and hyperhidrosis.

there was a clear trend for azithromycin to increase the time to the first exacerbation compared to placebo. Adverse events were similar in both groups, which indicated azithromycin was well tolerated.

The beneficial effect of azithromycin was apparent for the study population as a group, but patients with a high baseline LCQ total score experienced no effects of azithromycin on cough-specific health status and the other efficacy outcomes at all. Although all patients recruited for this study met the predefined definition of chronic productive cough, it appears that the LCQ could discriminate between patients who respond to azithromycin and those who did not. Perhaps, COPD patients with chronic cough are more heterogeneous than expected, depending on the degree of impairment of coughspecific health status, the LCQ might discriminate between different types or severity of cough in COPD patients. It has been shown before that chronic cough with persistent symptoms has a larger impact on activities of daily life than morning cough or incidental cough.[31]

Recent studies[15-21] assessing the effect of prophylactic antibiotics in patients with COPD and chronic bronchitis focused particularly on reducing exacerbations. Six of these studies used macrolides i.e. erythromycin, clarithromycin, and azithromycin respectively. These antibiotics belong to the same category, US FDA approved, and can thus be compared.[32] Four studies explored health status as a secondary outcome[16;18;19;21], of which one study did not include concurrent controls.[18] In these studies the disease specific and generic health status were measured as a secondary outcome only and findings were inconsistent. None of these studies addressed cough-specific health status specifically.

In one large clinical trial[16] the dose of azithromycin was 250 mg a day for one year, resulting in development of nasopharyngeal colonization with azithromycinresistant pathogens, 81% versus 41% for the azithromycin group and the placebo group respectively. It has been suggested that the daily dose might be more than needed, especially given these resistance problems. In our study, with azithromycin 250 mg three times per week, only one patient developed an azithromycinresistant *Haemophilus Influenzae*, although the follow up period was only three months. Our lower dose of azithromycin of 250 mg of three times a week seemed equally effective and sufficient.

Another important question is the optimal duration of treatment. In our study we chose to treat patients for 3 months. In 2 recent studies[16;33] patients were treated with prophylactic azithromycin for 6 months and for 1 year respectively. It is interesting to note that in both studies the largest effect was seen in the first 3 to 4 months, afterwards a more equal exacerbation rate was noticeable for both the azithromycin and the control group. Perhaps, an alternate treatment scheme of prophylactic azithromycin, e.g. every other 3 months, is preferable over continuous use, and thus preventing unnecessary treatment with long-term antibiotics, which has important consequences with respect to side effects, and bacterial resistance.

One obvious limitation of our study was the small group, though the study was sufficiently powered for the primary outcome, LCQ scores at 12 weeks. However, the pri-

mary outcome was missing in ten patients; in five cases data from nine weeks could be imputed which probably underestimated treatment response at 12 weeks. We chose to impute data with the last observation carried forward approach to increase power and precision, though there also limitations to this approach.[34,35] Another limitation is the MCID of the LCQ is not yet established in COPD patients with chronic cough; therefore the MCID in patients with chronic cough was used in this study. It will be clinically useful to determine a MCID of the LCQ specifically in COPD patients with chronic cough. Finally, since objective cough frequency does not always correlate with symptoms or cough-specific health status, the use of cough recorders at home to objectively assess cough would have been an interesting but costly adjunct to the study.[36]

Conclusions

In conclusion, this study showed that prophylactic azithromycin of 250 mg, three times a week for three months, provided significant and clinically relevant improvements in cough specific health status in patients with COPD and chronic productive cough. This was supported by improvements in disease specific and generic health status parameters, and although not powered to assess a reduction in exacerbation rate, the tendency was nevertheless clear. The effects were largely limited to those with a high burden of cough specific complaints at baseline. Interesting next steps would be studies limited to patients with a high LCQ, perhaps assessing also the level of airway inflammation. We believe it is an interesting thought to further elaborate on duration of macrolides treatment and whether it should be continuous or recurrent.

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Chapter 8

Summary, discussion and future perspectives

The studies described in this thesis address the question how to measure and to improve health status in patients with COPD. It consists of two parts:
Part I: Measurement of health status in patients with COPD. First, the psychometric properties of the most commonly used questionnaires in patients with COPD, the CCQ, CAT and LCQ, were evaluated. Furthermore, the psychometric properties of health status questionnaires were assessed in three specific subpopulations of patients with COPD, i.e. with chronic productive cough, with concomitant heart failure, and with stable disease in the outpatient clinic.
Part II: Improving health status in patients with COPD. In this part we evaluated the changes in health status by 3 different interventions: the addition of azitromycine, a change in follow up procedures in outpatient clinics, and a telemedicine model.

Background of this thesis

Measurement of health status in COPD
Measurement and follow-up of health status in patients with COPD is increasingly recognized to be important.[1] To facilitate measurement and follow-up of health status in clinical practice at least two short and practical questionnaires have been developed, the CCQ and the CAT.[2;3] For proper use of questionnaires, especially when those are used to guide clinical decisions, a thorough understanding of strengths and weaknesses is needed for adequate use and interpretation. Thus, it is important to know the psychometric properties of these disease-specific health status questionnaires, i.e. the discriminative value (construct validity, internal consistency, test-retest-reliability) and the evaluative value (agreement and responsiveness).[4] Over the past years, determination of the psychometric properties of health status questionnaires has become more commonplace.[4-6] The optimization of the methodological quality contributes to more trustworthy conclusions and interpretations.

There are two important issues concerning the use of the CCQ and the CAT and indeed of almost all disease-specific health status questionnaires in clinical practice. First, most were developed before publication of the gold standard for the development and validation of health status questionnaires, the Consensus-based Standards for the selection of health status Measurements Instruments (COSMIN), which were published in 2010.[6] Secondly, much is already known about the discriminative value of the CAT and CCQ in patients with COPD from validation studies.[7-10] However, the evaluative value of both questionnaires has not been fully assessed yet and remains unclear. From the date of publication, it is obvious that the aforementioned validation studies were not done according the COSMIN guidelines. Furthermore these validation studies were performed in patients with COPD in special settings, i.e. after an exacerbation or after pulmonary rehabilitation. These settings are not comparable to the setting of daily outpatient practice in which the questionnaires are most often used nowadays. Therefore,

we validated and compared these health status questionnaires, in this setting, and according to the COSMIN guidelines.

Improving health status in patients with COPD

Health status of patients with COPD depends on several aspects, severity of airflow limitation, comorbidity, risk of future events (exacerbations, hospitalizations) and symptoms (impact of disease).[1] The impact of disease and symptoms differs from patient to patient and from time to time. It has been reported that most patients with stable state COPD do not classify themselves as ill. The most common symptoms as dyspnea, cough and sputum are commonly described as a way of life.[11] Exacerbations of COPD are more stressful. To manage and prevent these situations two models of medical care to improve the health status of patients with COPD were studied in this dissertation, a telemedicine model and a care-on-demand model. Besides, improvement of health status in patients with COPD and chronic bronchitis was investigated.

Summary and discussion part I:

Measurement of health status in patients with COPD

Prevalence rates of chronic productive cough in the COPD population are approximately 15-44% in males and 6-17% in females. These rates increase with age and are strongly related to smoking.[12] Patients with COPD and chronic productive cough have more severe exacerbations with more frequent hospitalization than patients with COPD but without chronic bronchitis.[13] These exacerbations are associated with a deterioration in health status in patients with COPD.[14] To measure health status in patients with COPD and chronic productive cough, COPD-specific health status questionnaires are used. Unfortunately, only a small part of these COPD-specific questionnaires reflects cough-specific health status.[15] Thus the impact of chronic productive cough in patients with COPD is unknown. Furthermore, validated cough specific health status questionnaires for patients with COPD and chronic productive cough are absent.[16] Therefore in **Chapter 2**, the Leicester Cough Questionnaire (LCQ) was validated in patients with COPD and chronic productive cough. The LCQ is a cough-specific health status questionnaire and was originally designed for patients with chronic cough in a general population.[17] Our study showed that the discriminative and the evaluative part of the LCQ were adequate. The discriminative parts showed significant concurrent validity for the corresponding domains between the SGRQ and the LCQ (r_s -0.60, $p < 0.001$ between domains LCQ total and SGRQ total), internal consistency was acceptable (Cronbach's alpha coefficient of LCQ domains: physical 0.67, psychological 0.75, social 0.74 and total 0.86) and test-retest reliability was adequate (ICC's of the LCQ domains were physical 0.93, psychological 0.79, social 0.88 and total 0.92). The evaluative part, the agreement and the responsiveness of the LCQ were acceptable also. Agreement pre-

sented in a Bland-Altman plot showed a mean difference of the LCQ total score of 0.73 (±1.75), an upper limit of agreement of 4.16, and a lower limit of -2.70. Responsiveness had an AUC of 85%. This indicates that the LCQ is capable to detect change over time of health status in patients with COPD and chronic productive cough in the context of clinical research. We think that the LCQ is a relatively short questionnaire that has the potential to be used in clinical practice in the outpatient clinic for the follow up of patients with COPD and chronic productive cough. The LCQ can give additional information about the impact of chronic productive cough, in a more specific way than general COPD health status questionnaires. Unfortunately, the validation of the LCQ in COPD-patients was performed during a randomized controlled trial and this could have influenced the responsiveness and agreement. Ideally, the LCQ should be validated also in an outpatient setting; this could be performed in future research.

The Clinical COPD Questionnaire (CCQ)[2] and the COPD Assessment Test (CAT)[3] are the two most commonly used short COPD specific questionnaires in patients with COPD. Recently, both questionnaires were compared in two studies[9;18] to decide which questionnaire is most valid to use in clinical practice. In these 2 studies, only the discriminative part of the CCQ and the CAT was addressed. The evaluative part of the CCQ and the CAT, the responsiveness and the agreement, was not studied. We think that precisely the evaluative part is important in clinical practice. For measurement of health status in clinical practice it is essential that the CCQ and CAT questionnaire can distinguish stable from changed health status in COPD. Hence, in **Chapter 3** a comparison and validation is described between the CCQ and the CAT. Both questionnaires had similar psychometric properties. The discriminative value, measurement of health status of patients with COPD on individual level and group level at one moment in time, of both the CCQ and CAT was adequate. However, their usefulness in the follow-up of health status, the evaluative value, was limited on the individual level though acceptable on group level. This implies that a good instrument to perform follow-up of health status in individual patients with COPD in clinical practice remains to be established. Nevertheless, both questionnaires, the CAT and the CCQ can be used in clinical research.

An explanation of the limited evaluative value of these health status questionnaires could be the 'response shift phenomena'.[19] This phenomena suggests that underlying processes of appraisal differ across people and over time and can greatly affect how people answer questions on health status questionnaires.[19] One of the assumptions of validation studies is that the impact and the experience of the symptoms or disabilities of patients are stable. However, this assumption is questionable since patients adapt to deteriorations of symptoms or disabilities. Patients with COPD who perceive improvement after 6 weeks of treatment are requested to compare their health status with baseline, but may well have adapted to their disabilities and symptoms and lost memory of their baseline. Their improvement in patient reported outcomes could hence be influenced; response shift may attenuate or exaggerate health status. Consequently,

the evaluative value, agreement and responsiveness, of the disease-specific health status questionnaires would then also be underestimated or overestimated.

Heart failure is a frequent comorbidity in patients with COPD. Health status is reduced in patients with COPD and in patients with heart failure. For the follow-up of health status in patients with both COPD and heart failure, different disease-specific health status questionnaires are used. To examine whether one questionnaire could be used instead of two different disease specific questionnaires, in **Chapter 4** the most conventional disease-specific questionnaires for patients with coexistent COPD and heart failure, i.e. CCQ and Minnesota Living for Heart Failure Questionnaire (MLHF-Q), were compared and validated. In this study, we found that both the CCQ and the MLHF-Q are valid (correlations between the SF-36 and the CCQ and the MLHF-Q were moderate to strong) and reliable (internal consistency showed Cronbach's alfa's >0.7 and test-re-test-reliability showed ICC's ≥ 0.7) for patients with both COPD and HF on the group level. This is favourable for instance in clinical research or validation studies. The CCQ symptom domain did not adequately reflect symptom related health status in patients with coexistent COPD and HF, and the test-retest reliability (ICC 0.42 (0.10;0.66)) and construct validity (CCQ symptom domain with SF-36 pain domain -0.31 (p = 0.02) and SF-36 vitality domain -0.53 ($p < 0.001$)) were both limited. Probably, some symptoms in COPD and HF overlap to some degree, like dyspnea and cough, while other symptoms are rather different, like orthopnea or edema.[20] On the individual level, i.e. in clinical practice, the CCQ and the MLHF-Q were not able to differentiate between a clinically relevant change and measurement error in patients with COPD and HF in this study (the standard error of measurement was larger than the minimal important clinical difference). Ideally, a new questionnaire should be developed with a more complete reflection of combined diseases-specific health status of patients with both COPD and HF.

Summary and discussion part II:

Improvement of health status in patients with COPD

Telemedicine, care provided by electronic communication with timely contacts by a healthcare provider, may serve as an alternative or extension to traditional outpatient visits. Theoretically, a telemedicine model could be a way to prevent delay in treatment for patients with an exacerbation COPD and prevent deterioration of health status compared to traditionally planned outpatient visits. Despite several studies[21-23], the advantage of telemedicine in clinical practice in comparison with usual care is still not clear and the effect of telemedicine on healthcare utilization and health status is still debatable.

In **Chapter 5** a telemedicine model, biweekly phone calls initiated by a healthcare pro-

vider, was evaluated in patients with COPD. Surprisingly, results were opposite to our hypothesis; patients with COPD had more frequent exacerbations and health status deteriorated in the telemedicine group in comparison with the control group (CCQ total score difference between baseline and after 6 months 0.17 ± 0.19, 95%CI -0.21;0.55, $p = 0.38$). In this study we concluded that telemedicine alone, without any form of education, pulmonary rehabilitation or training, had no benefits for patients with COPD at all. This chapter contributes to the mixed picture of the usefulness of current models of telemedicine in COPD. An explanation might be that patients with COPD have rather different ways of coping with their symptoms and functional disabilities. Most patients with COPD consider themselves not as ill, though exacerbations are classified as illness.[11] Confronting patients with COPD with their symptoms and disabilities frequently may even have contributed to a deterioration of health status. Another explanation could be the lack of an educational component in our study. In a large randomized controlled trial[24], known as the Whole System Demonstrator, participants in the intervention group received telehealth care and education/feedback based on clinical measurements and symptom questions, while participants in the control group received usual care. Different telemedicine devices were used. In this study patients of the intervention group in comparison with the control group had significantly less admissions to the hospital (42.9% vs 48.2%, CI95% 0.70;0.97, $p = 0.017$) and less mortality (4.6% vs 8.3%, 0.39;0.75, $p < 0.001$). The main difference between our study and other telemedicine studies[21;22], like the Whole System Demonstrator[24], is the lack of the educational component or rehabilitation program combined with telemedicine. Education and rehabilitation both learn patients with COPD to cope with their symptoms.[11] Hence, it is difficult to distinguish the telemedicine effect from the educational component. Probably the improvement in health status, reduction in exacerbations and mortality were due to the educational component. Recently this hypothesis was confirmed by Pinnock et al 2013.[25] In this study both the intervention and the control group received education. During the trial, only the intervention group had a telemonitoring service, but no effect in health status and exacerbation frequency was found. From this study, it remains unclear whether the improvement in health status was the result of the educational component. Theoretically, an exacerbation COPD leads to an increase in symptoms and is a stressful situation for a patient with COPD. Patients try to tolerate this situation with cognitive and behavioral efforts, however they lack the tools to manage the situation.[26] This leads to deterioration of health status for patients with COPD.

The appointment on-demand system, a system that allows patients to self-refer when they consider a visit to the outpatient clinic is needed, has been investigated in several chronic diseases, i.e. inflammatory bowel disease (IBD) and rheumatoid arthritis (RA).[27-30] So far, no studies have examined the effectiveness of an on-demand system in patients with COPD. In **Chapter 6** the effects of an on-demand system in patients with COPD on health status and resource use of primary and secondary care were as-

sessed. Patients in the intervention group were educated to call the pulmonary nurse practitioner when symptoms like cough, dyspnea and sputum increased. The control group received usual care, i.e. fixed outpatients visits pre-planned by the pulmonologist. The on-demand system was comparable in terms of health status (difference of total CCQ score after 24 months -0.20±0.17,95%CI -0.55;0.14, $p = 0.24$). The symptom domain of the CCQ did show a significant and clinically relevant difference after 24 months in favor of the on-demand group (-0.4, $p < 0.04$), with a similar tendency for the SGRQ. Patients in the on-demand-group visited the GP significantly less ($p < 0.01$), but as per design did visit the pulmonary nurse practitioner more. Visits to pulmonologists and exacerbations were equally frequent in both groups. A cost-saving tendency from both the healthcare provider and healthcare insurance perspective was found in favor of the on-demand group. In conclusion, the on-demand system can be safely and cost-effectively applied in patients with COPD.
In contrast to the telemedicine model, the on-demand system gives patients the opportunity to contact healthcare providers when medical attention seemed needed, in our hands leading to more stable health status and improvement of the symptom-related health status. We believe that the on-demand-system is a viable option giving some degree of control to patients while alleviating the health care burden in the COPD outpatient care setting. However, these results were based on a pilot study since an on-demand-system in patients with COPD was not examined previously. The experiments described in the second part of this thesis are isolated interventions. In future studies multiple interventions need to be studied together and a larger trial should be performed to draw more definitive conclusions.

Chronic cough and sputum production are common symptoms in patients with COPD.[31] These symptoms are associated with progressive lung function loss, more exacerbations and more hospitalizations[13] leading to deterioration of health status. Despite optimization of inhalation medication, the exacerbation rate per year remains high.[32] An addition to the regular therapy could be prophylactic macrolides, azithromycin. Several studies have demonstrated that macrolides reduce the exacerbation frequency in patients with COPD.[33-35] The effect of macrolides on cough-specific health status on patients with COPD was never evaluated. Therefore we assessed the effects of prophylactic azithromycin, 250mg 3 times a week for 3 months, in patients with COPD and chronic productive cough in **Chapter 7**. Azithromycin improved cough-specific health status (LCQ) as primary outcome and disease-specific health status (Saint George's Respiratory Questionnaire), and generic health status (Short Form-36) as secondary outcomes, compared to placebo. Additionally a strong tendency for a reduction in number of exacerbations was found. Adverse events were similar in both groups, indicating that azithromycin was well tolerated. Remarkably, only the patients with large baseline impairments in cough specific health status benefitted from the prophylactic azithromycin in comparison with the control group, the benefit being visible not only in the LCQ but also in a reduction of exacerbations. The LCQ might therefore be useful to

select patients who will benefit from maintenance macrolide treatment.
By itself, it is notable that patients with COPD and presenting with chronic cough to a specific cough outpatient clinic can still have near normal scores on the LCQ. Perhaps, patients with COPD and chronic cough are more heterogeneous than expected. For instance since chronic cough with persistent diurnal symptoms might have a larger impact on activities of daily life than morning cough or incidental cough.[36]

Future perspectives for measurement and improvement of health status in patients with COPD

All questionnaires, and hence COPD-specific questionnaires should be validated for the specific population and setting before these questionnaires can be used in clinical practice.[4;37] In other words, a health status questionnaire is not valid by itself, it is valid in a specific population.[4] So, when a health status questionnaire is used in clinical practice, a patient must be comparable with the patient population in which the questionnaire was validated.[4] Patients with stable COPD are not comparable to those who recently had an exacerbation or a pulmonary rehabilitation program. Similarly, most likely, diverse settings of care make a difference, for instance the outpatient clinic, or in hospital.
A clinician has to be aware of the validity, reliability and responsiveness of a health status questionnaire in a specific population and situation. In this thesis, COPD-specific questionnaires, the Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT), were validated in the outpatient clinic setting, in patients with stable COPD. The evaluative value of the CCQ and the CAT in the outpatient clinic was not examined previously. Our findings suggest that the evaluative value of the CCQ and the CAT in stable patients with COPD is limited on individual level. On the contrary the discriminative value of the CAT and the CCQ was sufficient on the individual level. This implies that the CCQ and the CAT can be used in the outpatient clinic to determine COPD-specific health status at one moment in time in patients with COPD. However, the value of follow up (monitoring) of patients with COPD using the CCQ and the CAT is limited because the CAT and the CCQ are not able to differentiate between real changes over time and measurement error. Since our sample size was small, we do recommend assessing the evaluative value of the CCQ and CAT again in a larger sample size.
The generic health status questionnaire Short Form 36 (SF-36) has been validated in different populations and different situations. Unfortunately, the use of a generic health status questionnaire instead of COPD-specific health status questionnaires in the outpatient clinic in stable patients with COPD is also not without caveats. Many generic health status questionnaires are not short and practical to use in the outpatient clinic. Another disadvantage of use of a generic health status questionnaire in patients with COPD is that the validity is more limited in comparison with a COPD-specific health status questionnaire: a lower health status score measured with a generic health

status questionnaire does not mean that the diminished health status is COPD-related. Ideally, health status should be measured in the outpatient clinic with the best valid, reliable and responsive COPD-specific health status questionnaire for all different patients with COPD; with or without comorbidities, and with different phenotypes. In clinical practice using such divers health status questionnaires would be quite impracticable. A solution could be that one short and commonly used COPD-specific questionnaire, i.e. CCQ or CAT, be used in all different COPD phenotypes. This would, however necessitate that the validity, reliability and responsiveness are known in different settings and in different phenotypes, which unfortunately is the case only to a certain degree.
Additionally, clinicians would need to be able to interpret the results in the light of the above settings and phenotypes. Detailed information about management strategies and prospective algorithms are, however, not readily available and certainly not mentioned in the GOLD guidelines.[1] Secondly, the minimal clinical important difference (MCID) of the CCQ mental, functional and symptom domain have not been well established yet.[38] The latter makes it difficult to give individually tailored advices based on health status measurement because no treatment algorithm for clinical practice exists yet. This question is further pursued in two ongoing studies.[39;40] Kocks et al[40] hypothesized that a treatment algorithm based on health status measurement (the CCQ) should improve health status and other COPD-related outcomes, i.e. exacerbation frequency and health care utilization compared to usual care, the so-called MARCH-study, that wil give more clarity about the implementation of health status measurement in usual care. Another study that assesses the implementation of health status in clinical practice is the study of Slok et al.[39] This study[39] developed the Assessment of Burden of COPD (ABC) tool. This new ABC-tool is a patient-centred model, based on health status (CCQ), smoking status, exacerbation history, dyspnoea, body mass index (BMI), lung function and physical activity that facilitate shared decision making for healthcare provider and patient. This could theoretically lead to an individualized treatment plan and a treatment algorithm in clinical practice.
Another issue is the 'response shift phenomena' mentioned in the discussion section of chapter 3, which influences and can underestimate or overestimate the evaluative value of the COPD-specific health status questionnaires. This could be solved with a 'pre-test' (pre health status questionnaire) and 'post-test' (post health status questionnaire).[41] Patients complete a 'baseline questionnaire' at baseline and at the end of the study together with the 'final-questionnaires'. At the end of the study patients should try to memorize their symptoms and complaints at baseline. The difference between these two baseline questionnaires (one at baseline and one at the end of the study) gives an indication whether there is a 'response shift phenomena' and the magnitude of its effect. The latter can be used in larger validation studies.
In essence, a simple tool is needed to monitor the impact of the disease in individual patients that can be used to direct clinical decisions. Ideally, such a tool would make transfer of care feasible, from the doctor to the nurse to the patient or from the hospital to the home setting. The CCQ and the CAT appear promising as such elementary

tools, but the evaluative characteristics of both questionnaires in individual patients need further studies.

This thesis contains studies performed in a specialist setting. We believe that most patients with COPD can be successfully managed in primary care, but surely it would be of great interest to investigate whether better cooperation between primary and secondary care, preferably with use of a common health status assessment, could lead to better care and lower costs in patients with COPD.

It is quite possible that a primary care physician is far more appropriate than a pulmonologist to manage patients with COPD, even with advanced disease. It is however, important to realize that from several studies[42;43] it has become clear that a patient with only COPD is rare. Vanfleteren et al[44] reported that as many as 97% of patients with COPD had at least one additional comorbid condition. I postulate that perhaps, because of a more holistic approach, managing COPD and comorbidity may be more intuitive for a generalist than for a specialist. Alternatively, there may a need for pulmonologists with a subspecialisation in chronic conditions in the future. It will be a challenge to measure disease specific health status in patients with COPD and one or more other comorbidities. By whoever provided the best, patients deserve focussed, individualised care with emphasis on health status and a keen eye for all morbidities.

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Chapter 9

Nederlandse samenvatting voor niet ingewijden

Dankwoord

Curriculum Vitae

List of publications

Dit proefschrift staat, zoals zo vele proefschriften redelijk vol met jargon en begrippen die voor niet ingewijden wellicht vertroebelend werken bij het lezen.
Daarom volgt in deze samenvatting eerst een uitleg van een aantal belangrijke begrippen. Daarna volgen een samenvatting op hoofdlijnen van de eigenlijk resultaten.

Begrippen

Chronic Obstructive Pulmonary Disease (COPD)
COPD is een te voorkomen en behandelbare aandoening. De pulmonale component wordt gekenmerkt door luchtwegobstructie die niet geheel reversibel is. Deze luchtwegobstructie is meestal progressief en geassocieerd met een abnormale ontstekingsreactie van de long op schadelijke prikkels of gassen. De ernst van de aandoening wordt mede bepaald door de eventuele aanwezigheid van extrapulmonale effecten.[1]

Gezondheidstoestand (health status)
Gezondheidstoestand is het meest omvattende woord in het Nederlands voor health status. Hiermee wordt bedoeld de gezondheid zoals ervaren door personen zelf, beïnvloed door eigen gevoel en/of vooroordelen.[2]

Generieke vragenlijst
Generieke vragenlijsten zijn bruikbaar bij verschillende ziekten en bij de algemene populatie. Met deze vragenlijsten is het dus mogelijk om de invloed op de gezondheidstoestand van verschillende ziekten met elkaar te vergelijken. Het nadeel van generieke vragenlijsten is dat ze niet ingaan op specifieke problemen van een bepaalde ziekte en dat ze ook de invloed meten van andere ziekten wanneer iemand meerdere ziekten heeft.[3]

Ziektespecifieke vragenlijst
Ziektespecifieke vragenlijsten zijn speciaal ontwikkeld voor een bepaalde ziekte of aandoening, in dit promotieonderzoek COPD. Deze vragenlijsten zijn gevoeliger dan generieke vragenlijsten en hiermee is de kans veel groter dat klinisch belangrijke veranderingen gemeten kunnen worden. Het nadeel is dat er met ziekte specifieke vragenlijsten geen direct vergelijk tussen verschillende ziekten gemaakt kan worden.[3]

Validiteit
Valide waarnemingen geven (gemiddeld) juiste uitkomsten. Uitkomsten zijn onjuist als zij bijvoorbeeld systematisch een te hoge of te lage waarde hebben, of als zij een andere eigenschap meten dan die welke was bedoeld. Bij onderzoek in een steekproef wordt de validiteit o.a. bepaald door een correcte manier van steekproeftrekking.
Voorbeeld: Een klok die achterloopt, geeft geen valide tijdmeting. Een thermometer moet goed geijkt zijn om valide waarnemingen te geven. Een pH-meter die tempera-

tuurgevoelig is, meet behalve de zuurgraad ook (een beetje) de temperatuur en geeft dus niet altijd valide uitkomsten. Wie een Nederlandstalige intelligentietest afneemt bij een Amerikaan, meet geen intelligentie maar taalkennis. Bij enquêtes wordt de validiteit vooral bepaald door een juiste en concrete vraagstelling. Op de vraag: "Wat vind je van dit TV-programma?" komen geen valide antwoorden, omdat niet wordt gepreciseerd welke aspecten zijn bedoeld: amusementswaarde, informatiegehalte, vormgeving, of nog iets anders.[4]

Betrouwbaarheid
Betrouwbaar zijn waarnemingen, die onder dezelfde omstandigheden herhaald, dezelfde uitkomst geven. Betrouwbare uitkomsten hebben weinig spreiding. De steekproefomvang bepaalt mede de betrouwbaarheid van een uitkomst.
Voorbeeld: Een pH-meter met een sterk fluctuerende millivoltmeter geeft onbetrouwbare uitkomsten. Een enquête geeft een onbetrouwbaar beeld van de levende opinies, als de steekproef klein is. Vooral als de meningen in de bevolking over het onderwerp van de enquête sterk uiteenlopen, zullen verschillende kleine steekproeven zeer uiteenlopende resultaten opleveren.[4]

Responsiviteit
Hiermee wordt bedoeld of een meetinstrument in staat is om veranderingen (bijvoorbeeld in de gezondheidstatus) aan te tonen.[5]

Achtergrond

Gedurende decennia worden patiënten met COPD vervolgd middels objectieve metingen zoals longfunctieonderzoek. In eerdere studies[6] wordt echter beschreven dat de impact van COPD als ziekte op de patiënt niet kan worden ingeschat met alleen een spirometrie. Een completer beeld van de ernst en impact van COPD en een risicoinschatting kan worden verkregen door ook de gezondheidstoestand te beoordelen en het aantal exacerbaties in het voorafgaande jaar te monitoren. Met een exacerbatie wordt een longaanval bedoeld, een toename van de ernst van de klachten die meer is dan de gemiddelde dagelijkse variatie. Patiënten met COPD worden in het dagelijks leven sterk beïnvloed door hun chronische ziekte. Het verbeteren van de gezondheidstoestand bij COPD patiënten is daarom een belangrijk behandeldoel volgens de internationale richtlijnen.[6] In dit promotieonderzoek zijn verschillende uiteenlopende manieren onderzocht om dit behandeldoel te bereiken. De verschillende manieren bestonden uit onderhoudsantibiotica en optimalisering van poliklinische bezoeken. Om dit verantwoord te doen, is eerst uitgebreid gekeken naar de meetkenmerken van enkele veel gebruikte meetinstrumenten, ziektespecifieke vragenlijsten, om gericht de gezondheidstoestand te kunnen meten bij patiënten met COPD.

Dit proefschrift bestaat uit 2 delen.

Deel I: hierin werd onderzocht welk meetinstrument (vragenlijst) voor de gezondheidstoestand het best kan worden gebruikt bij welke patiënten met COPD.
Deel II: in dit deel werd gekeken of de gezondheidstoestand bij patiënten met COPD kan worden verbeterd.

Samenvatting Deel I: Het meten van gezondheidstoestand bij patiënten met COPD

Chronisch productief hoesten komt frequent voor bij patiënten met COPD en is geassocieerd met een slechtere prognose en gezondheidstoestand.[7] Er was nog geen vragenlijst bekend die de hoest-specifieke gezondheidstoestand kon meten bij patiënten met COPD waarbij chronische productieve hoest op de voorgrond staat. Een gevalideerd meetinstrument om de invloed van hoest op gezondheidstoestand bij patiënten met COPD te meten is el van groot belang. De Leicester Cough Questionnaire (LCQ)[8] is een gevalideerde hoest-specifieke vragenlijst bij patiënten met chronische hoest in een algemene populatie. In **Hoofdstuk 2** tonen we aan dat de LCQ een valide, precieze en responsieve vragenlijst te zijn om de gezondheidstoestand te meten bij patiënten met COPD met chronische productieve hoest in een klinisch onderzoek.

In **Hoofdstuk 3** werd onderzocht welke vragenlijst het meest geschikt is voor het monitoren van gezondheidstoestand tijdens poliklinische follow-up van patiënten met COPD. Voor het meten van de COPD-specifieke gezondheidstoestand bij klinisch onderzoek wordt wereldwijd vaak de St. George's Respiratory Questionnaire (SGRQ)[9] gebruikt. Dit is echter een lange vragenlijst van 51 vragen, die daarom belastend is voor de patiënt. Ook is het afnemen van de SGRQ erg tijdrovend tijdens een regulier poliklinisch bezoek.[10] De laatste jaren zijn er twee korte vragenlijsten gevalideerd om de COPD-specifieke gezondheidstoestand te meten, de Clinical COPD Questionnaire (CCQ) en de COPD Assessment Test (CAT).[11;12] Deze vragenlijsten zijn gevalideerd in verschillende studies.[10;13;14] Tijdens de validatie werd met name gekeken naar de validiteit van de vragenlijst. De betrouwbaarheid en de responsiviteit van de vragenlijst blijven vaak onderbelicht terwijl deze klinimetrische eigenschappen juist belangrijk zijn bij de follow-up van patiënten met COPD. Het is namelijk belangrijk dat er onderscheid gemaakt kan worden tussen een 'echte' verandering en een meetfout. De betrouwbaarheid en de responsiviteit van beide COPD-specifieke vragenlijsten, de CCQ en de CAT, blijken in dit hoofdstuk beperkt te zijn.

Wereldwijd wordt een geleidelijke toename van het aantal patiënten met hartfalen, COPD of een combinatie van beide ziektebeelden gezien.[15] Op dit moment wordt de

gezondheidstoestand bij patiënten met zowel hartfalen als COPD met afzonderlijke vragenlijsten gemeten. Bij patiënten met hartfalen wordt de ziekte-specifieke gezondheidstoestand gemonitord met de Minnesota living with Heart Failure Questionnaire (MLHF-Q).[16] Voor patiënten met COPD wordt in Nederland vaak de CCQ gebruikt.[11;17] In **Hoofdstuk 4** werden de psychometrische eigenschappen (validiteit en betrouwbaarheid) van beide vragenlijsten bij patiënten met zowel COPD als hartfalen vergeleken. In dit hoofdstuk blijkt dat zowel de CCQ als de MLHF-Q beiden hun beperkingen hebben voor de follow-up van patiënten met zowel COPD als hartfalen. Met name het domein 'symptomen' van de CCQ geeft geen optimale reflectie van de gezondheidstoestand bij patiënten met COPD én hartfalen. Idealiter zou er een nieuwe vragenlijst moeten worden ontworpen die een completere gezondheidstoestand weergeeft van de symptomen die passen bij patiënten met zowel COPD als hartfalen.

Samenvatting Deel II: Het verbeteren van gezondheidstoestand bij COPD-patiënten.

Het onvoorspelbare beloop van COPD met een afwisselende periode van een stabiele ziekte en exacerbaties[18] maakt het moeilijk om op het juiste moment, wanneer een patiënt met COPD zorg nodig heeft, een poliklinische afspraak bij de longarts in te plannen. Door de symptomen van patiënten met COPD om de 2 weken te monitoren door middel van telefonisch contact via een gespecialiseerde longverpleegkundige, telemedicine, is de verwachting dat verslechtering van symptomen vroegtijdig opgespoord kunnen worden. Hierdoor kan dan vervolgens direct en op het juiste moment een poliklinische afspraak bijvoorbeeld bij de longarts worden gemaakt en tijdig behandeling voor een exacerbatie worden gestart. Door op deze manier exacerbaties te voorkomen zal theoretisch gezien ook de gezondheidstoestand verbeteren.[19] In **Hoofdstuk 5** laten we zien dat telemedicine zonder enige vorm van educatie of longrevalidatie juist een negatief effect heeft op de gezondheidstoestand en zorgconsumptie zowel in de 1e als de 2e lijn van de gezondheidszorg. Mogelijk kan dit worden verklaard doordat patiënten met COPD zichzelf als 'niet-ziek' bestempelen als de COPD stabiel is. Pas tijdens een exacerbatie vinden patiënten met COPD dat ze 'ziek' zijn.[20] Bij onze vorm van telemedicine werd een patiënt om de week gebeld en wordt een patiënt dus om de week herinnerd aan het feit dat er sprake is van een chronische ziekte en de symptomen daarvan wat kan leiden tot de gevonden verslechtering van de gezondheidstoestand.

Het vervolg onderzoek op hoofdstuk 5 werd daarom een on-demand-systeem. Hierbij initieert de patiënt een poliklinische afspraak bij de longarts op het moment dat de patiënt toename van symptomen ervaart, een poliklinische afspraak 'on-demand'. In een eerdere studie lijkt dit te kunnen voor zorgen dat een exacerbatie tijdig wordt behandeld en ziekenhuisopname en verslechtering van de gezondheidstoestand worden

voorkomen.[19] Daarmee zou dit ook kunnen zorgen voor afname van onnodige zorgconsumptie (poliklinische afspraken en exacerbaties bij longarts en huisarts). In de huidige literatuur is hier zeer weinig over bekend, en met name is dit nog niet eerder onderzocht bij patiënten met COPD. Onze pilot studie, **Hoofdstuk 6**, laat zien dat een on-demand systeem het symptoom domein van de gezondheidstoestand van patiënten met COPD verbetert, en een trend heeft om de zorgconsumptie in de 1e en 2e lijn te verlagen en de kosteneffectiviteit te verhogen.

Chronische hoest en sputumproductie, chronische bronchitis genoemd, is een veelvoorkomende klacht van patiënten met COPD.[21] Het is geassocieerd met een sneller verlies van longfunctie en frequentere exacerbaties.[7] Hierdoor leidt het tot een slechtere gezondheidstoestand.[19] Een recente grote studie heeft aangetoond dat het aantal exacerbaties bij patiënten met COPD afneemt bij het gebruik van azitromycine onderhoud naast optimale inhalatiemedicatie.[22] De hoest-specifieke gezondheidstoestand bij patiënten met COPD is niet eerder onderzocht, terwijl juist hoest het dagelijks leven van patiënten met COPD negatief beïnvloedt en beperkt. In **Hoofdstuk 7** werd aangetoond dat profylactische azitromycine leidt tot een verbetering van de hoest-specifieke gezondheidstoestand bij patiënten met COPD met chronische bronchitis.

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Curriculum Vitae

The author of this thesis was born in Zeist, the Netherlands, on the 29th of May 1982. In 1994 she attended the Montessori Lyceum Herman Jordan in Zeist where she graduated (Athenaeum) in 2000. In 2000 she started Biology at the University of Utrecht and obtained her propedeutical exam in 2001. This stimulated her interest for research. Subsequently she studied Medicine at the University Medical Centre of Utrecht. In 2008 she graduated and started working as a resident in the Antonius Hospital, location Utrecht. During her shift at the department of pulmonary diseases she discovered that she preferred a combination of research and clinical practice. From 2009 to 2010 she started as a research resident in the Isala Hospital in Zwolle. Her first project was the validation of the Leicester Cough Questionnaire in COPD patients with chronic cough; this would be the start of her PhD program. In 2010 she started her specialisation of pulmonology and continued the PhD program of measurement and improvement of health status in patients with COPD; the results are presented in this thesis. In 2014 she switched her career to a more broad-spectrum, family medicine.
She is engaged to Pelle van Waes and they have a daughter, Hannelore.

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