Does Quality of Life of COPD Patients as Measured by the Generic EuroQol Five-Dimension Questionnaire Differentiate Between COPD Severity Stages?*

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Objective: **To assess the discriminative properties of the EuroQol five-dimension questionnaire (EQ-5D) with respect to COPD severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria in a large multinational study.**

Methods: **Baseline EQ-5D visual analog scale (VAS) scores, EQ-5D utility scores, and St. George Respiratory Questionnaire scores were obtained from a subset of patients in the Understanding the Potential Long-term Impact on Function with Tiotropium trial, which was a 4-year placebo-controlled trial designed to assess the effect of tiotropium on the rate of decline in FEV_1 in COPD patients aged ≥ 40 years, an FEV_1 of < 70% predicted, an FEV_1/FVC ratio of ≤ 70%, and a smoking history of ≥ 10 pack-years.**

Results: **A total of 1,235 patients (mean post bronchodilator FEV_1, 48.8% predicted) from 13 countries completed the EQ-5D. The EQ-5D VAS and utility scores differed significantly among patients in GOLD stages 2, 3, and 4, also after correction for age, sex, smoking, body mass index (BMI), and comorbidity ($p < 0.001$). The mean EQ-5D VAS scores for patients in GOLD stages 2, 3, and 4 were 68 (SD, 16), 62 (SD, 17), and 58 (SD, 16), respectively. The mean utility scores were 0.79 (SD, 0.20) for patients in GOLD stage 2, 0.75 (SD, 0.21) for patients in GOLD stage 3, and 0.65 (SD, 0.23) for patients in GOLD stage 4. Effect sizes for the difference in utility scores between patients in GOLD stages 3 and 4 were more than twice as high as those for the difference between patients in GOLD stages 2 and 3. Gender, postbronchodilator FEV_1 percent predicted, the number of hospital admissions and emergency department visits in the year prior to baseline measurements, measures of comorbidity, and BMI were independently associated with EQ-5D utility. EQ-5D utility scores also differed between patients from different countries. French patients especially had lower utility scores than US patients. Utility scores calculated with the US value set were on average 5% higher than those calculated with the UK value set.**

Conclusions: **Increasing severity of COPD was associated with a significant decline in EQ-5D VAS scores and utility scores. These results demonstrate that a generic instrument can assess COPD impact on quality of life and that the scores discriminate between patient groups of known severity. These utility scores will be useful in cost-effectiveness assessments.**

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Key words: COPD; disease severity; EuroQol five-dimension questionnaire; Global Initiative for Chronic Obstructive Lung Disease; health status; quality of life; utility

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; BMI = body mass index; ED = emergency department; EQ-5D = EuroQol five-dimension questionnaire; GOLD = Global Initiative for Chronic Obstructive Lung Disease; QALY = quality adjusted life year; SGRQ = St. George Respiratory Questionnaire; TTO = time-tradeoff; UPLIFT = Understanding the Potential Long-term Impact on Function with Tiotropium; VAS = visual analog scale

An increasing number of treatments and interventions for COPD have been and will be subjected to cost-effectiveness studies to provide information for priority setting by health-care decision makers. In many European, North American, and other countries, reimbursement authorities and academic bodies have issued methodological guidelines for conducting cost-effectiveness studies. These guidelines advocate the use of quality-adjusted life-years (QALYs) in addition to clinical outcomes.[1–4] QALYs are calculated as the sum of the products of time spent in certain health states and the utility scores of these health states. Utility scores are the valuations of health states that are anchored on a numeric scale ranging from death (0) to perfect health (1). In Europe, the EuroQol five-dimension questionnaire (EQ-5D) is the instrument that is the most widely used for generating these utility scores,[5] and many countries, including the United States, have published their own set of population-based EQ-5D weights to perform the valuation.[5,6]

The cost-effectiveness of several COPD interventions has been assessed using cost per QALY ratios,[7–14] and some of these have used the EQ-5D to obtain the utility scores.[8,13] Most of these interventions directly affect outcomes, like exacerbation and hospitalization rates, that have been shown to influence survival, as a result of which their potential impact in terms of QALYs is large. The gain in QALYs resulting from COPD treatments that merely affect the quality of life of patients may only become apparent when the time horizon of the economic analysis is fairly long, in many instances even lifelong. This makes necessary an extension of the time horizon that is well beyond that of most clinical trials. This is one of the reasons why economic models are extensively used in cost-effectiveness assessments, especially those of chronic diseases. Several models estimating the cost-effectiveness of COPD interventions have been published.[14–17] All of these models are so-called *state transition* models (or Markov models) that simulate the progression of COPD over different stages of disease severity. These models also have in common that they define COPD severity in terms of FEV_1 percent predicted and estimate QALYs by assigning EQ-5D utility scores[14,16,17] or other utility scores[15] to these COPD severity stages. Hence, it is important to study the ability of the EQ-5D to discriminate between different stages of COPD severity. Since the EQ-5D is a generic health-related quality-of-life instrument that captures the impact of comorbidity and other factors on quality of life, the aim of the current analyses is to estimate the association between EQ-5D and disease severity independent of comorbidity and other factors known, or expected, to be related to quality of life. Its ability to discriminate is compared to that of a disease-specific quality-of-life instrument, the St. George Respiratory Questionnaire (SGRQ). No such study has been conducted previously in such a large multinational group of physician-diagnosed COPD patients with a wide range of lung function impairment as the subgroup of patients from the Understanding the Potential Long-term Impact on Function with Tiotropium (UPLIFT) trial[18] that were studied here. This multinational group of patients allowed us to address the association between the country of recruitment and COPD utility. It also allowed us to study whether the ability of the EQ-5D to discriminate between COPD severity stages depends on the value set that is used to generate the utility scores.

Materials and Methods

Setting and Patients

This study used data from a subset of 1,235 patients from 13 countries who completed the EQ-5D at baseline of the UPLIFT trial.[18] Because the EQ-5D was added via protocol amendment more than midway through the recruitment period, only the last 1,235 patients of those countries with significant enrollment remaining could be included in this study. Patients were enrolled sequentially from the time of ethics committee approval of the protocol amendment in each particular country until the enrollment completion of the UPLIFT trial.[18] The UPLIFT trial is a 4-year randomized, double-blind, placebo-controlled, parallel-group trial that was designed to determine whether tiotropium reduces the rate of decline in FEV_1 over time. It includes approximately 6,000 COPD patients (postbronchodilator FEV_1, $< 70\%$ predicted; FEV_1/FVC ratio, $\leq 70\%$); age, ≥ 40 years; cigarette smoking history of at least 10 pack-years).[18] The EQ-5D and SGRQ were completed at the randomization visit prior to spirometry and prior to the start of the administration of the study medication.

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Besides age, gender, and information on smoking, patient characteristics included the duration of diagnosed COPD in years, body mass index (BMI), self-reported COPD-related health-care utilization prior to baseline, the presence or absence of home oxygen use, and concomitant diagnoses. Smoking was expressed as self-reported current smoking status (smoking or ex-smoking) and smoking history in terms of the number of pack-years. BMI was calculated as weight (in kilograms) divided by the height squared (in meters). COPD-related health-care utilization was measured as the number of emergency department (ED) visits resulting in hospital admission, the number of ED visits not resulting in hospital admission, the number of direct hospital admissions, the number of unscheduled urgent visits to physicians, and the number of scheduled visits to physicians in the year prior to enrollment. Comorbidity was expressed as the presence of any current concomitant diagnosis, the number of concomitant diagnoses, and the Charlson index score.[19] The Charlson index contains 19 conditions. Each condition has an associated weight ranging from 1 to 6; the higher the score, the more severe the condition. The score on the Carlson index is calculated as the sum of weights assigned to each condition that a patient has. Concomitant diagnoses were also grouped by 25 system organ classes, which were further collapsed into 10 "medical system" groups to reduce the number of variables in the analyses.

EQ-5D

The EQ-5D is a self-administered, generic, health-related quality-of-life questionnaire that contains two sections, a descriptive section and a valuation section.[20,21] The descriptive section is a health status classification instrument with the following five dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Each dimension is divided into the following three levels of functioning: no problems; some problems; and extreme problems. Respondents are asked to describe their health status by ticking off one level of functioning for each of the five dimensions. In the second section, respondents are asked to value their overall health status on a visual analog scale (VAS). This VAS is a simple rating scale ranging from 0 (defined as the worst imaginable health state) to 100 (defined as the best imaginable health state). Using a set of weights (*ie*, the value set), the descriptive information on health status can be converted into a single aggregate utility on a scale anchored at 1, which represents perfect health, and 0, which represents death. A number of countries have published their own value sets[5]; in the primary analysis, we employed the most widely used value set, known as the "MVH A1 value set," which was developed in the United Kingdom in the Measurement and Valuation of Health study.[22] This set of utility weights was chosen because it is recommended by the EuroQol Group[5] for use in cost-effectiveness/utility studies for comparison with other studies, and because these weights were generated from a large sample of the general public in the United Kingdom using the time-tradeoff (TTO) technique. The TTO is a preference-based method asking the respondent to trade length of life for quality of life. In an alternative analysis, the recently published US value set was used.[6] This US set was obtained in a replication of the Measurement and Valuation of Health study, using the same TTO protocol. There is little evidence on the minimum clinically meaningful difference in EQ-5D score. A recent study,[23] analyzing data from eight studies in 11 different patient groups, reported a mean minimally important difference of 0.074, but there was a wide variation in estimates of the minimally important difference between the studies. In the remainder of this article, *EQ-5D VAS* will be used to indicate the patient valuation on the VAS, *EQ-5D utility* will be used to indicate the utility scores obtained after applying a value set, and *EQ-5D scores* will be used to indicate both.

SGRQ

The SGRQ is a self-administered disease-specific questionnaire that is designed to measure the impact of pulmonary disease on health-related quality of life and well-being. The questionnaire contains 50 items that can be aggregated into an overall score and three subscores for "symptoms," "activity," and "impact." Scores range from 0 to 100, with a lower score representing a better quality of life. A change in score of 4 units is consistent with a clinically relevant change in the patient.[24,25] The SGRQ is the most frequently used quality-of-life questionnaire in patients with COPD, in whom it was reported to be valid, reliable, and responsive to change due to pharmacologic and nonpharmacologic therapy.

Lung Function and COPD Severity

Both pre-bronchodilator therapy and post-bronchodilator therapy FEV_1 values were measured in the morning using calibrated spirometers. After the pre-bronchodilator therapy FEV_1 was measured, four inhalations of 20 μg of ipratropium bromide were administered, followed by four inhalations of 100 μg of salbutamol 60 min later. The post-bronchodilator therapy FEV_1 was obtained 30 min after salbutamol inhalation. The FEV_1 percent predicted was calculated using European Community for Steel and Coal/European Respiratory Society equations.[26] Using the post-bronchodilator therapy FEV_1 percent predicted, patients were classified into categories of moderate COPD (FEV_1, $< 80\%$ and $\geq 50\%$ predicted), severe COPD (FEV_1, $< 50\%$ and $\geq 30\%$ predicted), and very severe COPD (FEV_1, $< 30\%$ predicted), conforming to the boundaries of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2, 3, and 4, respectively.[27]

Statistical Analysis

Differences in patient characteristics between GOLD stages were tested using the Pearson χ^2 test for categoric variables, one-way analysis of variance (ANOVA) for continuous variables with normal distributions, and the Kruskal-Wallis test for variables lacking normal distributions. Differences in the percentages of patients reporting any problems vs no problems on the EQ-5D dimensions were tested with the Pearson χ^2 test. To study the presence of ceiling and floor effects in the EQ-5D dimensions, for the EQ-5D VAS, the EQ-5D utility, and the SGRQ total and individual domain scores the proportions of patients having the best possible score (ceiling effect) and the worst possible score (floor effect) were reported.

Discriminative validity is a specific type of construct validity that is defined here as the capacity of the EQ-5D VAS, the EQ-5D utility, and the SGRQ total and domain scores to differentiate between the GOLD stages of COPD severity. First, differences among the three GOLD stages were tested using ANOVA without adjustments for patient characteristics. *Post hoc* tests of the three pairwise differences in severity stage were performed using the Bonferroni correction for multiple testing. Second, multivariate analysis of covariance (ANCOVA) was performed with adjustments for age, gender, current smoking status, smoking history, BMI, and either the number of concomitant diagnoses or the Charlson index of comorbidity.

To assess the magnitude of the difference in scores between the GOLD stages, effect sizes were calculated as the mean

differences between two consecutive GOLD stages divided by the pooled SD. Differences in utility scores calculated with the UK value set and the US value set were assessed using a *t* test.

The association between the number of concomitant diagnoses and EQ-5D scores or SGRQ scores was assessed using ANCOVA with two factors (*ie*, GOLD stage and the presence or absence of any concomitant diagnosis). The same analyses were performed with the number of concomitant diagnoses grouped according to the 25th and 75th percentile, and with the Charlson index grouped by a score of 0, 1, or ≥ 2. Interaction terms were included to study whether the impact of comorbidity on EQ-5D scores was higher in more severely ill COPD patients. To gain further understanding, concomitant diagnoses were grouped by medical system, and differences in EQ-5D scores between patients with or without comorbidity in a certain medical system were tested using *t* tests.

Finally, the association between EQ-5D utility scores and all patient characteristics, known or expected to be related to quality of life, including FEV_1 percent predicted as a continuous variable, health-care utilization, and country of recruitment, was studied with backward, stepwise, multiple linear regression analyses using the EQ-5D utility as the dependent variable. Variables were removed from the regression equation when their p value was > 0.10. It was prespecified that any two patient characteristics that showed an intercorrelation of > 0.4 were not entered into the regression analyses at the same time.[28] Moreover, the collinearity statistics of the independent variables, as measured in terms of tolerance, were checked to prevent high correlations between the variables in the regression model. The tolerance of an independent variable *i* is defined as $1 - Ri^2$, where Ri^2 is the multiple correlation coefficient when the *i*th variable is predicted from the other independent variables. The tolerance can vary between 0 and 1, and should be large, otherwise *i* is almost a linear combination of the other independent variables. The overspecification of the regression models is avoided by using a conservative number of independent variables relative to the number of patients (*ie*, one or two variables per 100 patients), depending on the model. All analyses were performed using a statistical software package (SPSS, version 12; SPSS; Chicago, IL).

Results

Table 1 shows the characteristics of the 1,235 patients included in the study. The mean duration of COPD was approximately 10 years. Thirty-four percent were active smokers. The mean smoking history was approximately 48 pack-years. Most patients (85.7%) had comorbidity. The median number of concomitant diagnoses per patient was three. Patients most frequently experienced vascular disor-

Table 1—*Patient Characteristics at Baseline for the Subset of Patients in this Study and All Patients in the UPLIFT Trial**

Characteristics	Patients Included in This Study (n = 1,235)	All Patients Included in the UPLIFT Trial (n = 5,993)
Male gender, No.	902 (73.0%)	4474 (74.7%)
Age, yr	64.5 (8.4)	64.5 (8.5)
Current smokers, No.	423 (34.3%)	1826 (30.5%)
Smoking history, pack-yr	48.1 (27.8)	48.7 (27.9)
Duration of COPD, yr	10.7 (9.6)	10.0 (8.4)
FEV_1		
Pre-bronchodilator therapy		
L	1.15 (0.40)	1.10 (0.40)
% predicted	40.79 (11.91)	39.34 (12.02)
Post-bronchodilator therapy		
L	1.38 (0.44)	1.32 (0.44)
% predicted	48.77 (12.19)	47.56 (12.78)
BMI	26.8 (5.1)	26.0 (5.1)
Patients with concomitant diagnoses, No.	1058 (85.7%)	4932 (82.3%)
Concomitant diagnoses per patient, No.	4.1 (4.1)	3.5 (3.7)
Patients using home oxygen, No.	67 (5.4%)	287 (4.8%)
ED visits not resulting in hospital admission†	0.13 (0.51)	0.18 (0.93)
ED visits resulting in hospital admission†	0.15 (0.56)	0.16 (0.55)
Direct hospital admissions†	0.06 (0.31)	0.09 (0.41)
Unscheduled urgent physician visits†	0.52 (1.17)	0.61 (1.39)
Scheduled physician visits†	3.07 (3.00)	3.71 (3.62)
EQ-5D		
VAS score	64.84 (16.41)	NA
Utility score	0.76 (0.21)	NA
SGRQ		
Total score	45.00 (16.98)	45.98 (17.12)
Symptoms score	49.71 (23.15)	50.24 (22.48)
Activities score	60.68 (19.23)	61.65 (19.50)
Impact score	34.52 (19.11)	35.65 (19.24)

*Values are given as the mean (SD), unless otherwise indicated. NA = not applicable.
†COPD-related health-care utilization in the year prior to baseline.

ders (48%), musculoskeletal disorders (34%), metabolic disorders (32%), GI disorders (26%), and cardiac disorders (25%). The mean score on the Charlson index of comorbidity was 0.51, and the median score was 0. The average BMI was in the normal range, and 3.2% of the patients had a BMI < 18.5. In the year before the baseline measurements were made, 3.7% of patients were hospitalized for COPD at least once, 8.8% of patients had one or more COPD-related ED visits, and 26.5% of patients had one or more unscheduled urgent visits to a physician. The majority of patients were living in the United States (34.5%), followed by the Czech Republic (17.5%), Spain (11.9%), Denmark (8.4%), Germany (4.9%), Poland (4.8%), the Netherlands (4.4%), Italy (4.4%), France (3.1%), Hungary (2.5%), the Russian Federation (1.5%), Belgium (1.4%), and Australia (0.8%). Table 1 also shows that the subset of patients in this study did not differ systematically from the total patient population in the UPLIFT trial.[18]

Table 2 shows patient characteristics grouped by GOLD severity stage. A total of 50.7% of patients had stage 2 COPD, 41.8% of patients had stage 3 COPD, and 7.4% of patients had stage 4 COPD. GOLD stages were comparable with respect to the gender distribution, the number of pack-years smoked, and the duration of COPD, but they differed significantly with respect to age, percentage of current smokers, BMI, and health-care utilization in the year prior to the study. Patients in GOLD stage 4 were younger, had a lower BMI, and a higher number of ED visits resulting in COPD-related hospital admission, and a higher proportion of them were using home oxygen than those in stages 2 and 3. There were more current smokers who were in GOLD stage 2 and 4 than were in stage 3. The frequency of unscheduled urgent visits among patients in GOLD stage 3 and 4 was higher than for those in stage 2. Also, the other indicators of health-care utilization and the number of concomitant diagnoses tended to increase as COPD severity increased. However, the Charlson index and the comorbidity profile that resulted from grouping concomitant diagnoses by medical system did not differ significantly between patients in different GOLD stages of COPD (data on comorbidity profile not shown).

Figure 1 shows that the percentage of patients reporting any problems on the EQ-5D dimensions of mobility, self-care, and usual activities increased with increased COPD severity. Differences on the dimensions pain/discomfort and anxiety/depression were not statistically significant, although the percentage of patients reporting problems on these dimensions was higher for patients in GOLD stage 4 than for patients in GOLD stages 2 and 3.

There are indications of a ceiling effect on the EQ-5D utility scale, since the percentage of patients with the best possible EQ-5D utility was 22.9%, whereas it was only 1.1% on the EQ-5D VAS, 0.2% on the SGRQ total score, 1.1% on the SGRQ symptom score, 0.7% on the SGRQ activity score, and 1% on the SGRQ impact score. The percentage of patients with the best possible EQ-5D utility of 1 decreased from 27.8% among patients in GOLD

Table 2—*Patient Characteristics by GOLD Stage

Characteristics	Moderate (n = 622)	Severe (n = 513)	Very Severe (n = 91)	p Value†
Male gender, No.	444 (71.4%)	383 (74.7%)	69 (75.8%)	0.385‡
Age, yr	64.0 (8.4)	65.6 (8.2)	61.6 (8.4)	< 0.001§
Current smokers, No.	231 (37.1)	153 (29.8)	33 (36.3)	0.03‡
Smoking history, pack-yr	47.6 (25.7)	48.1 (29.1)	51.2 (34.1)	0.507§
Duration of COPD, yr	11.0 (10.1)	10.7 (9.5)	9.6 (6.0)	0.449§
BMI	27.0 (5.0)	26.9 (5.1)	24.4 (5.0)	< 0.001§
Concomitant diagnoses, No.	4.0 (4.0)	4.1 (3.9)	4.9 (4.7)	0.149‖
Charlson index score	0.50 (0.87)	0.53 (0.85)	0.52 (0.82)	0.821‖
Patients using home oxygen, No.	19 (3.1)	32 (6.3)	15 (16.5)	< 0.001‡
ED visits not resulting in hospital admission¶	0.12 (0.50)	0.14 (0.48)	0.20 (0.69)	0.366‖
ED visits resulting in hospital admission¶	0.11 (0.46)	0.15 (0.54)	0.42 (1.08)	<0.001‖
Direct hospital admissions¶	0.05 (0.27)	0.06 (0.31)	0.12 (0.45)	0.133‖
Unscheduled urgent visits to physician¶	0.43 (1.03)	0.61 (1.33)	0.61 (1.11)	0.039‖
Scheduled physician visits¶	2.88 (2.83)	3.25 (3.16)	3.27 (3.21)	0.097‖

*Values are given as the mean (SD), unless otherwise indicated.
†Tests of whether the three groups are equal.
‡χ^2 test.
§Analysis of variance.
‖Kruskall-Wallis test.
¶COPD-related health-care utilization in the year prior to baseline.

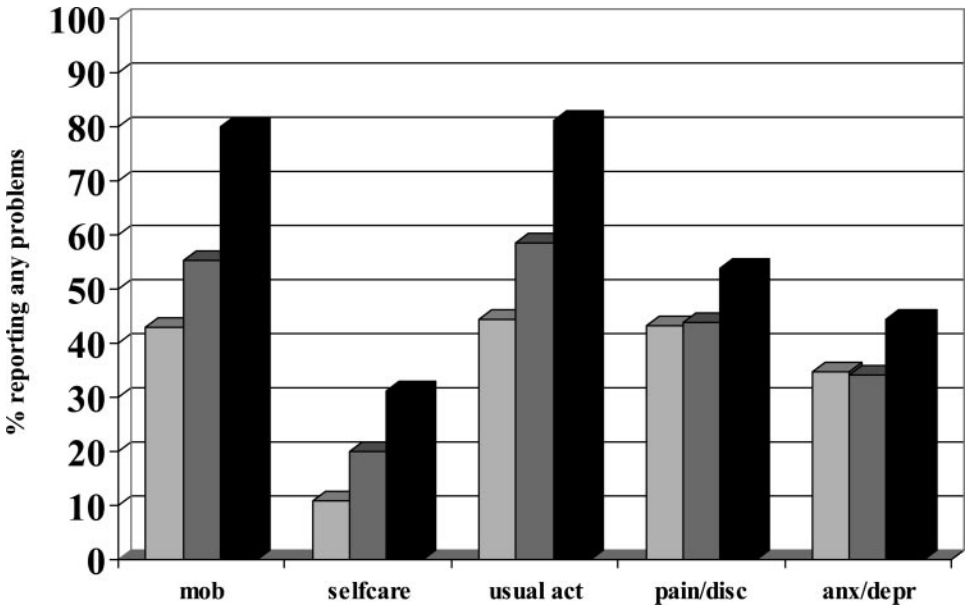

FIGURE 1. Percentage of patients in each COPD severity stage who reported any problems on the EQ-5D dimensions (collapsing the three levels into two: no problems vs any problems). First bar = moderate COPD; second bar = severe COPD; third bar = very severe COPD; mob = mobility; act = activity; disc = discomfort; anx/dep = anxiety/depression. Footnote below Figure 1. $p < 0.001$ (by χ^2 test) for mobility, self-care, and usual activities; differences in pain/discomfort and anxiety/depression are not statistically significant.

stage 2 and 19.7% among patients in GOLD stage 3 to 4.4% among patients in GOLD stage 4. None of the scales demonstrated floor effects.

Without adjusting for any differences in patient characteristics, there were statistically significant differences in EQ-5D VAS and EQ-5D utility scores among patients in the three GOLD stages. *Post hoc* analyses with Bonferroni correction for multiple testing showed that all pairwise comparisons between patients in the three GOLD stages were statistically significant. After adjusting for age, gender, current smoking status, the number of pack-years of smoking, BMI, and the number of concomitant diagnoses, pairwise differences in EQ-5D VAS and utility scores remained highly statistically significant (Table 3). These results did not change after adjusting for the Charlson index instead of the number of concomitant diagnoses.

Table 3—*EQ-5D VAS and Utility Scores and SGRQ Scores by COPD Severity**

Variables	Severity of COPD by GOLD Stage			p Value†
	Moderate	Severe	Very Severe	
EQ-5D				
VAS	67.74 (66.51–68.97)	62.45 (60.97–63.92)	57.84 (54.52–61.16)	< 0.001
Utility score				
UK value set	0.787 (0.771–0.802)	0.750 (0.731–0.768)	0.647 (0.598–0.695)	< 0.001
US value set	0.832 (0.821–0.843)	0.803 (0.790–0.816)	0.731 (0.699–0.762)	< 0.001
SGRQ				
Total score	41.89 (40.55–43.23)	46.51 (45.08–47.93)	57.31 (54.37–60.24)	< 0.001
Symptoms score	46.51 (44.63–48.39)	51.55 (49.64–53.48)	60.13 (56.05–64.21)	< 0.001
Activities score	56.49 (54.98–58.00)	62.76 (61.16–64.36)	76.42 (73.32–79.53)	< 0.001
Impact score	32.08 (30.58–33.57)	35.54 (33.89–37.19)	45.53 (41.81–49.25)	< 0.001

*Values are given as the mean (parametric 95% confidence interval), unless otherwise indicated.

†ANCOVA was adjusted for age, gender, current smoking status, pack-years of smoking, BMI, and number of comorbidities. Significant *post hoc* differences in EQ-5D VAS scores were found between patients in GOLD stages 2 and 3 ($p < 0.001$), stages 3 and 4 ($p < 0.014$), and 2 and 4 ($p < 0.001$). Significant *post hoc* differences in EQ-5D utility scores calculated with the UK value set were found between patients in GOLD stages 2 and 3 ($p = 0.001$), stages 3 and 4 ($p < 0.001$), and stages 2 and 4 ($p < 0.001$). Significant *post hoc* differences in EQ-5D utility scores calculated with the US value set and SGRQ scores were found between all pairwise comparisons of GOLD stages (all p values < 0.001).

The importance of the differences among patients in different GOLD stages is investigated by calculating effect sizes, as shown in Figure 2. Both the EQ-5D utility scores and the SGRQ differentiate much better between patients with very severe and severe COPD (Fig. 2, *bottom*, *b*) than between those with moderate and severe COPD (Fig. 2, *top*, *a*). There is a more than twofold increase evident in effect size between Figure 2, *top*, *a*, and Figure 2, *bottom*, *b*. The only exception is the patient's own valuation on the EQ-5D VAS, in which the effect size of the difference between patients with moderate COPD and those with severe COPD is somewhat larger than the effect size of the difference between patients with severe COPD and those with very severe COPD. Patients with very severe COPD had a 7.4% lower EQ-5D VAS score than did patients with severe COPD, who in turn had a 7.1% lower EQ-5D VAS score than did patients with moderate COPD. Patients with very severe COPD had 13.7% lower EQ-5D utility scores (using the UK value set) than did patients with severe COPD, who in turn had only 4.7% lower scores than did patients with moderate COPD. Differences between GOLD stages in the SGRQ total and domain scores were of a higher order of magnitude than the differences in EQ-5D scores. Patients with very severe COPD had a 23.2% worse SGRQ total score than did patients with severe COPD, who in turn had an 11.0% worse score than did patients with moderate COPD.

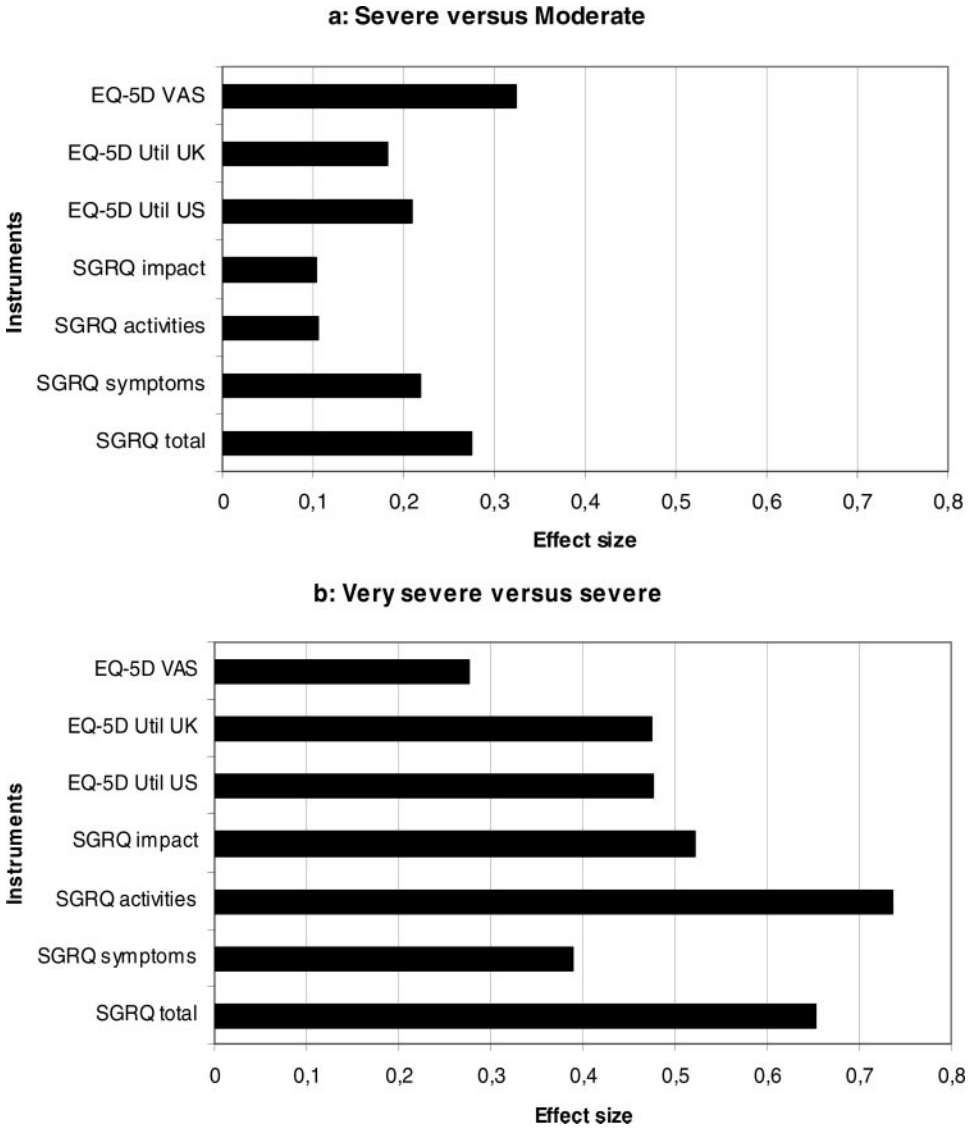

FIGURE 2. Effect sizes calculated as the mean difference between moderate and severe COPD divided by the pooled SD (*top*, *a*) and the mean difference between severe and very severe divided by the pooled SD (*bottom*, *b*); util = utility.

Utility scores calculated with the US value set were significantly higher than those calculated with the UK value set. The mean difference was −0.052 (95% confidence interval, −0.055 to −0.048). Table 3 shows that differences between the three GOLD stages of COPD severity remained highly statistically significant when replacing the UK value set with the US value set. Effect sizes of the differences between GOLD stages in EQ-5D utility scores calculated with the UK or US value set were similar (Fig. 2).

Since patients with very severe COPD had more concomitant diagnoses than those with less severe disease, Table 4 addresses the question of whether the association between GOLD stage and quality-of-life scores is influenced by comorbidity. The numbers of concomitant diagnoses were grouped using the 25th and 75th percentiles, which were one and six, respectively. The absolute number of concomitant diagnoses was significantly associated with worse EQ-5D utility scores ($p < 0.001$) and worse SGRQ total scores ($p < 0.001$), independent of GOLD stage. Also a higher Charlson index score was associated with a worse EQ-5D utility score, independent of GOLD stage ($p = 0.002$). However, there was no significant interaction between GOLD stages and the presence or absence of comorbidity, between GOLD stages and the three groups of comorbidities shown in Table 4, or between GOLD stages and the Charlson index score. Neither a higher number of comorbidities nor a higher Charlson index score was associated with a worse EQ-5D VAS score. When grouped by system organ class patients with cardiac, vascular, GI, musculoskeletal, neurologic, psychiatric, renal, and urinary disorders, and disorders of the immune system had lower EQ-5D utility scores than patients without these disorders (all p values were < 0.05). Except for the system organ classes "benign and malignant neoplasms" ($p = 0.003$) and "reproductive system and breast disorders" ($p = 0.006$), the EQ-5D VAS scores did not differ between patients with and without these comorbidities.

Since the EQ-5D utility and not the VAS is the variable to be used in cost-effectiveness analyses, the relative contributions of the severity of lung function impairment, comorbidity, country, and other patient characteristics to this score were investigated in multivariate linear regression analyses (Table 5). Gender, post-bronchodilator therapy FEV_1 percent predicted, number of hospital admissions, number of ED visits not resulting in hospital admission, number of concomitant diagnoses, and BMI were independently associated with EQ-5D utility. Male patients had a 0.057 higher utility than female patients. For each 10-U decrease in FEV_1 percent predicted, EQ-5D utility scores decreased by 0.03. A more frequent use of emergency care (either ED visits or hospital admissions) in the year before study recruitment decreased the utility. Although highly significant, the impact of an increasing number of concomitant diagnoses is small. The model that includes dummy variables for the countries that participated in this study (last two columns of Table 5) showed that, after correction for the other variables, the utility scores of Danish patients were 0.06 higher than the utility scores of US patients, whereas the utility scores of Italian, Czech, Polish, and French patients were between 0.04 and 0.15 lower.

Given the large number of patients ($> 1{,}200$), analyses were based on parametric tests, even though EQ-5D scores were not normally distributed. All analyses were repeated using nonparametric tests. The p values were very similar, and the differences between the results of analyses using parametric and nonparametric tests were very small and did not change any of the conclusions. Log-transforming EQ-5D utility scores before running regression analyses did not improve the proportion of variance explained.

Discussion and Conclusion

This study has demonstrated that the GOLD staging of COPD severity corresponds to significant differences in generic health-related quality of life, as assessed by the EQ-5D VAS and utility scores. Importantly, these differences were maintained after correction for other variables that were known to or were expected to affect quality of life, especially comorbidity. This finding demonstrates that GOLD staging of COPD severity corresponds not only to differences in disease-specific quality of life, but also to differences in the general perception of quality of life. Hence, the utility estimates for each severity stage can be used in models, especially models designed to estimate the cost-effectiveness of preventive and therapeutic interventions in COPD.

The analyses showed that the magnitude of the difference in EQ-5D utility score between patients with moderate and severe COPD was rather small, whereas the difference in EQ-5D utility score between patients with severe and very severe COPD was more than twice as large as the difference between patients with moderate and severe COPD. These findings parallel the observation that the differences between patients with severe and very severe COPD in terms of the number of ED visits and hospital admissions prior to trial entry, BMI, duration of COPD, and number of pack-years of smoking (Table 2) were more pronounced than the differences between patients with moderate and

Table 4—*Mean EQ-5D and SGRQ Scores in Patients With Different Stages of COPD Severity and Different Number of Comorbidities

Variables	Patients With Moderate COPD			Patients With Severe COPD			Patients With Very Severe COPD		
	0–1 CDs	2–5 CDs	≥ 6 CDs	0–1 CDs	2–5 CDs	≥ 6 CDs	0–1 CDs	2–5 CDs	≥ 6 CDs
VAS score	67.76	66.11	70.38	62.44	63.06	61.51	55.08	59.81	58.00
Utility score	0.850	0.787	0.716	0.795	0.761	0.686	0.683	0.656	0.610
SGRQ total score	40.73	41.44	43.85	46.14	45.31	48.78	56.22	57.29	58.18

*CD = concomitant diagnosis. Patients were grouped by the 25th and 75th percentile of the number of concomitant diagnoses, which were 1 and 6, respectively.

severe COPD. As expected, the magnitude of the difference in SGRQ scores is greater than the magnitude of the difference in EQ-5D utility scores, but it is noteworthy that the SGRQ score also showed a greater difference between patients with severe and very severe COPD than between those with moderate and severe COPD. These findings differ from those of a previous study,[29] which reported the greatest worsening of health status as taking place between patients with moderate and severe COPD. However, the lack of statistically significant differences between patients in consecutive stages other than those with moderate and severe COPD in that study is probably due to the small sample size. Our findings are in agreement with a modeling study[16] that applied EQ-5D utility scores by GOLD stage. This study reported an even smaller difference (< 0.01) between patients with moderate and severe COPD, whereas the difference between patients with severe and very severe COPD was about 0.2. These differences were neither statistically tested nor discussed.

The difference in SGRQ scores between patients in consecutive GOLD stages of COPD severity exceeded the threshold value of the minimal clinically relevant difference of 4 U. The minimal important difference in EQ-5D scores has not been established, although a recent article[23] reported a mean of 0.07, but the range of estimates was wide. The difference in EQ-5D utility scores between patients with moderate and severe COPD did not reach this threshold value, whereas the difference between patients with severe and very severe COPD did.

Unlike the EQ-5D utility scores and the SGRQ scores, the EQ-5D VAS shows a similar worsening when moving from moderate to severe COPD, as

Table 5—*Multivariate Linear Regression Analyses With EQ-5D Utility (UK Value Set) as Dependent Variable*

Variables	EQ-5D Utility Score (0–1)			
	Model 1*		Model 2†	
	Coefficient (SE)	p Value	Coefficient (SE)	p Value
Constant	0.688 (0.038)	< 0.001	0.705 (0.035)	< 0.001
Gender (male vs female)	0.057 (0.013)	< 0.001	0.061 (0.013)	< 0.001
Post-bronchodilator therapy FEV_1 % predicted	0.003 (< 0.001)	< 0.001	0.003 (< 0.001)	< 0.001
No. of ER visits not resulting in hospital admission	− 0.029 (0.012)	0.013	− 0.033 (0.012)	0.006
No. of hospital admissions	− 0.020 (0.009)	0.033	− 0.023 (0.009)	0.012
No. of CDs	− 0.010 (0.001)	< 0.001	− 0.011 (0.002)	< 0.001
BMI	− 0.003 (0.001)	0.022	− 0.003 (0.001)	0.017
Smoking status (current vs former)			− 0.028 (0.012)	0.023
Denmark vs USA			0.060 (0.022)	0.006
Italy vs United States			− 0.058 (0.029)	0.041
Czech Republic vs United States			− 0.039 (0.017)	0.017
France vs United States			− 0.149 (0.037)	< 0.001
Poland vs United States			− 0.067 (0.028)	0.018
Adjusted R^2	11%		13%	

*Model 1 is a model without country dummies. The variables removed from the stepwise linear regression in model 1 were as follows: pack-years of smoking; age; duration of COPD; using home oxygen; smoking status; and unscheduled urgent visits to a physician.

†Model 2 is a model with country dummies. The variables removed from the stepwise linear regression in model 2 were as follows: pack-years of smoking; age; duration of COPD; using home oxygen; unscheduled urgent visits to a physician; and country dummies for the other countries.

that moving from severe to very severe COPD. This disparity might reflect the higher sensitivity of a patient's own valuation of his or her health status. However, the EQ-5D VAS score was not sensitive to comorbidity. Comorbidity is known to affect generic health-related quality of life in COPD patients,[30] and measuring the impact of comorbidity is one argument for using generic quality-of-life instruments. In our study, regression analyses showed a higher number of concomitant diagnoses to be associated with worsening EQ-5D utility scores, independent of COPD severity and other patient characteristics. There were no indications of a greater impact of comorbidity in patients in more severe stages of COPD. The unexpected finding that the patient valuation on the EQ-5D VAS was not sensitive to comorbidity might be related to the possibility that patients who volunteer for and are enrolled in a COPD trial focus their health perception primarily on the disease under investigation.

Validation studies of the EQ-5D in COPD have been conducted before in relatively small single-country or single-center studies.[31–33] These studies have not addressed the discriminative properties of the EQ-5D with respect to the GOLD stages of disease severity. Our study used baseline data from the UPLIFT trial.[18] This 4-year trial is designed to assess the impact of tiotropium on the natural course of COPD. It provides a unique opportunity to address the issue of the discriminative validity of the EQ-5D, because of its large sample size, the wide variety of countries from which patients were enrolled, and the complete registration of comorbidity. The UPLIFT trial[18] was less restrictive with respect to the inclusion criteria than is common among COPD trials. The only exclusion criteria were a history of asthma or pulmonary resection, an exacerbation or respiratory infection in the month before study entry, the use of oxygen for > 12 h a day or a disease that might influence the results or the ability to participate in the study. There is no upper age limit, and there are no restrictions to the use of concomitant medications other than use of open-label anticholinergic agents during the treatment period. Nevertheless, the patient population may not be entirely representative of all patients with moderate-to-very severe COPD, because enrolled patients may have been more stable and less likely to have life-threatening comorbidity given that this would interfere with the ability to observe them for 4 years. This might explain the absence of a difference in the percentage of patients reporting problems on the anxiety/depression domain between the COPD severity stages. It might also explain the absence of an interaction between GOLD stage and comorbidity, especially when comorbidity is expressed as the Charlson index score, because only very severe conditions in that index get a high weight.

EQ-5D utility scores were found to vary by country. After adjusting for other variables, French, Italian, Czech, and Polish patients had significantly lower utility scores than US patients, whereas Danish patients had significantly higher values. The magnitude of the difference varied between 4% and 15% of the scale of 0 to 1. These between-country differences were noted despite the study-wide use of the same set of weights, namely, those obtained from the UK general population. In addition, utility scores calculated with the US value set were significantly higher than those calculated with the UK value set, with the magnitude of the difference being approximately 5%. Although both set of weights are based on the TTO method, this difference is partly due to methodological differences, such as differences in the statistical models used to estimate the weights or differences in the transformation of negative values. Moreover, the UK weights were obtained in the early 1990s, whereas the US weights were obtained in 2002. Nevertheless, when comparing directly elicited values for EQ-5D health states using exactly the same methods, Johnson et al[34] found that the US population assigned consistently higher values to the same health states than the UK population. The difference was on average 0.1 but increased when health states became worse. The UK and US value sets are likely to be used as alternatives to obtain utility scores. Theoretically, the choice of weights to calculate the EQ-5D utility scores in economic analyses, whether empirical cost-effectiveness studies appended to clinical trials or modeling studies, should, whenever possible, be based on the country that is represented in the analyses. However, the consequence of the higher EQ-5D utility scores generated by the US value set is that there is less room for improvement, resulting in less QALY gains and a less favorable cost-effectiveness ratio compared to the UK value set.[35]

This analysis was conducted to assess whether the most widely used classification system of COPD severity (*ie*, the GOLD classification) corresponds to differences in EQ-5D scores. The threshold values of this lung function classification were taken as a given, and we acknowledge that the threshold values of any classification instrument are to a certain extent arbitrary. We were not searching for a classification that discriminates best between COPD patients with different levels of quality-of-life impairment. A composite classification instrument that includes variables independently associated with quality of life, analogous to the body mass index, airflow obstruc-

tion, dyspnea, exercise capacity (BODE) index,[36] would probably better serve this purpose.

The EQ-5D utility had a relatively large proportion of responses in the best category. This proportion decreases over GOLD stages 2 to 4. This confirms the presence of a ceiling effect,[34] implying that the EQ-5D is not the preferred instrument for distinguishing between less severe COPD states. Patients with mild COPD, according to the GOLD classification, were not investigated in the present study.

Besides the ceiling effect limiting the sensitivity of the EQ-5D utility to differences in patients with less severe COPD, the EQ-5D has the additional problem of not capturing the impact that COPD exacerbations have on quality of life. This problem applies equally to the EQ-5D, the SGRQ, and other generic or COPD-specific quality-of-life instruments. The EQ-5D has no recall period and asks for a description of a patient's health "today." Even if there is a recall period, as in the symptoms domain of the SGRQ, these quality-of-life instruments are usually administered during a stable phase of the disease, as a result of which they do not capture the impact of exacerbations. This should be taken into account when using the EQ-5D utility scores from this study in modeling studies. It would be a step forward if we could obtain utility scores for COPD health profiles that combine the description of a patient's underlying COPD severity stage with the description of that patient's exacerbation profile in terms of the frequency, severity, and impact of the exacerbation. Such health profiles are particularly suitable for describing episodic or fluctuating diseases such as COPD.[37]

In conclusion, this large multinational study generated utility scores that can be used in modeling studies. It demonstrated that the EQ-5D VAS and EQ-5D utility are capable of differentiating among moderate, severe, and very severe COPD, as defined by the GOLD criteria. The differences remained after correction for other variables, such as comorbidity. The reduction in generic quality of life is much more apparent when patients progress from severe to very severe COPD than when they progress from moderate to severe COPD. The between-country differences that were found in this study also have implications for the use of EQ-5D utility scores in cost-utility studies of COPD interventions. Given the differences between the UK and US value sets, limiting empirical multinational cost-utility studies to the use of only one set of weights is necessary to ensure that QALYs are comparable. When models are used to adapt trial results to better represent the target country or setting, a country-specific set of weights is to be preferred.

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