

# Proactive palliative care for patients with COPD (PROLONG): a pragmatic cluster controlled trial

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**Background and aim:** Patients with advanced chronic obstructive pulmonary disease (COPD) have poor quality of life. The aim of this study was to assess the effects of proactive palliative care on the well-being of these patients.

**Trial registration:** This trial is registered with the Netherlands Trial Register, NTR4037.

**Patients and methods:** A pragmatic cluster controlled trial (quasi-experimental design) was performed with hospitals as cluster (three intervention and three control) and a pretrial assessment was performed. Hospitals were selected for the intervention group based on the presence of a specialized palliative care team (SPCT). To control for confounders, a pretrial assessment was performed in which hospitals were compared on baseline characteristics. Patients with COPD with poor prognosis were recruited during hospitalization for acute exacerbation. All patients received usual care while patients in the intervention group received additional proactive palliative care in monthly meetings with an SPCT. Our primary outcome was change in quality of life score after 3 months, which was measured using the St George Respiratory Questionnaire (SGRQ). Secondary outcomes were, among others, quality of life at 6, 9 and 12 months; readmissions; survival; and having made advance care planning (ACP) choices. All analyses were performed following the principle of intention to treat.

**Results:** During the year 2014, 228 patients (90 intervention and 138 control) were recruited and at 3 months, 163 patients (67 intervention and 96 control) completed the SGRQ. There was no significant difference in change scores of the SGRQ total at 3 months between groups ( $-0.79$  [95% CI,  $-4.61$  to  $3.34$ ],  $p=0.70$ ). However, patients who received proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months ( $-6.22$  [ $-11.73$  to  $-0.71$ ],  $p=0.04$ ) and had more often made ACP choices (adjusted odds ratio  $3.26$  [ $1.49$ – $7.14$ ],  $p=0.003$ ). Other secondary outcomes were not significantly different.

**Conclusion:** Proactive palliative care did not improve the overall quality of life of patients with COPD. However, patients more often made ACP choices which may lead to better quality of care toward the end of life.

**Keywords:** COPD, proactive palliative care, quality of life, advance care planning, readmission, survival

## Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and caused 3.1 million deaths (5.6% of total deaths) in 2012.<sup>1,2</sup> This progressive life-threatening lung disease has an unpredictable course characterized by episodes of gradual decline punctuated by acute severe exacerbations.<sup>3</sup> After the first hospitalization for an acute exacerbation of COPD (AECOPD), 50% of patients die within 3.6 years.<sup>4</sup> Patients with advanced COPD have a high symptom burden,

including breathlessness, fatigue, cough, and anxiety.<sup>5</sup> Their quality of life is poor and often even worse than patients with lung cancer.<sup>6</sup>

Early or proactive palliative care can improve the quality of life of patients with cancer<sup>7-9</sup> and heart failure.<sup>10,11</sup> This kind of care is not restricted to end-of-life care but can be delivered earlier in the disease course by anticipating on wishes and needs of patients, in order to prevent and relieve suffering from problems in the physical, psychosocial, and spiritual domain.<sup>2</sup> Patients with lung cancer receiving proactive palliative care even had longer survival while receiving less aggressive treatments.<sup>8</sup> Prolonged survival has also been observed in patients with refractory breathlessness (cancer, COPD, chronic heart failure [CHF], and interstitial lung disease).<sup>12</sup> In this study of Higginson et al,<sup>12</sup> early introduction of a palliative breathlessness support service improved breathlessness mastery, a quality of life domain of the Chronic Respiratory Disease Questionnaire. Although proactive palliative care has been shown to improve the quality of life and prolong survival of patients with various life-threatening diseases, it is still not common for patients with COPD to receive this care.<sup>13</sup> Since little is known about the effects of proactive palliative care in COPD, research is needed to be able to improve care for this patient group.<sup>13</sup>

We report a pragmatic cluster controlled trial of proactive palliative care in patients with COPD. A cluster design was chosen to prevent contamination and to minimize ethical concerns of patients and clinicians with respect to randomization and gate keeping. We hypothesized that patients with COPD who received proactive palliative care integrated with usual care compared to patients who received usual care only would have better quality of life, lower levels of psychological distress, fewer and shorter hospital admissions for an AECOPD, and prolonged survival and that receiving proactive palliative care would increase the number of patients with whom advance care planning (ACP) choices were made.

## Patients and methods

### Study design

This trial is registered with the Netherlands Trial Register, NTR4037. A pragmatic cluster controlled trial (quasi-experimental design) was performed in general hospitals in the Netherlands with a general hospital as cluster (three control and three intervention). Patients were recruited between January 6, 2014 and January 8, 2015, and each patient was followed up for 1 year. Hospitals were selected for the intervention group based on the presence of a specialized

palliative care team (SPCT). A pretrial assessment was performed to be able to control for confounders on hospital level. All outcome measures were on patient level.

### Participants

Patients with COPD, 18 years or older, who had a hospital admission for an AECOPD were considered for the PROLONG study.<sup>14</sup> Patients were excluded if they could not speak Dutch, had severe cognitive disorders, or if they were being treated by an SPCT at the moment of inclusion. The attending pulmonologist selected and approached potential participants. Exclusion because of severe cognitive disorder was based on judgment of the pulmonologist. If the patient agreed to participate, an informed consent was signed. For the intervention study described here, only patients with poor prognosis were regarded. To identify these patients, the pulmonologist completed a standard checklist consisting of a set of 11 indicators derived from the literature.<sup>14</sup> If meeting two or more indicators, the patient was considered to have a poor prognosis and eligible to participate in the study. The set of indicators of poor prognosis is presented in Table 1.<sup>15,16</sup>

**Table 1** Set of indicators of poor prognosis

**A patient hospitalized for AECOPD is considered to have poor prognosis when meeting  $\geq 2$  of the following indicators:**

1. Hypoxemia ( $\text{PaO}_2 < 8$  kPa) or hypercapnia ( $\text{PaCO}_2 > 6$  kPa) at discharge
2. Treatment of the exacerbation with NIV
3. Patient needs professional home care service for personal care after discharge
4. Negative answer to the surprise question: "Would I (as lung specialist) be surprised if this patient would have a subsequent readmission for AECOPD within 8 weeks and/or would die in the next year?"
5. The diagnosis of a severe comorbidity such as:
  - a. Non-curable malignancy or
  - b. Cor pulmonale (proven or non proven) or
  - c. Proven CHF or
  - d. Diabetes mellitus with neuropathy or
  - e. Renal failure, clearance  $< 40$  (GFR: in mL/min)
6. CCQ total, day version  $> 3$
7. MRC dyspnea =5
8.  $\text{FEV}_1$  (measured before AECOPD)  $< 30\%$  of predicted
9. BMI  $< 21$  or unplanned weight loss ( $> 10\%$  weight loss in last 6 months or  $> 5\%$  in last month)
10. Previous hospital admissions for AECOPD (last 2 years  $\geq 2$  and/or last year  $\geq 1$ )
11. Age  $> 70$  years

**Abbreviations:** AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CCQ, Clinical COPD Questionnaire; CHF, chronic heart failure;  $\text{FEV}_1$ , forced expiratory volume in 1 second; GFR, glomerular filtration rate; MRC dyspnea, Medical Research Council dyspnea questionnaire; NIV, noninvasive ventilation.

The study protocol was approved by the medical ethics committee (METC) of the Radboud University Medical Center, Nijmegen (METC protocol number 2012/260). Thereafter, research approval was received in all participating hospitals. Our protocol followed CONSORT recommendations,<sup>14</sup> but there were two protocol deviations. First, patients participating in other COPD-related studies were withdrawn from the intention-to-treat analysis from the moment they entered the other study. Second, patients who signed the informed consent but died in hospital during inclusion were also excluded as the pulmonologist was not able to complete the checklist because it consisted of indicators for posthospital mortality. A comprehensive description of the methods is given in the published protocol.<sup>14</sup>

## Randomization

A cluster design was chosen to prevent contamination and to minimize ethical concerns of patients and clinicians with respect to randomization and gate keeping. Contamination would certainly have taken place because our intervention involved a close cooperation between pulmonary team and SPCT. At the time of hospital recruitment, a minority of hospitals in the Netherlands had the availability of an SPCT. Since only four hospitals with an SPCT were willing to participate, it was not possible to create comparable groups through randomization in our trial. Instead, we performed a pragmatic cluster controlled trial (quasi-experiment), in which three hospitals with an SPCT were selected for the intervention and three hospitals without an SPCT for the control group. To control for confounders on hospital level, a pretrial assessment was performed in which hospitals were compared on baseline characteristics over the year before trial (the number of hospitalizations and hospitalization days for AECOPD per patient, and percentage of patients hospitalized for an AECOPD who died in hospital). All outcome measures were on patient level, and patients performed a pre- and post-intervention measurement.

The study was single blinded. Clinicians were aware of treatment allocation, while patients were unaware of the existence of another group.

## Interventions

All patients received usual care. In the intervention group, patients received additional proactive palliative care from an SPCT. Patients had a first consultation with the SPCT during the initial hospitalization, or the latest within 1 week after hospital discharge. Thereafter, the SPCT had monthly

meetings with the patient in the outpatient setting, preferably face to face but alternatively by telephone, for 1 year or until death.

Since delivering proactive palliative care for patients with COPD was not common for members of the SPCTs, they received a training, aimed at the specific problems in this patient group, which was provided by academic palliative care professionals of the Radboud University Medical Center, Nijmegen. Training was based on the specific guidelines for palliative care in COPD<sup>17</sup> and consisted of two 3-hour meetings. The first meeting took place in the month before trial, and the second during the first month of trial. The training consisted of the following topics: how to communicate future care planning and end-of-life aspects with the patients and their families; how to create a patient-tailored proactive palliative care plan; how to proactively anticipate on illness and death scenarios; how to organize transfer of care to the pulmonologist and general practitioner (GP); and how to perform a proactive palliative care plan in cooperation with the pulmonologist.

## Data collection

Data collection took place using questionnaires completed by the patients and by retrospectively collecting data from their medical files over the trial period (Table 2).<sup>18-21</sup>

ACP choices documented in medical files were defined as agreements about: not to be resuscitated (NTBR) policy, intensive care unit (ICU) admission, palliative dyspnea treatment, palliative sedation, treatment of future infections with antibiotics (AB), and preferred place of death. These ACP choices were our objective outcome measures which served as a proxy for measuring whether ACP conversations had taken place.

## Outcomes

The primary outcome was change in the quality of life from baseline after 3 months measured with the St George Respiratory Questionnaire (SGRQ). Secondary questionnaire outcomes were change of the SGRQ from baseline after, respectively, 6, 9, and 12 months and change of the McGill Quality of Life Questionnaire (McGill) and the Hospital Anxiety and Depression Scale (HADS) from baseline after, respectively, 3, 6, 9, and 12 months. Secondary outcomes retrospectively retrieved from the medical files of the patients over the trial period are presented in Table 2.

## Statistical analysis

Based on our primary outcome, change in quality of life measured with the SGRQ from baseline after 3 months,

**Table 2** Overview of data collection per time point

Data collection	B	3 m	6 m	9 m	12 m	R
Questionnaires						
Demographic questionnaire (age, pack years, sex, marital status, place, and conditions of living and education)	X					
SGRQ (COPD quality of life questionnaire; symptoms, activities, and impacts subscales)	X	X	X	X	X	
McGill (palliative quality of life questionnaire; phys symptoms, phys and psych well-being, existential, and support subscales)	X	X	X	X	X	
HADS (psych well-being questionnaire; anxiety and depression subscales)	X	X	X	X	X	
Medical files (information over the 1-year trial period)						
Number of readmissions to hospital						X
Number of readmissions to hospital for AECOPD						X
Date of first readmission for AECOPD						X
Number of days of readmission to hospital for AECOPD						X
Choices of ACP documented in the medical file at baseline						X
Choices of ACP documented in the medical file after 1 year or at death						X
Did the patient die within 1 year after inclusion?						X
Date of death						X

**Note:** X's indicate the times that that type of data was collected.

**Abbreviations:** ACP, advance care planning; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; B, baseline; HADS, Hospital Anxiety and Depression Scale; m, months; McGill, McGill Quality of Life Questionnaire; phys, physical; psych, psychological; R, retrospectively; SGRQ, St George Respiratory Questionnaire.

we estimated that 64 patients were needed in each arm to detect a mean difference of 9 (SD 16) with a *p*-value of 0.05 at a power of 80%.<sup>22</sup> To adjust for clustering at hospital level (intraclass correlation coefficient [ICC]=0.01, three hospitals per arm) and to allow for an additional loss to follow up of 10%, a total of 86 patients were required in each arm.

We used the valid CASTOR data management system to ensure good clinical practice.<sup>23</sup> Data were analyzed using R software, version 3.1.2. Frequencies, means, and standard deviations (SDs) were used to describe the study variables. Linear mixed models with a random intercept for hospitals to account for clustering were used to study the effects of proactive palliative care on the primary and secondary outcomes. The models contained an adjustment for baseline scores of which selection was based on theoretical background and differences between groups at baseline. The analysis followed the principle of intention to treat. Missing data were handled using available case analysis.

Survival was plotted using the Kaplan–Meier method. We calculated survival rates until 365 days from enrollment in both groups. A Cox proportional hazard test was used to assess the effect of proactive palliative care on survival with adjustment for baseline characteristics. Again, mixed models with a random intercept for hospitals were used.

## Results

In six general hospitals, 780 patients were screened, of whom 228 (90 intervention and 138 control) were included in the intention-to-treat analysis (Figure 1).

Baseline characteristics at hospital level over the year before trial (2013) are presented in Table 3.

Tables 4 and 5 summarize the demographics and baseline characteristics of the study population, respectively. In the intervention group, compared to the control group, more patients had severe dyspnea scores, were living alone, and were suffering from CHF. No substantial differences were seen between groups on baseline outcome measures.

Important change scores relative to baseline and the associated tests of effects between groups are presented in Table 6.<sup>24</sup> The outcomes of the McGill and HADS subscales are presented in Table S1. In the linear mixed models, the baseline scores on patient level adjusted for were: baseline questionnaire score, sex, condition of living, level of education, pack years, Medical Research Council (MRC) dyspnea score, forced expiratory volume in 1 second (FEV<sub>1</sub> %) of predicted value, presence of comorbidity, number of indicators met, and number of admissions for AECOPD in the previous 2 years. To account for differences at baseline on hospital level, we also adjusted for number of hospitalizations for AECOPD per patient in the year before the trial (2013).

Incorrectly filled out questions were noticed at the McGill physical symptoms subscale. In an open text field, patients had to describe a troublesome physical symptom and indicate its seriousness on a visual analog scale (VAS). This question proved to be subject to misinterpretation. Patients often listed not a physical symptom but a disease (eg, diabetes), or a complaint of other origin (eg, snoring partner). To prevent from too many missing values, we calculated the McGill

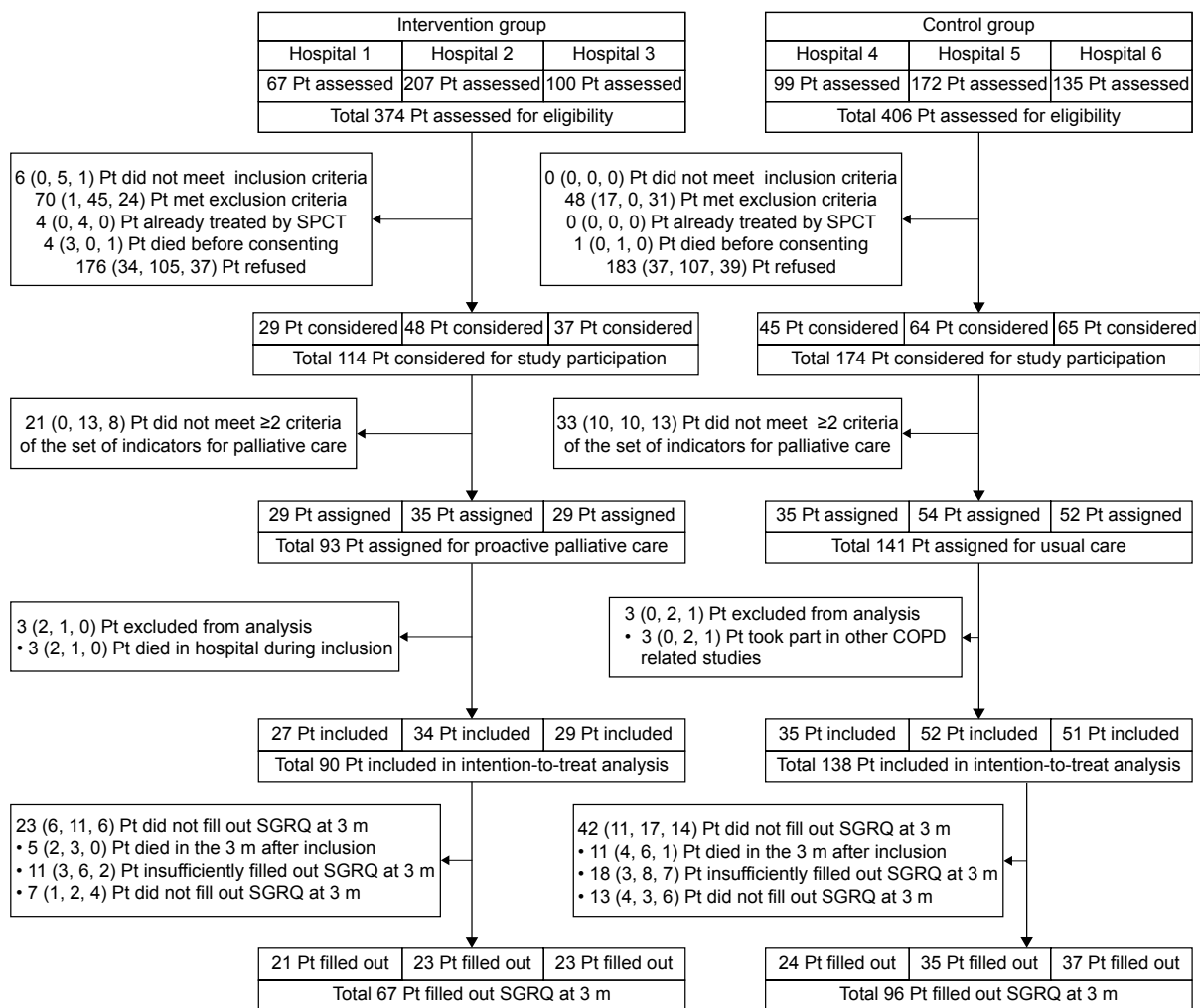


Figure 1 Trial profile.

Notes: Data presented as N (n for H1, n for H2, n for H3) unless otherwise indicated for Intervention group. Data presented as N (n for H4, n for H5, n for H6) unless otherwise indicated for Control group.

Abbreviations: m, months; Pt, patients; SGRQ, St George Respiratory Questionnaire; SPCT, specialized palliative care team; H1, hospital 1; H2, hospital 2; H3, hospital 3; H4, hospital 4; H5, hospital 5; H6, hospital 6.

total score by taking the mean of the remaining four of the five subscales.

The primary outcome of change scores in SGRQ total at 3 months did not differ significantly between groups (mean [SD] observed change score in intervention group -1.84 [12.20] vs control group 0.20 [12.05],  $p=0.70$ ).

There was a significant difference between groups in the change scores of the impact subscale of the SGRQ at 6 months (-5.73 [16.21] vs 0.86 [18.73],  $p=0.04$ ). We also

noted a significant difference between groups in number of patients who made ACP choices during the year of trial (76.7% vs 59.4%, adjusted odds ratio [OR] 3.26 [95% CI 1.49-7.14],  $p=0.003$ ). Of the 36.8% of patients (30.0% intervention and 41.3% control) who had not made ACP choices at baseline, 85.7% (100% intervention and 78.9% control) made ACP choices within the next year. Whereas, of the 63.2% of patients (70.0% intervention and 58.7% control) who had already made ACP choices at baseline, 54.9%

Table 3 Baseline characteristics at hospital level over the year before trial (2013)

Characteristics	Intervention				Control			
	Hospital 1	Hospital 2	Hospital 3	Mean	Hospital 4	Hospital 5	Hospital 6	Mean
Hospitalizations for AECOPD per patient (n)	1.32	1.60	1.24	1.39	1.23	1.51	1.21	1.32
Hospitalization days for AECOPD per patient (n)	9.21	10.58	10.15	9.98	9.30	12.32	10.43	10.68
Patients with AECOPD who died in hospital (%)	0.08	0.07	0.07	0.073	0.06	0.12	0.06	0.08

Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.



**Table 4** Demographics of the intention-to-treat population

Demographics	Overall (n=228)	Intervention (n=90)	Control (n=138)
Age (years)	68.54 (9.34)	68.67 (9.08)	68.45 (9.54)
Pack years	40.00 (31.76)	41.58 (28.95)	38.92 (33.62)
Sex			
Male	110 (48.2%)	46 (51.1%)	64 (46.4%)
Marital status <sup>a</sup>			
Unmarried	16 (7.0%)	5 (5.6%)	11 (8.0%)
Married	145 (63.6%)	51 (56.7%)	94 (68.1%)
Divorced	25 (11.0%)	12 (13.3%)	13 (9.4%)
Widowed	39 (17.1%)	22 (24.4%)	17 (12.3%)
Living situation <sup>a</sup>			
Single	71 (31.1%)	36 (40.0%)	35 (25.4%)
Not single	145 (63.6%)	49 (54.4%)	96 (69.6%)
Place of residence <sup>a</sup>			
Home, independent of home care	144 (63.2%)	60 (66.7%)	84 (60.9%)
Home, dependent of home care	74 (32.5%)	27 (30.0%)	47 (34.1%)
Residential home	3 (1.3%)	1 (1.1%)	2 (1.4%)
Nursing home	1 (0.4%)	1 (1.1%)	0 (0%)
Highest level of education <sup>a</sup>			
No education	2 (0.9%)	1 (1.1%)	1 (0.7%)
Elementary school	38 (16.7%)	16 (17.8%)	22 (15.9%)
Secondary school	57 (25.0%)	18 (20.0%)	39 (28.3%)
Primary education	45 (19.7%)	17 (18.9%)	28 (20.3%)
Secondary education	57 (25.0%)	30 (33.3%)	27 (19.6%)
Higher/university education	23 (10.1%)	8 (8.9%)	15 (10.9%)

**Notes:** Data are given as n (%) or mean (standard deviation). <sup>a</sup>Because of missing values, some numbers do not add up to 100%.

(66.7% intervention and 45.7% control) made additional ACP choices within the next year. All other secondary outcome measures were not significantly different between groups. One year after enrollment, 52 patients with poor prognosis (22.8%) had died. The Kaplan–Meier curve is shown in Figure 2. The Cox proportional hazard test showed that survival was not significantly different between groups (adjusted hazard ratio [HR] 0.74 [95% CI 0.34–1.62],  $p=0.45$ ).

## Discussion

This is the first study to explore the effects of proactive palliative care in a large group of patients with COPD with poor prognosis (n=228). We did not find an effect on our primary outcome: the change in quality of life measured using the SGRQ from baseline to 3 months was not different between groups. However, patients receiving proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months than patients receiving usual care. The change in symptoms and activity level (SGRQ symptoms and activity subscale) was not different between groups at 3, 6, 9, and 12 months. Moreover, there was a relevant difference in the number of patients who made ACP choices during the year of trial, in favor of the intervention group. We did not find a difference in other questionnaire outcomes, nor

in number and length of hospital admissions or in survival between groups.

There are several possible reasons at the level of identification, organization, patient, outcome measure, and disease course that may explain the failure to show an improvement of quality of life in patients with COPD by means of proactive palliative care in our study. First, 22.8% of patients identified as having a poor prognosis died; it is possible that our criteria for poor prognosis were too broad. Second, patients with advanced COPD are often homebound until they enter an acute phase with hospitalization.<sup>25</sup> Continuity of palliative care can therefore only be achieved with a coordinated, multidisciplinary care approach.<sup>26</sup> This requires collaboration between primary and secondary health care professionals. Although GPs were informed about the intervention and the SPCT was encouraged to collaborate with GPs, it is unknown to what extent this occurred. Third, patients with COPD generally have a lower social economic status (SES), ie, on average a lower level of education and less financial means compared to other patient groups.<sup>27</sup> These aspects have an impact on COPD health outcomes.<sup>27</sup> Indeed, some patients in our study had difficulties understanding certain questions, which resulted in the return of incomplete questionnaires. Besides, some patients lacked financial means to afford

**Table 5** Baseline characteristics of the intention-to-treat population

Characteristics	Overall (n=228)	Intervention (n=90)	Control (n=138)
Clinical characteristics			
FEV <sub>1</sub> (L)	1.07 (0.49)	1.05 (0.47)	1.08 (0.50)
Predicted FEV <sub>1</sub> (%)	42.51 (18.87)	40.79 (16.09)	43.70 (20.55)
VC (L)	2.60 (0.82)	2.63 (0.83)	2.58 (0.82)
Predicted VC (%)	79.84 (20.67)	79.75 (21.90)	79.90 (19.89)
GOLD stage <sup>a,b</sup>			
0	10 (4.4%)	4 (4.4%)	6 (4.3%)
I	7 (3.1%)	2 (2.2%)	5 (3.6%)
II	51 (22.4%)	16 (17.8%)	35 (25.4%)
III	87 (38.2%)	43 (47.8%)	44 (31.9%)
IV	63 (27.6%)	24 (26.7%)	39 (28.3%)
Comorbidity			
Non-curable malignancy	12 (5.3%)	8 (8.9%)	4 (2.9%)
Cor pulmonale	12 (5.3%)	3 (3.3%)	9 (6.5%)
CHF	16 (7.0%)	11 (12.2%)	5 (3.6%)
DM with neuropathy	9 (3.9%)	2 (2.2%)	7 (5.1%)
Renal failure	13 (5.7%)	2 (2.2%)	11 (8.0%)
Comorbidity total	58 (25.4%)	24 (26.7%)	34 (24.6%)
Hospitalizations for AECOPD in previous 2 years (n)	1.95 (2.57)	2.28 (3.1)	1.73 (2.14)
Indicators met (n)	4.35 (1.64)	4.42 (1.51)	4.30 (1.72)
MRC dyspnea <sup>a</sup>			
0	4 (1.8%)	3 (3.3%)	1 (0.7%)
1	6 (2.6%)	3 (3.3%)	3 (2.2%)
2	6 (2.6%)	1 (1.1%)	5 (3.6%)
3	31 (13.6%)	5 (5.6%)	26 (18.8%)
4	44 (19.3%)	15 (16.7%)	29 (21.0%)
5	134 (58.8%)	63 (70.0%)	71 (51.5%)
CCQ total	3.45 (0.97)	3.48 (0.88)	3.44 (1.03)
Outcome measures			
SGRQ total score	68.12 (14.43)	69.00 (13.37)	67.50 (15.15)
SGRQ symptoms score	69.80 (17.39)	70.93 (15.06)	69.06 (18.78)
SGRQ activity score	86.84 (13.65)	87.38 (13.61)	86.47 (13.72)
SGRQ impacts score	57.57 (19.56)	58.16 (18.77)	57.16 (20.13)
McGill total score	5.16 (1.18)	5.06 (0.98)	5.25 (1.31)
McGill physical well-being	4.03 (2.26)	4.28 (2.28)	3.87 (2.23)
McGill physical symptoms	3.08 (1.84)	2.91 (1.77)	3.21 (1.89)
McGill psychological	5.82 (2.61)	5.92 (2.60)	5.76 (2.63)
McGill existential	5.55 (1.67)	5.61 (1.47)	5.51 (1.80)
McGill support	7.39 (1.91)	7.61 (1.63)	7.24 (2.07)
HADS total score	16.87 (7.80)	16.48 (7.88)	17.13 (7.78)
HADS anxiety	8.78 (4.48)	8.75 (4.53)	8.80 (4.47)
HADS depression	8.12 (4.29)	7.74 (4.12)	8.37 (4.40)

**Notes:** Data are given as n (%) or mean (SD). <sup>a</sup>Because of missing values, some numbers do not add up to 100%. <sup>b</sup>GOLD stage according to last known data in medical file; inclusion in the study based on judgment pulmonologist.

**Abbreviations:** AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CCQ, Clinical COPD Questionnaire; CHF, congestive heart failure; DM, diabetes mellitus; FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative on Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; McGill, McGill Quality of Life Questionnaire; MRC dyspnea, Medical Research Council dyspnea questionnaire; SD, standard deviation; SGRQ, St George Respiratory Questionnaire; VC, vital capacity.

transportation to the hospital, physical therapy, or even a walker. Fourth, for some patients with advanced COPD, filling in questionnaires may have been too demanding. Although all enrolled patients did consent to fill out questionnaires, about one out of five patients did not fully complete or return them. Incomplete data collection in advanced COPD

has also been reported before.<sup>28,29</sup> Perhaps in this population, the use of a qualitative instead of a quantitative approach is preferable for measuring changes in patient-reported outcomes.<sup>28</sup> Finally, there are differences in the palliative trajectory between patients with cancer and those with COPD. The palliative trajectory of COPD is less predictable since

**Table 6** Change scores relative to baseline of the primary outcome (SGRQ total at 3 months) and secondary outcomes and associated tests of effects between groups

Outcomes	Descriptives				Analysis of difference between groups for changes over time <sup>a</sup>		
	Intervention		Control		Estimated difference (95% CI)	Effect size <sup>b</sup>	p-value
	n	Mean (SD) observed change from baseline	n	Mean (SD) observed change from baseline			
SGRQ total <sup>c</sup>							
3 months	62	-1.84 (12.20)	88	0.20 (12.05)	-0.79 (-4.61 to 3.34)	0.17	0.70
6 months	55	-4.66 (12.09)	70	-1.64 (13.11)	-2.20 (-6.63 to 2.22)	0.24	0.36
9 months	53	-3.94 (11.34)	69	0.29 (11.90)	-4.26 (-8.55 to 0.03)	0.36	0.07
12 months	45	-2.88 (13.14)	63	-0.50 (12.48)	-1.70 (-6.71 to 3.32)	0.19	0.54
SGRQ symptoms <sup>c</sup>							
3 months	72	-4.34 (15.79)	109	-6.78 (20.92)	3.62 (-1.71 to 9.01)	-0.13	0.21
6 months	65	-6.17 (17.41)	86	-4.40 (19.77)	-0.54 (-6.27 to 5.20)	0.09	0.86
9 months	59	-6.08 (19.88)	85	-6.37 (20.70)	-0.47 (-6.78 to 5.85)	-0.01	0.89
12 months	53	-5.55 (18.34)	77	-6.88 (20.90)	3.77 (-4.72 to 12.25)	-0.07	0.49
SGRQ activity <sup>c</sup>							
3 months	63	-1.74 (14.88)	91	-0.37 (10.92)	0.31 (-3.40 to 4.01)	0.11	0.87
6 months	57	-2.60 (12.67)	77	-1.78 (12.22)	0.83 (-2.96 to 4.61)	0.07	0.69
9 months	57	-2.03 (11.92)	77	0.17 (11.25)	-0.70 (-4.34 to 2.95)	0.19	0.72
12 months	47	-2.45 (12.45)	70	-0.44 (11.86)	-2.06 (-6.10 to 1.98)	0.17	0.35
SGRQ impact <sup>c</sup>							
3 months	73	-2.10 (15.94)	107	0.10 (19.42)	-2.69 (-7.62 to 2.24)	0.12	0.31
6 months	63	-5.73 (16.21)	85	0.86 (18.73)	-6.22 (-11.73 to -0.71)	0.37	0.04
9 months	59	-4.36 (14.58)	81	1.24 (16.53)	-5.30 (-10.71 to 0.11)	0.36	0.07
12 months	51	-1.27 (18.24)	78	0.25 (20.74)	-2.78 (-9.49 to 3.93)	0.08	0.45
McGill total <sup>d,e</sup>							
3 months	60	0.08 (1.62)	79	0.13 (1.73)	0.26 (-0.30 to 0.83)	0.03	0.43
6 months	51	-0.04 (1.50)	70	-0.10 (1.59)	0.22 (-0.24 to 0.69)	-0.04	0.38
9 months	44	0.05 (1.49)	62	-0.22 (1.56)	0.14 (-0.45 to 0.73)	-0.18	0.71
12 months	44	-0.17 (1.55)	56	-0.23 (1.65)	0.30 (-0.40 to 1.00)	-0.04	0.44
HADS total <sup>c</sup>							
3 months	76	0.22 (6.81)	112	0.27 (6.30)	-0.29 (-2.19 to 1.61)	0.01	0.78
6 months	66	0.46 (7.20)	90	0.39 (6.43)	-0.28 (-2.39 to 1.83)	-0.01	0.81
9 months	62	-0.01 (7.20)	87	0.33 (6.50)	-0.49 (-2.92 to 1.94)	0.05	0.71
12 months	55	0.85 (6.99)	81	1.50 (6.62)	-1.01 (-3.52 to 1.51)	0.10	0.46
Readmissions for AECOPD (n)	90	1.72 (1.76)	135	1.65 (2.00)	-0.08 (-0.39 to 0.23) <sup>f</sup>	0.04	0.62
Days of readmission for AECOPD (n)	62	20.27 (18.12)	91	17.57 (14.27)	0.07 (-0.25 to 0.39) <sup>g</sup>	0.17	0.57
	n	n (%)	n	n (%)	Adjusted OR (95% CI)		p-value
Patients who made ACP choices	90	69/90 (76.7%)	138	82/138 (59.4%)	3.26 (1.49 to 7.14)	NA	0.003
	n	n (%)	n	n (%)	Adjusted HR (95% CI)		p-value
Patients who died	90	20/90 (22.2%)	138	32/138 (23.7%)	0.74 (0.34–1.62)	NA	0.45

**Notes:** Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. Analyses were performed following the principle of intention to treat. Missing data were handled using available case analysis. The ICCs of the questionnaire outcome measures were all very small near 0 and therefore not displayed. <sup>a</sup>Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. <sup>b</sup>Effect sizes are Cohen's *d*, 0.20 is small, 0.50 is moderate, and 0.80 is large.<sup>24</sup> <sup>c</sup>Change score interpretation: low score better. <sup>d</sup>McGill total score was calculated without the McGill physical symptoms subscale. <sup>e</sup>Change score interpretation: high score better. <sup>f</sup>Negative binomial regression analysis. <sup>g</sup>Because of skewness of distribution, a logarithm of the variable "number of days of readmission for AECOPD" was used.

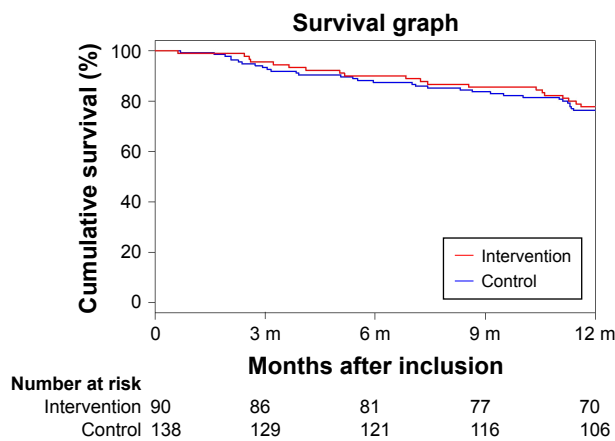
**Abbreviations:** ACP, advance care planning; AECOPD, acute exacerbation of COPD; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; ICC, intraclass correlation coefficient; McGill, McGill Quality of Life Questionnaire; OR, odds ratio; SD, standard deviation; SGRQ, St George Respiratory Questionnaire.

episodes of gradual decline are punctuated by acute severe exacerbations;<sup>3</sup> therefore, these acute exacerbations may have influenced findings defined at fixed time points.

Patients who received proactive palliative care experienced less impact of their COPD at 6 months. Although

this may have been a chance finding, as it was a secondary outcome, merely an effect on the SGRQ impact subscale was also observed in the Glasgow supported self-management trial for patients with moderate-to-severe COPD.<sup>29</sup> In addition, Higginson et al<sup>12</sup> found no effect on quality of life from





**Figure 2** Kaplan–Meier plot of survival according to the study group.

**Note:** The Cox proportional hazard test showed that survival was not significantly different between the intervention and control group, adjusted HR 0.74 (95% CI 0.34–1.62),  $p=0.45$ .

**Abbreviations:** CI, confidence interval; HR, hazard ratio.

early introduction of a palliative breathlessness support service for patients with refractory breathlessness (including COPD), but they did find improved breathlessness mastery, a quality of life domain of the Chronic Respiratory Disease Questionnaire. In contrast to patients with cancer in the palliative trajectory, for patients with advanced COPD in the palliative trajectory disease, oriented care remains necessary until the last weeks of life. It is possible that resilience to improve overall quality of life (especially symptoms and activity) is exhausted in this patient group, but further research is needed to test this hypothesis.

We did not find a difference in number and length of hospital readmissions. Previous research has demonstrated that the frequency of readmissions for an AECOPD is associated with functional limitation and poor health-related quality of life.<sup>30</sup> The fact that there was no change in either of the conditions (SGRQ activity score and SGRQ total) between groups may explain our finding. Furthermore, post-discharge mortality is associated with COPD severity as well as specific comorbidities, especially cardiac disease.<sup>30</sup> More patients in the intervention compared to the control group had severe dyspnea scores and CHF; however, we controlled for these confounders and found no difference in 1-year survival between groups.

During ACP conversations, patients are informed about their diagnosis, prognosis, their treatment options, and treatment consequences. Besides, patients can express their values and preferences for life-sustaining treatments with the goal of improving the quality of their end-of-life care.<sup>31</sup> In our study, more patients in the intervention group made ACP choices and consequently had ACP conversations during the year. As follow-up of patients was too short, we were not able to confirm

earlier findings that those ACP conversations actually increased the quality of end-of-life care.<sup>32,33</sup> Further research is needed.

Our study has strengths and limitations. Although our pragmatic cluster controlled design completely ruled out contamination, this design was subject to selection bias at hospital level. However, by using outcomes of a pretrial assessment, we were able to control for confounders at hospital level. Besides, the small ICCs indicate that differences between hospitals not noteworthy contributed to the concerned study outcomes. Next, pulmonologists were aware of treatment allocation which may have caused bias. Our baseline data suggest that in the intervention group pulmonologists may have included patients with more advanced COPD since those patients would profit from extra support, whereas pulmonologists in the control group may have included patients with less advanced COPD in order to not additionally burden more vulnerable patients. We used these differences in patients' baseline characteristics to control for confounders at patient level. However, it is unclear whether all important differences were taken into account and the true effect may therefore be underestimated in this study. Furthermore, attrition is common in long duration trials testing palliative interventions and does not necessarily reflect poor design or conduct.<sup>34</sup> The proportion of missing data typically increases with study duration;<sup>34</sup> however, our proportion of missing data (28.5% at 3 months) was relatively low compared to the weighted estimate for missing data at primary end point of the palliative interventions (23.1% at 28 days, median time), reported in a systematic review.<sup>34</sup> Nevertheless, the width of 8 of the 95% CI of the primary outcome proved that, if present, our study had the power to detect the necessary minimal important difference (MID) of 4.<sup>35</sup> Since the attrition rates in both groups were comparable, the threat to compromise the internal validity was minimal.<sup>34</sup> We also have no reason to assume that the participating hospitals are not representative of other hospitals; consequently, our findings can be generalized to other general hospitals.

## Conclusion

In this study, proactive palliative care did not improve the quality of life of patients with COPD at 3 months, as measured with the SGRQ. There are several possible reasons for this on identification, organization, patient, outcome measure, and disease course levels. Therefore, we recommend that future research on the effectiveness of proactive palliative care on quality of life in this patient group should take our findings into account. However, this study did demonstrate that proactive palliative care increased the number of patients who made ACP choices, and we therefore suggest that

proactive palliative care in COPD should place emphasis on supporting patients through ACP conversations to improve their quality of care toward the end of life.<sup>32,33</sup>

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## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** Change scores relative to baseline of McGill and HADS subscales and associated tests of effects between groups

Outcomes	Descriptives				Analysis of difference between groups for changes over time <sup>a</sup>		
	Intervention		Control		Estimated difference (95% CI)	Effect size <sup>b</sup>	p-value
	n	Mean (SD) observed change from baseline	n	Mean (SD) observed change from baseline			
McGill <sup>c</sup> physical well-being							
3 months	61	0.15 (2.95)	85	0.72 (2.87)	0.15 (-0.64 to 0.95)	-0.21	0.72
6 months	52	-0.35 (2.60)	73	-0.37 (2.88)	0.54 (-0.16 to 1.23)	0.01	0.16
9 months	47	0.43 (2.94)	64	-0.39 (2.75)	0.69 (-0.13 to 1.51)	0.29	0.13
12 months	44	-0.16 (2.82)	59	0.08 (2.97)	-0.14 (-1.22 to 0.93)	-0.08	0.82
McGill <sup>c</sup> physical symptoms							
3 months	34	0.65 (2.50)	39	-0.03 (2.32)	0.66 (-0.37 to 1.68)	0.28	0.27
6 months	28	0.57 (2.20)	37	-0.03 (2.42)	1.09 (0.08 to 2.11)	0.26	0.12
9 months	30	0.69 (2.91)	37	-0.41 (2.52)	0.97 (-0.05 to 1.99)	0.41	0.11
12 months	24	-0.19 (2.15)	32	-0.57 (2.46)	-0.13 (-1.20 to 0.82)	0.16	0.85
McGill <sup>c</sup> psychological							
3 months	73	0.21 (2.82)	110	0.33 (2.67)	-0.01 (-0.79 to 0.76)	-0.04	0.97
6 months	66	0.16 (2.97)	91	0.23 (2.70)	0.15 (-0.70 to 0.99)	-0.02	0.77
9 months	61	0.38 (2.43)	87	0.09 (2.64)	0.35 (-0.49 to 1.20)	0.11	0.44
12 months	55	0.27 (2.18)	80	-0.17 (2.95)	0.49 (-0.38 to 1.37)	0.17	0.30
McGill <sup>c</sup> existential							
3 months	75	0.37 (1.75)	111	0.24 (2.29)	0.36 (-0.22 to 0.95)	0.06	0.27
6 months	67	0.29 (1.61)	92	0.38 (2.17)	-0.01 (-0.52 to 0.49)	-0.05	0.99
9 months	63	0.08 (2.03)	89	0.14 (2.18)	-0.26 (-0.96 to 0.45)	-0.03	0.58
12 months	55	0.08 (2.18)	82	-0.01 (2.21)	0.03 (-0.70 to 0.75)	0.04	0.94
McGill <sup>c</sup> support							
3 months	73	-0.48 (1.96)	104	-0.63 (2.46)	0.37 (-0.27 to 1.01)	0.07	0.28
6 months	65	-0.93 (2.32)	89	-0.36 (2.17)	-0.34 (-1.01 to 0.32)	-0.26	0.39
9 months	59	-0.63 (1.97)	86	-0.98 (2.29)	0.21 (-0.50 to 0.93)	0.16	0.58
12 months	53	-0.66 (2.25)	78	-0.99 (2.10)	0.52 (-0.25 to 1.28)	0.15	0.21
HADS <sup>d</sup> anxiety							
3 months	76	-0.29 (4.03)	111	-0.27 (3.77)	-0.12 (-1.21 to 0.97)	-0.01	0.83
6 months	66	-0.46 (4.35)	90	-0.52 (3.75)	0.02 (-1.26 to 1.29)	0.01	0.98
9 months	62	-1.23 (4.29)	87	-0.26 (3.79)	-0.65 (-2.11 to 0.81)	-0.24	0.41
12 months	55	-0.38 (4.34)	81	0.17 (3.82)	-0.12 (-1.55 to 1.32)	-0.14	0.88
HADS <sup>d</sup> depression							
3 months	76	0.51 (3.65)	111	0.53 (3.59)	-0.25 (-1.33 to 0.83)	-0.01	0.66
6 months	66	0.91 (3.83)	89	0.90 (3.67)	-0.30 (-1.43 to 0.82)	0.00	0.61
9 months	62	1.20 (3.91)	87	0.59 (3.55)	0.15 (-1.11 to 1.41)	0.16	0.82
12 months	55	1.21 (3.88)	80	1.20 (3.79)	-0.78 (-2.30 to 0.74)	0.00	0.42

**Notes:** Associated tests of effects between groups were estimated by linear mixed models, adjusted for baseline covariates. Analyses were performed following the principle of intention to treat. Missing data were handled using available case analysis. Descriptive data are mean (SD) unless otherwise stated. The ICCs of the questionnaire outcome measures were all very small near 0 or 0 and therefore not displayed. <sup>a</sup>Associated tests of effect between groups were estimated by linear mixed models, adjusted for baseline covariates. <sup>b</sup>Effect sizes are Cohen's d, 0.20 is small, 0.50 is moderate, and 0.80 is large. <sup>c</sup>Change score interpretation: high score better. <sup>d</sup>Change score interpretation: low score better.

**Abbreviations:** CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; ICC, intraclass correlation coefficient; McGill, McGill Quality of Life Questionnaire; SD, standard deviation.

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