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Early View

Original article

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Exacerbation action plans for patients with COPD and comorbidities: a randomised controlled trial

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Take home message

Patient-tailored exacerbation action plans for COPD patients with comorbidities did not reduce exacerbation days, but reduced exacerbation duration and the risk of having ≥1 respiratory-related hospitalisation during follow-up, without excess mortality

ABSTRACT

This international randomised controlled trial evaluated whether COPD patients with comorbidities, trained in using patient-tailored multi-disease exacerbation action plans, had fewer COPD exacerbation days than usual care (UC).

COPD patients (GOLD II-IV) with ≥1 comorbidity (ischaemic heart disease, heart failure, diabetes, anxiety, depression) were randomised to a patient-tailored self-management intervention (n=102) or UC (n=99). Daily symptom diaries were completed for 12 months. The primary outcome "COPD exacerbation days/patient/year" was assessed using intention-to-treat analyses.

No significant difference was observed in the number of COPD exacerbation days/patient/year (self-management: median 9.6 (IQR 0.7-31.1); UC: median 15.6 (IQR 3.0-40.3); Incidence Rate Ratio (IRR) 0.87 (95% CI 0.54; 1.39); p=0.546). There was a significantly shorter duration per COPD exacerbation for self-management (self-management: median 8.1 (IQR 4.8-10.1) days; UC: median 9.5 (IQR 7.0-15.1) days; p=0.021), with no between-group differences in the total number of respiratory hospitalisations (IRR 0.76 (95% CI 0.42;1.35); p=0.348), but a lower probability of ≥1 respiratory-related hospitalisation compared to UC (Relative Risk (RR) 0.55 (95% CI 0.35; 0.87); p=0.008). No between-group differences were observed in all-cause hospitalisations (IRR 1.07 (95% CI 0.66; 1.72)) or mortality (self-management: n=4 (3.9%); UC: n=7 (7.1%); RR 0.55 (95% CI 0.17; 1.84)).

Patient-tailored exacerbation action plans for COPD patients with comorbidities did not significantly reduce exacerbation days, but reduced the duration per COPD exacerbation and the risk of having at least one respiratory-related hospitalisation during follow-up, without excess all-cause mortality.

Key words: Chronic Obstructive Pulmonary Disease; comorbidity; self-management; symptom flare up; hospitalisations; Randomised Controlled Trial

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung condition with distressing exacerbations that contribute to impaired quality of life and increased hospitalisations, mortality and healthcare costs. Many COPD patients have comorbidities [1,2] that further reduce quality of life [3] and are associated with an increased risk of COPD exacerbations, hospitalisations, mortality, and higher costs [1,2,4,5]. Evidence for COPD self-management interventions and action plans that are tailored for comorbidities is lacking.

A COPD self-management intervention is defined as "structured, but personalised, and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease" [6]. COPD exacerbation action plans are an integral part of COPD self-management interventions and have proven to reduce exacerbation duration, hospitalisations, and healthcare costs, and improve quality of life in COPD patients without comorbidities [7-10]. Benefits arise from earlier initiation of appropriate treatment, decreasing the severity of exacerbations, accelerating recovery, and reducing healthcare utilisation [11,12]. However, it is challenging to generalise these results to routine clinical practice in the wider COPD population, as most self-management studies have excluded COPD patients with comorbidities. The applicability, effectiveness and safety of symptom-based COPD action plans may be limited when comorbidities are present as comorbid symptoms may overlap with COPD symptoms leading to the initiation of incorrect or delayed treatment. Hence, the need for evidence-based exacerbation action plans that are tailored for existing comorbidities [13].

In the COPE-III study [14] we designed patient-tailored action plans (online supplement) for both COPD and comorbidities (ischaemic heart disease (IHD), chronic heart failure (CHF), diabetes mellitus (DM), anxiety, depression) [14,15]. A copy can be requested by the corresponding author. We evaluated whether patients with COPD and $\geq$1 comorbidity, trained in using patient-tailored symptom-based exacerbation action plans embedded in a multi-disease self-management intervention, had fewer COPD exacerbation days over 12 months than usual care (UC) [14].

METHODS

Detailed methods including a statistical analysis plan of this 1-year international multicentre open parallel-group randomised controlled trial (RCT) are published elsewhere [14]. The study was approved by the Medical Ethical Committee Twente (NL39516.044.12) and the Southern Adelaide Clinical Human Research Ethics Committee (37-12). Participants' written informed consent was obtained prior to data collection.

Patients

Between 2012 and 2015, patients were recruited from the outpatient departments of respiratory medicine of two hospitals in the Netherlands (Medisch Spectrum Twente, Enschede; Canisius-Wilhelmina Ziekenhuis, Nijmegen) and three in Australia (Repatriation General Hospital, Adelaide; Royal Adelaide Hospital, Adelaide; Flinders Medical Centre, Adelaide). Patients with COPD and one to five highly prevalent comorbidities were selected for this study. These comorbidities were chosen because of symptom overlap with COPD exacerbations, and/or their potential to become unstable during COPD exacerbations: IHD (history of myocardial infarction, angina pectoris); CHF (2008 ESC guidelines [16]), DM (glucocorticoid-induced, or stable type 1 or 2); active symptoms of anxiety and/or depression (≥11 Hospital Anxiety and Depression Scale (HADS) [17,18]), and/or anxiety or depression symptoms being treated at the time of inclusion.

After baseline measurements, patients were allocated to self-management or UC by an independent research assistant who was masked to treatment assignment and randomisation schedule, using a computerised minimisation program [19]. Allocation was stratified per hospital for smoking status, modified Medical Research Council dyspnoea (mMRC) score, number of comorbidities, and being on a waiting list for pulmonary rehabilitation. Blinding of patients and personnel to treatment group was not possible. Wherever possible, though, assessors of outcomes were blinded to treatment group.

At inclusion all patients described their individual symptom levels in a stable health state on a ‘What are my “usual” symptoms' card and were educated to complete daily symptom diaries for 12 months (online supplement). The colour-coded patient-tailored diaries included symptoms of COPD and comorbidities diagnosed at baseline [14]. On each day of the study patients were asked to compare their symptoms in the last 24 hours to their “usual” symptoms, and, if symptom levels had increased, to report the level of change for each symptom listed in their diary (i.e. no change, slightly increased, or significantly increased). Completed diaries including information regarding unscheduled healthcare visits and use of additional medications were returned at the end of each month. Incomplete diary data were compared with hospital admission data. Subsequently, patients were phoned to complete missing diary data, to provide feedback on diary use, to adjust symptom levels on the “What are my “usual” symptoms’ card if necessary (e.g. after an exacerbation), and to reinforce self-management behaviours (self-management group only). For the self-management group, exacerbation action plans for COPD, CHF, IHD, anxiety and depression were directly linked to the diaries. For diabetes, this link was indirect, as patients were prompted to check their blood glucose levels when the COPD action plan directed them to take glucocorticoid because of a COPD exacerbation. Additional details on the self-management and the UC sessions are provided in Table 1 (and online supplement).

Table 1. Content and components of self-management and usual care sessions

	Self-management intervention group	Usual care control group
Week 1	Group session: - knowledge regarding COPD and comorbidities - symptom recognition and monitoring - self-treatment (action plan linked to diary) - breathing and relaxation exercises - Dutch patients with diabetes: extra session on how to check and regulate blood glucose levels when necessary - Australian patients with diabetes: extra session on how to check blood glucose levels when necessary	Group session: - complete 'what are my "usual" symptoms' card - diary training
Week 2	Individual session: - complete 'what are my "usual" symptoms' card - diary training - exacerbation action plan training - mastery of skills; e.g. correct inhaler techniques (re-iterated when necessary), early recognition of exacerbations, self-initiating correct and proper actions	Group session: - re-iteration use of diary - feedback on diary completion
Week 3	Group session: - importance of physical fitness and exercise - diet and lifestyle behaviors - re-iteration diary and action plan use - re-iteration of breathing and relaxation exercises	Phone call 1*
Week 4	Individual session: - re-iteration use of diary and action plan - feedback on diary completion - feedback on actions	Phone call 2*
Week 8	Phone call 1†	Phone call 3*
Week 20	Phone call 2†	Phone call 4*
Week 36	Phone call 3†	Phone call 5*

* Approximately 5-10 minutes each
† Approximately 10-15 minutes each

Outcomes

The total number of COPD exacerbation days/patient/year was defined as the primary outcome. We also analysed the number of COPD exacerbations/patient/year, the duration per COPD exacerbation/patient/year and the severity of a COPD exacerbation day. COPD exacerbation data were collected from the symptom diaries. The onset was defined as a 'clear negative change in two symptoms classified major (dyspnoea, sputum purulence, sputum volume) or one major and one minor symptom (coughing, wheezing, fever) from baseline, for ≥2 consecutive days' [20,21]. Recovery was defined as 'the first day of: 1) three consecutive successive days that the patient has returned to his normal baseline health state; or 2) seven consecutive days on which patients continuously reported no or a slightly increase of COPD symptoms compared to baseline'. The duration per COPD exacerbation

was calculated by dividing the number of COPD exacerbation days by the number of COPD exacerbations. The severity of a COPD exacerbation day was determined by the sum of the individual relative changes from baseline daily symptom scores for major and minor COPD symptoms (for algorithm: see online supplement). Other secondary outcomes are described in detail elsewhere [14] and summarised in Table 2.

Table 2. Matrix of outcome measures and assessments

	Baseline (hospital)	**6 months (per mail)**	**12 months (hospital)**
Baseline characteristics	X		
Post-bronchodilator spirometry (FEV_1, FEV_6, FVC)	X		X
COPD Assessment Test (CAT)	X		X
modified Medical Research Council (mMRC) dyspnoea score	X	X	X
Health-related quality of life			
EQ5D and Visual Analogue Scale (VAS)	X	X	X
Chronic Respiratory Disease Questionnaire (CRQ)	X	X	X
Subjective fatigue			
Identity-Consequence Fatigue Score (ICFS)	X	X	X
Anxiety and depression symptoms			
Hospital Anxiety Depression Scale (HADS)	X	X	X
Confidence and competence			
COPD Self-Efficacy Scale (CSES)	X	X	X
CRQ mastery domain	X	X	X
Patient's self-management behaviour and knowledge			
Partners in Health (PIH) scale	X		X
Cost and healthcare utilisation			
Healthcare resource use for 12 months, EQ5D for utilities			X
Patient's adherence action plans, satisfaction and confidence			
Semi-structured interviews and daily symptom diary (retrospective)			X

EQ5D: EuroQol 5 Dimensions; FEV_1: Forced Expiratory Volume in one second; FEV_6: Forced Expiratory Volume in six seconds; FVC: Forced (expiratory) Vital Capacity.

Statistical analysis

Based on the exacerbation rates/patient/day from the COPE-II study [9] (intervention: 0.116; control: 0.176, both with an estimated SD of 0.17) and allowing for overdispersion and an attrition rate of 10%, 105 patients per group provided 80% power to detect an effect of this size, with a two-tailed p-<0.05.

Analyses were conducted on an intention-to-treat basis and reported in accordance with CONSORT guidelines [22]. Differences in baseline characteristics between self-management and UC were analysed using common statistical procedures, such as chi-square tests, T-tests and Mann-Whitney U tests, as appropriate.

If there were <4 consecutive days of missing diary data, these were completed using a predefined algorithm that combined last observation carried forward and next observation carried backward to the missing value. Since these data were considered missing completely at random, this single imputation technique was considered valid [23]. If ≥4 consecutive diary days of were missing, the missing entries were not considered to be completely at random. Therefore, a negative binomial regression imputation method was used to complete these diary days for the overdispersed individual patient count variable (COPD exacerbation days). This parametric method assumes an underlying negative binomial model for the imputed variable (given other predictors).

Analyses of the total number of COPD exacerbation days/patient/year (primary outcome) and COPD exacerbations/patient/year were conducted in three steps (online supplement), using imputed data in negative binomial regression models. The imputed values for missing diary days were calculated based on: 1) the observed number of COPD exacerbation days or exacerbations; 2) variables that correlated to exacerbation days or exacerbations; and 3) variables that explained missing days (online supplement). Incidence Rate Ratio's (IRR) were calculated. Sensitivity analyses were conducted by including only observed data (without any imputations). The between-group difference in duration per COPD exacerbation was analysed using a Mann-Whitney U test. The results for between-group differences at 12 months of follow-up for comorbid exacerbations (CHF, anxiety, depression, IHD events) are presented in the online supplement. Between-group differences of secondary continuous variables over the 12-month period were assessed using linear mixed-effect models for repeated measurements analyses. Relative risks were calculated for the probability of ≥1 hospitalisation and analysed using Z-tests.

All analyses were carried out using SPSS v 24.0 with a p-value <0.05 considered statistically significant.

RESULTS

Patients

In total, 201 patients with moderate to severe COPD were included (aged 68.5 (SD 8.9) years; 64.2% male; 19.9% current smokers; 1.6 (SD 0.8) specified comorbidities at baseline) (Table 3). At baseline, there were no significant differences between self-management (n=102) and UC (n=99) groups, except for the 6-minute walking distance (6MWD) (self-management: 330 (SD 116) metres; UC: 378 (SD 112) metres, p=0.006). The 12-month follow-up was completed by 83.3% of the individuals in the self-management group and 84.8% in the UC group (Figure 1). Patients completed 81.3% (self-management: 82.3%; UC: 80.2%) of the diary data.

Table 3. Baseline characteristics of the self-management intervention and usual care control group

	Self-management (n=102)	**Usual care (n=99)**
Age (years)	68.8 (9.0)	68.2 (8.9)
Gender (male)	66 (64.7%)	63 (63.6%)
Smoker	20 (19.6%)	20 (20.2%)
COPD exacerbations 2 years prior to study participation	3.0 (2.0-4.0)	3.0 (2.0-4.0)
Hospitalisations 1 year prior to study participation	1.0 (0-1.0)	1.0 (0-1.0)
Pack years[£]	41.0 (22.0-52.8)	37.3 (24.8-53.8)
Body Mass Index (kg/m^2)	29.8 (6.8)	29.6 (6.4)
Dyspnoea score (mMRC)	2.17 (1.02)	2.04 (1.10)
Post-bronchodilator spirometry		
FEV_1 (l)	1.42 (0.53)	1.36 (0.50)
FEV_1 % predicted	53.4 (16.1)	50.7 (14.3)
FEV_1/FVC	49.3 (14.3)	48.5 (12.2)
GOLD COPD classification		
GOLD II	60 (58.8%)	54 (54.5%)
GOLD III	35 (34.3%)	39 (39.4%)
GOLD IV	7 (6.9%)	6 (6.1%)
BODE score[β]	3.31 (2.11)	3.32 (2.18)
6-minute walking distance[†]	330 (116)	378 (112)[*]
Self-reported exercise (hours/week)[‡]	4.0 (2.0-8.0)	5.0 (2.0-10.0)
Education level		
Not completed primary school	4 (3.9%)	5 (5.1%)
Primary education	14 (13.7%)	11 (11.1%)
Not completed secondary school	38 (37.3%)	26 (26.3%)
Secondary education	18 (17.6%)	23 (23.2%)
Trade school	22 (21.6%)	25 (25.3%)
Undergraduate	1 (1%)	3 (3%)
Postgraduate	4 (3.9%)	4 (4%)

Unknown	1 (1%)	2 (2%)
Cognitive impairment (MMSE)	28.5 (27.0-29.0)	29.0 (26.0-30.0)
Health literacy confidence[±]	49 (48.0%)	57 (57.6%)
COPD-specific health status (CAT)[Ω]	19.4 (5.6)	18.0 (7.2)
General health status (VAS)	60.9 (14.3)	60.6 (17.9)
Quality of life domains (CRQ)		
Dyspnoea	4.25 (1.38)	4.22 (1.49)
Fatigue	3.77 (1.15)	3.84 (1.28)
Emotional	4.71 (1.26)	4.65 (1.07)
Mastery	4.89 (1.16)	4.90 (1.14)
Self-management knowledge and behaviour (PIH)[π]	77.9 (10.3)	78.4 (10.3)
Knowledge and coping	35.1 (7.3)	35.5 (7.2)
Symptom management, adherence to treatment	42.9 (4.5)	42.9 (4.4)
Self-efficacy domains (CSES)		
Negative affects	1.72 (0.90)	1.54 (0.77)
Emotional arousal	1.61 (0.83)	1.50 (0.82)
Physical exertion	2.47 (0.82)	2.36 (0.89)
Environment	2.02 (0.78)	1.95 (0.87)
Behavioural risk factors	1.76 (0.97)	1.58 (0.80)
Fatigue (ICFS)	224.4 (81.7)	220.8 (80.8)
Experiences	47.8 (16.8)	45.9 (15.5)
Impacts	40.5 (18.1)	41.6 (18.1)
Anxiety and depression domains (HADS)		
Anxiety symptoms	6.94 (4.39)	6.86 (3.82)
Depression symptoms	6.78 (3.95)	6.60 (3.87)
Specified comorbidities	1.61 (0.79)	1.58 (0.77)
Adapted Charlson Index[$]	2.61 (0.83)	2.70 (0.86)
Ischaemic Heart Disease	43 (42.2%)	50 (50.5%)
Chronic Heart Failure	24 (23.5%)	23 (23.2%)
Anxiety[δ]	27 (26.5%)	19 (19.2%)
Depression[δ]	31 (30.4%)	26 (26.3%)
Diabetes Mellitus	39 (38.2%)	39 (39.4%)

Data are presented as n (%), mean (SD) or median (interquartile range).

[*]Statistically significant different ($p<0.01$).
[£]Pack-years: self-management n=99; usual care n=96.
[β]BODE score: self-management n=99; usual care n=97.
[†]6-minute walking distance: self-management n=94; usual care n=85.
[‡]Self-reported exercise: self-management n=94; usual care n=89.
[±]Health literacy confidence: self-management n=100; usual care n=97.
[Ω]COPD-specific health status (CAT): self-management n=99; usual care n=95.
[π]Self-management knowledge and behaviour (PIH): self-management n=101; usual care n=98.
[$]We used an adapted version of the Charlson Index to classify comorbidities. Only the comorbidities included in our study were classified and scored as follows: pulmonary disease = 1; angina =1; chronic heart failure = 1; myocardial infarction = 1; diabetes mellitus =1; anxiety = 1; depression = 1. Self-management n=89; usual care n=88.
[δ]Active symptoms of anxiety and/or depression (cut-off score ≥11 from the HADS), and/or anxiety or depression symptoms being treated at the time of inclusion.

BODE: Body mass index, Obstruction, Dyspnoea, Exercise capacity; CAT: COPD Assessment Test; CRQ: Chronic Respiratory Disease Questionnaire; CSES: COPD Self-Efficacy Scale; FEV_1: Forced Expiratory Volume in one second; FVC: Forced (expiratory) Vital Capacity; GOLD (2011): Global initiative for chronic Obstructive Lung disease; HADS: Hospital Anxiety Depression Scale; ICFS: Identity-Consequence Fatigue Score; mMRC: modified Medical Research Council dyspnoea scale; MMSE: Mini Mental State Examination; PIH: Partners in Health scale; VAS: Visual Analogue Scale. Health literacy was measured by asking patients for their confidence in completing medical forms by themselves.

COPD exacerbations

A total of 446 COPD exacerbations (self-management n=216; UC n=230) were extracted from the diary data. Sixty-six (64.7%) self-management patients had at least one COPD exacerbation compared to 70 (70.7%) UC patients (RR 0.92 (95% CI 0.76; 1.11); p=0.363)) (Table 4). There was no statistically significant difference in the median number of COPD exacerbation days/patient/year (self-management: median 9.6 (IQR 0.7-31.1) days; UC: median 15.6 (IQR 3.0-40.3) days; IRR 0.87 (95% CI 0.54; 1.39); p=0.546). Sensitivity analyses including only observed diary data rendered similar results (Table 4). Excluding patients with an extremely long COPD exacerbation duration (>300 days) and thus a potential chronic deterioration of symptoms showed comparable results.

A statistically significant and clinically relevant shorter duration per COPD exacerbation was found for self-management (median 8.1 (interquartile range (IQR) 4.8-10.1) days) compared to UC patients (median 9.5 (IQR 7.0-15.1) days) (p=0.021). Sensitivity analyses including only observed diary data showed similar results (Table 4).

There was no difference in severity per COPD exacerbation day (self-management: median 4.1 (IQR 0-6.0); UC: median 5.0 (IQR 0-9.0); p=0.068) (Table 4).

Table 4. COPD exacerbations: results from negative binomial regression and Mann-Whitney U analyses for between-group differences at 12 months of follow-up

	Self-management (n=102)	Usual care (n=99)	Treatment effect (self-management vs. usual care)	
			IRR (95% CI) or RR (95% CI) or difference in duration	p-value
COPD exacerbations (complete data set with imputations)				
COPD exacerbations				
Median (IQR)	1.1 (0.1-3.9)	2.0 (0.7-4.0)		
Rate (per 100-person years)	2.4	2.7	0.91 (0.67; 1.25)	0.558*
COPD exacerbation days				
Median (IQR)	9.6 (0.7-31.1)	15.6 (3.0-40.3)		
Rate (per 100-person years)	28.7	34.2	0.87 (0.54; 1.39)	0.546*
Patients with ≥1 COPD exacerbation	n=66	n=71	0.90 (0.75; 1.09)	0.286±
Duration per COPD exacerbation (days), median (IQR)	8.1 (4.8-10.1)	9.5 (7.0-15.1)	-1.4	0.021†
COPD exacerbations (observed)				
COPD exacerbations				
Median (IQR)	1 (0-3)	2 (0-3)		
Rate (per 100-person years)	2.1	2.3	0.91 (0.65; 1.26)	0.561*
COPD exacerbation days				
Median (IQR)	9 (0-27.5)	13 (0-39)		
Rate (per 100-person years)	24.9	28.7	0.90 (0.56; 1.43)	0.640*
Patients with ≥1 COPD exacerbation	n=66	n=70	0.92 (0.76; 1.11)	0.363±
Duration per COPD exacerbation (days), median (IQR)	7.7 (4.3-10.0)	9.4 (6.5-14.6)	-1.7	0.012†
Severity per COPD exacerbation day, median (IQR)	4.1 (0-6.0)	5.0 (0-9.0)		0.068†

Data are presented as median (interquartile range) per patient per year or rate (per 100-person years).

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression analyses.
†Non-parametric Mann-Whitney U test for data related to duration.
±Z-test.

CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; IRR: Incidence Rate Ratio; RR: Relative Risk.

Hospitalisations

There were 106 (self-management n=47; UC n=59) respiratory-related hospitalisations (mean 0.53 (SD 1.09)) reported (Table 5). The self-management group had a lower probability of ≥1 respiratory-related hospitalisation compared to UC (Relative Risk (RR) 0.55 (95% CI 0.35; 0.87); p=0.008), with no between-group differences in duration per respiratory-related hospitalisation (self-management: mean 8.68 (SD 6.5) days; UC: 7.34 (SD 4.4) days; p=0.570) and in total respiratory hospital admission rates (IRR 0.76 (95% CI 0.42; 1.35); p=0.348). The total number of respiratory-related hospitalisation days per patient was numerically lower in the self-management group, but this difference was not statistically significant (Table 5).

At baseline 125 patients were diagnosed with CHF and/or IHD, in whom 20 cardiac-related hospitalisations were observed. No between-group differences were observed in cardiac-related hospitalisations (self-management: n=12; UC: n=8; p=0.215).

A total of 151 all-cause hospitalisations were extracted from diary data and medical records. No between-group differences in the number of all-cause hospitalisations were observed, nor in the total number of hospitalisation days or duration per all-cause hospitalisation. There was also no difference in the risk of ≥1 all-cause hospitalisation between study groups (RR 0.88 (95% CI 0.62; 1.24); p=0.455) (Table 5).

Table 5. Hospitalisations during 12 months of follow-up in the self-management and usual care group

	Self-management (n=102)	Usual care (n=99)	Treatment effect (self-management vs. usual care)	
			IRR (95% CI) or RR (95% CI) or difference in duration	p-value
Respiratory-related hospitalisations (primary respiratory-related problem)				
Number of hospitalisations (n; mean (SD))	47; 0.46 (1.15)	59; 0.60 (1.03)		
Rate (per 100 person-years)	46.1	59.6	0.76 (0.42; 1.35)	0.348*
Days rate (per 100 person-years)	3.8	4.3	0.92 (0.49; 1.73)	0.789*
Patients with ≥1 respiratory-related hospitalisation	n=21	n=37	0.55 (0.35; 0.87)	0.008±
Duration per hospitalisation (days) (mean (SD))	8.68 (6.50)	7.34 (4.41)	1.3	0.570†
All-cause hospitalisations				
Number of hospitalisations (n; mean (SD))	79; 0.77 (1.39)	72; 0.73 (1.23)		
Rate (per 100 person-years)	77.5	72.7	1.07 (0.66; 1.72)	0.796*
Days rate (per 100 person-years)	6.7	5.2	1.26 (0.73; 2.17)	0.405*
Patients with ≥1 hospitalisation	n=37	n=41	0.88 (0.62; 1.24)	0.455±
Duration per hospitalisation (days) (mean (SD))	9.36 (7.63)	6.99 (4.34)	2.4	0.235†

All hospitalisation data were skewed. However, the medians with interquartile ranges are not presented as they are less informative.

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression analyses.
†Non-parametric Mann-Whitney U test for data related to duration.
±Z-test.

CI: Confidence Interval; IRR: Incidence Rate Ratio; RR: Relative Risk; SD: standard deviation

Exacerbations in comorbid conditions

The results from analyses for between-group differences for comorbid exacerbations and flare-ups are presented in the online supplement. There was no effect of the self-management intervention on the number of CHF exacerbations, CHF exacerbation days, or duration per CHF exacerbation, nor for the number or duration of anxiety or depression flare-ups. There was a trend towards a higher prevalence of anxiety flare-up days in the self-management group that did not reach statistical significance (IRR 3.94 (0.84; 18.3); p=0.081). However, this was mainly driven by two patients in the self-management group with >100 days of anxiety flare-ups. Patients in the self-management group (n=43) reported a total of 972 days with IHD events (e.g. pain/pressure in arm(s), shoulder(s)) versus 983 in the UC group (n=50), with no significant between-group difference in the number of IHD events per patient per year. Comorbid DM was diagnosed in 39 self-management and 39 UC patients. Fourteen patients in the self-management group instituted additional glucose-lowering treatment.

Other secondary outcomes

No between-group differences were observed in all-cause mortality (self-management n=4 (cardiac n=1, other n=3); UC n=7 (respiratory n=1, cardiac n=2, other n=4); RR 0.55 (95% CI 0.17; 1.84); p=0.328).

The patients reported 371 courses of oral prednisolone and 247 courses of antibiotics. No significant difference in the number of oral prednisolone courses or antibiotics was reported between the study groups (Table 6). A significantly higher number of self-management patients (n=34, 51.5%) than UC patients (n=23, 32.9%) with a COPD exacerbation initiated a course of oral prednisolone within two days from the COPD exacerbation start (p=0.028) (Table 6).

Table 6. Courses of oral prednisolone and antibiotics during 12 months of follow-up in the self-management and usual care group

	Self-management (n=102)	Usual care (n=99)	Treatment effect (self-management vs. usual care)	
			IRR (95% CI) or difference in duration	p-value
Oral prednisolone courses				
Number of courses (n; median (IQR))	208; 1.0 (0-3.0)	163; 1.0 (0-2.0)		
Courses rate (per 100 person-years)	2.0	1.6	1.24 (0.83; 1.85)	0.293*
Number of exacerbations treated ≤2 days from COPD exacerbation start (n (%))	138 (63.9)	107 (46.5)		0.266†
Number of patients who initiated ≤2 days from COPD exacerbation start in ≥75% of exacerbations (n (%))	34 (51.5)	23 (32.9)		0.028†
Antibiotics courses				
Number of courses (n; median (IQR))	130; 0 (0-2.0)	117; 0 (0-2.0)		
Courses rate (per 100 person-years)	1.3	1.2	1.08 (0.70; 1.67)	0.736*

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression analyses.
†Chi-square test.

CI: Confidence Interval; IQR: interquartile range; IRR: Inicidence Rate Ratio.

Self-management led to a significant reduction in the behavioural risk factors domain of the COPD Self-Efficacy Scale (CSES) (difference -0.26 (95% CI -0.52; -0.01)) and a significantly worse emotional function Chronic Respiratory disease Questionnaire (CRQ) domain compared to UC (difference -0.41 (95% CI -0.70; -0.11)) (Table 7). No between-group differences were observed for other secondary outcomes (Table 7).

Table 7. Secondary outcome mean changes from baseline at 6 and 12 months of follow-up in the self-management and usual care group

	Self-management		Usual care		Self-management vs. usual care
	Δ from baseline at 6 months (n)	**Δ from baseline at 12 months (n)**	**Δ from baseline at 6 months (n)**	**Δ from baseline at 12 months (n)**	**Δ between-group difference (95% CI)**
Dyspnoea score (mMRC)[‡]	0.07 (83)	0.28 (80)	0.03 (76)	0.08 (78)	0.21 (-0.09; 0.50)
FEV_1 % predicted[†]	N/A	-1.71 (81)	N/A	-0.61 (75)	-1.09 (-3.52; 1.33)
FEV_1/FVC[†]	N/A	-0.06 (81)	N/A	-0.80 (75)	0.69 (-1.43; 2.81)
General health status (VAS)[†]	0.07 (83)	1.23 (79)	-0.40 (68)	-1.87 (75)	3.54 (-1.53; 8.61)
COPD health status (CAT)[‡]	N/A	1.32 (74)	N/A	0.56 (73)	0.54 (-1.02; 2.10)
CRQ dyspnoea[†]	-0.23 (83)	-0.29 (79)	-0.14 (77)	-0.03 (80)	-0.26 (-0.59; 0.08)
CRQ fatigue[†]	-0.23 (83)	-0.09 (79)	0.20 (77)	0.12 (80)	-0.20 (-0.49; 0.10)
CRQ emotional function[†]	-0.15 (83)	-0.10 (79)	0.19 (77)	0.30 (80)	-0.41 (-0.70; -0.11)[*]
CRQ mastery[†]	-0.07 (83)	0.11 (79)	0.22 (77)	0.30 (80)	-0.18 (-0.48; 0.11)
ICFS fatigue experiences[‡]	2.02 (83)	1.63 (77)	-3.85 (76)	-1.62 (79)	3.11 (-0.79; 7.03)
ICFS fatigue impacts[‡]	5.03 (84)	3.04 (77)	-3.25 (76)	-0.81 (80)	3.04 (-2.56; 8.64)
CSES negative affects[‡]	-0.04 (66)	-0.10 (66)	0.04 (68)	0.03 (70)	-0.16 (-0.37; 0.06)
CSES emotional arousal[‡]	-0.06 (74)	-0.11 (70)	0.05 (72)	-0.01 (78)	-0.14 (-0.33; 0.06)
CSES physical exertion[‡]	-0.09 (82)	-0.03 (78)	-0.05 (73)	-0.04 (79)	0.01 (-0.24; 0.26)
CSES environment[‡]	-0.03 (80)	-0.05 (77)	-0.07 (71)	-0.02 (77)	-0.03 (-0.25; 0.19)
CSES behavioural risk factors[‡]	-0.12 (78)	-0.14 (76)	0.03 (70)	0.11 (76)	-0.26 (-0.52; -0.01)[*]
PIH total[†]	N/A	2.90 (78)	N/A	2.89 (79)	0.28 (-2.43; 3.00)
PIH knowledge and coping[†]	N/A	2.17 (78)	N/A	1.99 (79)	0.47 (-1.30; 2.23)
PIH symptom management, adherence to treatment[†]	N/A	0.73 (78)	N/A	0.90 (79)	0.18 (-1.33; 1.68)
HADS anxiety[‡]	-0.41 (82)	-0.76 (79)	-0.91 (76)	-1.15 (80)	0.22 (-0.77; 1.21)
HADS depression[‡]	-0.13 (82)	-0.34 (79)	-0.59 (79)	-0.49 (80)	0.15 (-0.68; 0.97)

Note: A higher score indicates: [‡]worse; [†]better outcome.

[*]Statistically significant at a $p<0.05$ level; linear mixed-effect models for repeated measurements analyses.

CAT: COPD Assessment Test; CI: confidence interval; CRQ: Chronic Respiratory Disease Questionnaire; CSES: COPD Self-Efficacy Scale; FEV_1: Forced Expiratory Volume in one second; FVC: Forced (expiratory) Vital Capacity; HADS: Hospital Anxiety Depression Scale; ICFS: Identity-Consequence Fatigue Score; mMRC: modified Medical Research Council dyspnoea scale; PIH: Partners in Health scale; VAS: Visual Analogue Scale. N/A: not applicable.

DISCUSSION

This international multicentre RCT showed that self-management did not significantly reduce the number of COPD exacerbation days compared to usual care in COPD patients with comorbidities. Nevertheless, self-management was associated with a reduction in duration of COPD exacerbations and a reduced risk of having at least one respiratory-related hospitalisation during follow-up. No changes in all-cause hospitalisations and mortality were detected. Our results demonstrate that COPD patients may benefit from using exacerbation action plans that are tailored for comorbidities.

In this study, the number of COPD exacerbation days/patient/year (primary outcome) was numerically lower in the self-management group (9.6 days) compared to UC (15.6 days), however this difference was not statistically significant. The severity per exacerbation day was also numerically lower, although not statistically significant, in the self-management group (median 4.1) compared to UC (median 5.0). This may be because the study was underpowered. The mean number of 34 exacerbation days per patient per year in the usual care control group was much lower than the 64 a-priori anticipated. Our power calculation was based on the COPE-II study results of patients without severe comorbidities [9]. Reasonably, one would have expected an even higher rate of exacerbations in the COPE-III population with comorbidities. Improvements in usual care over time may be an explanation for the improved exacerbation rate [10]. Whereas all patients had at least three exacerbations or one respiratory-related hospitalisation in the two years preceding study entry, one third of the patients in the self-management group had no COPD exacerbation during the 12-month follow-up period, and could therefore not have benefited from the action plan. The effect of improvement of usual care and consequences for trial designs (i.e. less room for improvement) should be carefully considered in designing future studies of COPD interventions. This is also underlined by another recently published COPD self-management study that reported no effect in the primary outcome due to much lower event rates in the control group than anticipated [24].

There was no significant between-group difference in the number of COPD exacerbations. This was expected as action plans were only activated after the onset of an exacerbation. Self-management was

associated with quicker initiation of prednisolone courses, which may have contributed to an earlier initiation of appropriate self-treatment of deteriorating COPD symptoms and therefore a shorter duration of COPD exacerbations. However, it is not possible to definitively determine which component(s) of the exacerbation action plan were responsible for the positive effects on exacerbation days and duration.

Whereas this study was not powered to detect an effect of exacerbation action plans on hospitalisations, we observed a significant reduced risk of having at least one respiratory-related hospitalisation during follow-up in self-management patients. This effect was larger than in our previous study in COPD patients without comorbidities [9]. Non-respiratory and cardiac-related hospitalisations, and exacerbations in comorbid conditions were observed more often in the self-management group, although these differences were not statistically significant. Since we did not power for exacerbations in comorbid conditions, conclusions from these results are limited. The numerical increase in non-respiratory and cardiac-related hospitalisations may however be explained by the relevant action plans. These directed self-management group patients to contact a case-manager or healthcare provider for support if the cause of symptom deterioration was unclear. This was for safety reasons; its importance was highlighted by a study that was prematurely terminated due to excess all-cause mortality in the intervention group [25]. While our study was not powered to assess mortality, all-cause, cardiac-, and respiratory-related deaths were all lower in the self-management group, providing some evidence that multi-modal action plans with ongoing case-manager support are safe. Forthcoming cost analyses will assess the cost-effectiveness of the self-management intervention as the majority of costs in COPD patients with comorbidities are related to treatment of exacerbations, with hospitalisation costs as a major component [4,26].

The self-management intervention improved patients' self-efficacy in preventing breathing difficulty, but decreased patients' perceptions of emotional health, albeit without negative changes in overall emotional function (HADS scores). Behaviour change techniques (i.e. goal setting, action planning, self-monitoring) [27] were used to improve patient self-regulation skills as well as targeted uptake and

optimal use of appropriate self-management behaviours. The lower emotional function scores may have resulted from greater awareness of emotional symptoms associated with patients' health status, and this may be reflected in their responses in the CRQ domain. However, one should be cautious with the interpretation of these findings as they are not supported by other secondary outcomes.

Tailored approaches with individualised care plans are required to reduce treatment burden and optimise care for patients with COPD and comordities [28]. Efforts to improve this have focused on standardised care for each disease [29]. However, for COPD patients with multiple morbidities, these disease-specific recommendations may be inappropriate and lead to an excessive patient burden (e.g. increased exacerbations and length of hospitalisations) [29]. Although previous studies on COPD self-management interventions were not all without comorbidities [10], those studies used COPD-specific action plans and did not account for treatment adjustments related to comorbidities. The results of the current study should encourage healthcare providers to monitor comorbidities in COPD self-management interventions and exacerbation action plans, targeting timely treatment actions for each disease, anticipating better treatment effectiveness, and also increased safety.

Our RCT has several strengths. This is the first study in which COPD exacerbation action plans that included actions for comorbidities have been evaluated. By including COPD patients with comorbidities our patient group is typical of those treated in usual practice. Ongoing case-manager support, highlighted as a key component to reduce COPD (re)admissions [30] and emphasised as critical in the latest COPD self-management review regarding exacerbation plans [12], was offered to reinforce the patients' decision making and targeted behavioural change. While our self-management intervention included case-manager phone support, it was not a case-management programme, but a self-management intervention since the patient was in control through patient-initiated actions [6]. Two recent published showed reduced mortality in more complex COPD patients (those having comorbidities, frequent hospitalisations and/or exacerbations) who were offered intensive case-management interventions [24,31]. Another strength of our study was the use of symptom diaries with a high completion rate (59,629 diary days; 81.3%), comparable to another multicentre RCT of

exacerbation action plans [11]. Moreover, the diaries enabled calculation of daily symptom scores, minimised recall bias, and yielded information on day-to-day variability [32].

Our study has also limitations. Firstly, the baseline 6MWD in the self-management group was 48 metres shorter, which is clinically significant and has been related to poorer outcomes, including increased mortality [33]. This baseline between-group difference in 6MWD is however likely to have resulted in under- and not overestimation of the benefits of self-management. Secondly, contact with case-managers *per se* could have produced positive effects. However, while 52.9% of the self-management patients reported contact with the study office, the majority of the contacts were regarding logistics (e.g. check appointment dates, ask for a new diary). Thirdly, a small number of patients with a long exacerbation duration may not have properly adjusted their individual symptom levels on their 'What are my "usual" symptoms' card, and/or may not have fully recovered from their exacerbation [34]. A significant change in COPD symptoms - meeting our predefined definition of an acute COPD exacerbation - may have converted into a stepwise chronic deterioration of symptoms that was not recognised as such by the case-managers. This highlights a potential limitation of the use of paper versions of symptom diaries. Real-time symptom monitoring could be a more effective way to help patients and healthcare providers to recognise when recovery after an exacerbation is prolonged. Furthermore, algorithms could be used to indicate that individual 'baseline "usual" symptoms' need to be redefined. However, there were only two patients with extremely long COPD exacerbation durations (>300 days) and sensitivity analyses excluding these patients did not change results. Fourthly, because of the nature of the self-management intervention, blinding of patients to group assignment was not possible, potentially introducing performance bias (e.g. more symptom awareness and recognition in the self-management group compared to UC). Fifthly, many patients declined participation (42%), often because of logistic issues and time commitments associated with a RCT. Furthermore, the need for patients to be in a stable phase at the start of the study hampered patient inclusion because COPD exacerbations or flare-ups of comorbidities are common in this complex patient population. However, if this self-management intervention was included as part of

usual clinical practice, fewer barriers would be in place to preclude its use. Finally, we cannot define which parts of the intervention may have been driven the study effects.

In summary, although the *number* of COPD exacerbation days was not significantly lower in the self-management group, this study provides new evidence that exacerbation action plans for COPD patients with comorbidities embedded in an individualised, multi-faceted self-management intervention could be an effective tool to reduce the *duration* of COPD exacerbations and the risk of having a respiratory-related hospitalisation, without excess all-cause mortality. For the implementation of a successful self-management intervention for patients with COPD and comorbidities we recommend using a patient-tailored approach, that includes an individual assessment of COPD and comorbidities, information on self-management, daily self-monitoring of symptoms, exacerbation action plans for COPD and comorbidities, and case-manager support for feedback and motivation.

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References

1. Anecchino C, Rossi E, Fanizza C, De Rosa M, Tognoni G, Romero M. Prevalence of chronic obstructive pulmonary disease and pattern of comorbidities in a general population. *Int J Chron Obstruct Pulmon Dis* 2007;2(4):567-74.
2. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, Rutten EP, Op 't Roodt J, Wouters EF, Franssen FM. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187(7):728-35.
3. Huber MB, Wacker ME, Vogelmeier CF, Leidl R. Comorbid Influences on Generic Health-Related Quality of Life in COPD: A Systematic Review. *PLoS One* 2015;10(7):e0132670.
4. Chen W, FitzGerald JM, Sin DD, Sadatsafavi M. Excess economic burden of comorbidities in COPD: a 15-year population-based study. *Eur Respir J* 2017;50(1):1-10.
5. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. *Int J Chron Obstruct Pulmon Dis* 2015;10:95-109.
6. Effing TW, Vercoulen JH, Bourbeau J, Trappenburg J, Lenferink A, Cafarella P, Coultas D, Meek P, van der Valk P, Bischoff EW, Bucknall C, Dewan NA, Early F, Fan V, Frith P, Janssen DJ, Mitchell K, Morgan M, Nici L, Patel I, Walters H, Rice KL, Singh S, Zuwallack R, Benzo R, Goldstein R, Partridge MR, van der Palen J. Definition of a COPD self-management intervention: International Expert Group consensus. *Eur Respir J* 2016;48(1):46-54.
7. Zwerink M, Brusse-Keizer M, van der Valk PD, Zielhuis GA, Monninkhof EM, van der Palen J, Frith PA, Effing T. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;19;3:CD002990.
8. Bourbeau J, van der Palen J. Promoting effective self-management programmes to improve COPD. *Eur Respir J* 2009;33(3):461-3.

9. Effing T, Kerstjens H, van der Valk, Zielhuis G, van der Palen J. (Cost)-effectiveness of self-treatment of exacerbations on the severity of exacerbations in patients with COPD: the COPE II study. *Thorax* 2009;64(11):956-62.
10. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, van der Palen J, Effing TW. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017;8:CD011682.
11. Trappenburg JC, Monninkhof EM, Bourbeau J, Troosters T, Schrijvers AJ, Verheij TJ, Lammers JW. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax* 2011;66(11):977-84.
12. Howcroft M, Walters EH, Wood-Baker R, Walters JA. Action plans with brief patient education for exacerbations in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016;12:CD005074.
13. Morgan MD. Action plans for COPD self-management. Integrated care is more than the sum of its parts. *Thorax* 2011;66(11):935-6.
14. Lenferink A, Frith P, van der Valk P, Buckman J, Sladek R, Cafarella P, van der Palen J, Effing T. A self-management approach using self-initiated action plans for symptoms with ongoing nurse support in patients with Chronic Obstructive Pulmonary Disease (COPD) and comorbidities: The COPE-III study protocol. *Contemp Clin Trials* 2013;36(1):81-9.
15. Effing TW, Lenferink A, Buckman J, Spicer D, Cafarella PA, Burt MG, Bassett KL, van Ommeren C, Anesbury S, van der Valk PD, Frith PA, van der Palen J. Development of a self-treatment approach for patients with COPD and comorbidities: an ongoing learning process. *J Thorac Dis* 2014;6(11):1597-605.
16. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart

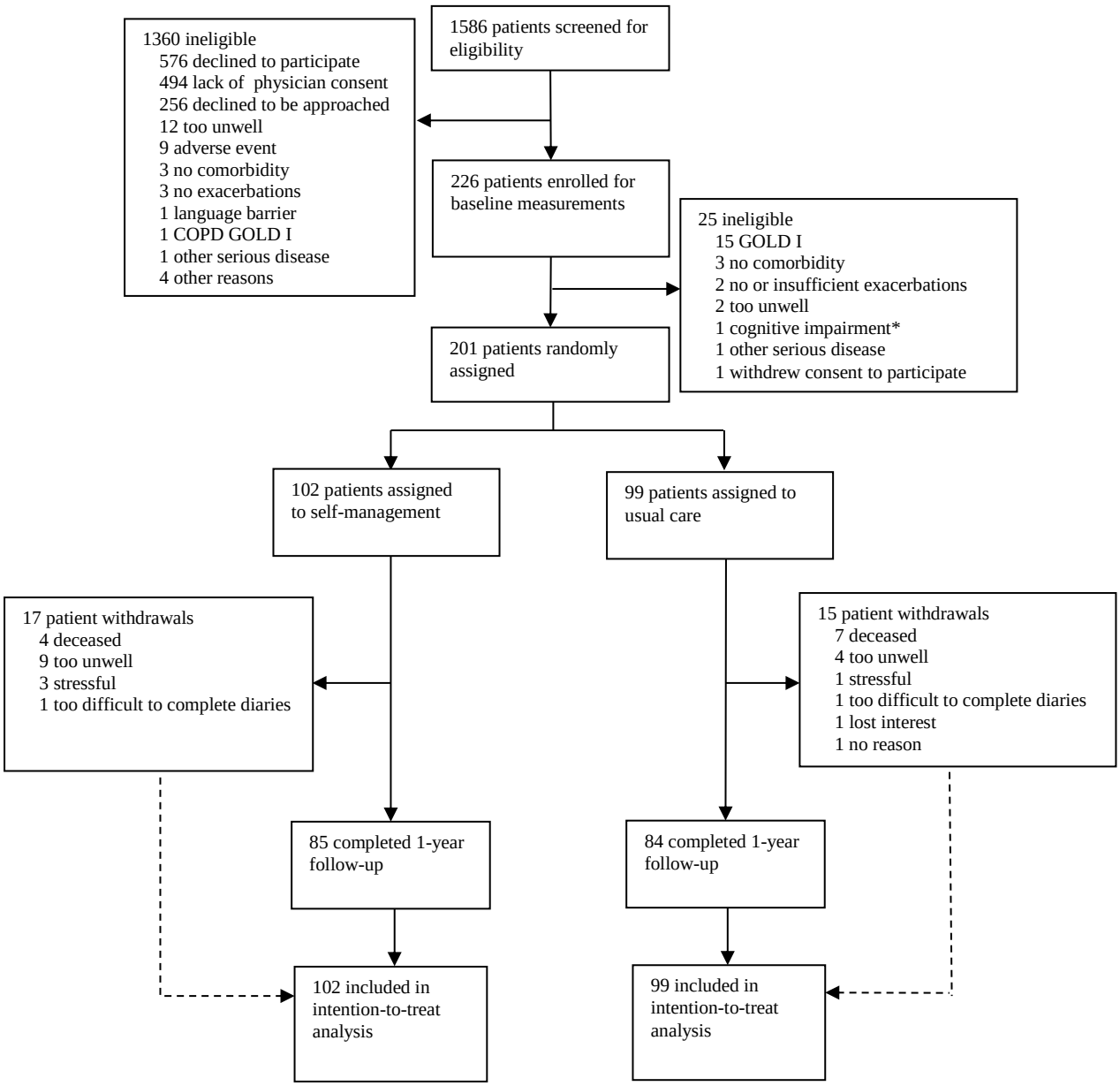
Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive CareMedicine (ESICM). *Eur Heart J* 2008;29(19):2388–442.

17. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361–70.
18. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997;27(2):363–70.
19. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005;330(7495):843.
20. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106(2):196-204.
21. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117(5 Suppl 2):398S-401S.
22. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276(8):637-9.
23. Newgard CD, Lewis RJ. Missing Data: How to Best Account for What Is Not Known. *JAMA* 2015;314(9):940-1.
24. Kessler R, Casan-Clara P, Koehler D, Tognella S, Luis Viejo J, Dal Negro RW, Díaz-Lobato S, Reissig K, González-Moro JSR, Devouassoux G, Chavaillon J, Botrus P, Arnal J, Ancochea J, Bergeron-Lafaurie A, De Abajo C, Randerath WJ, Bastian A, Cornelissen CG, Nilius G, Texereau JB, Bourbeau J. COMET: a multicomponent home-based disease-management programme versus routine care in severe COPD. *Eur Respir J* 2018;51(1):1-14.
25. Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, Thwin SS, Huang GD, Robbins R, Sriram PS, Sharafkhaneh A, Mador MJ, Sarosi G, Panos RJ, Rastogi P, Wagner TH, Mazzuca SA, Shannon C, Colling C, Liang MH, Stoller JK, Fiore L, Niewoehner DE. A

comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalisations: a randomized, controlled trial. *Ann Intern Med* 2012;156(10):673-83.

26. van Boven JFM. Costly comorbidities of COPD: the ignored side of the coin? *Eur Respir J* 2017;50(1):1700917.
27. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;46(1):81-95.
28. Vanfleteren LE, Spruit MA, Franssen FM. Tailoring the approach to multimorbidity in adults with respiratory disease: the NICE guideline. *Eur Respir J* 2017;49(2):pii:1601696.
29. Salisbury C, Man MS, Bower P, Guthrie B, Chaplin K, Gaunt DM, Brookes S, Fitzpatrick B, Gardner C, Hollinghurst S, Lee V, McLeod J, Mann C, Moffat KR, Mercer SW. Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet* 2018;392(10141):41-50.
30. Benzo R, Vickers K, Novotny PJ, Tucker S, Hoult J, Neuenfeldt P, Connett J, Lorig K, McEvoy C. Health Coaching and COPD Rehospitalization: a Randomized Study. *Am J Respir Crit Care Med* 2016;194(6):672-80.
31. Rose L, Istanboulian L, Carriere L, Thomas A, Lee H, Rezaie S, Shafai R, Fraser I. Program of Integrated Care for Patients with Chronic Obstructive Pulmonary Disease and Multiple Comorbidities (PIC COPD(+)): a randomised controlled trial. *Eur Respir J* 2018;51(1):1-10.
32. Leidy NK, Sexton CC, Jones PW, Notte SM, Monz BU, Nelsen L, Goldman M, Murray LT, Sethi S. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. *Thorax* 2014;69:443-9.
33. Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J, Calverley PM, Tal-Singer R, Agusti A, Coxson HO, Lomas DA, MacNee W, Rennard S, Silverman EK, Crim CC, Yates J, Wouters EF, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study investigators. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. *J Am Med Dir Assoc* 2012;13: 291–97.

34. Wageck B, Cox NS, Holland AE. Recovery following acute exacerbations of Chronic Obstructive Pulmonary Disease - A review. *COPD* 2019;16(1):93-103.



*Mini Mental State Examination < 24

Figure 1. Flowchart patient enrolment COPE-III study

Figure E1. Example completed 'What are my "usual" symptoms' card

What are my "usual" symptoms

Date: ..... / ..... /..... **RANDnr**: .....

1. COPD

Breathlessness:

- After 10 – 15 meters or up to 20 meters. After and with showering and bending over. Not at rest.
- Walks 5 – 6 meters on flat ground is limit, 5-10 minutes recovery. Limited in most activities, but can manage personal care. Just needs 10-15 minutes to recover

Sputum production:

- None for days to weeks, then sudden production of ½ egg cupful at random times. Daily cough, more in colder weather.
- Daily once or twice, 10 cent piece amount.

Colour of sputum:

- White and clear.
- White foam - opaque

2. Chronic Heart Failure

Weight: 85 kg

Fluid retention:

- Ankles swollen up to sock level, leaving a sock mark (today swollen to mid-calf and pitting)
- No swelling of ankles, but if outside in hot weather can swell slightly. No bloating. Can't lean head on shoulder.

Breathlessness during the night:

- Only on exertion.
- None – uses CPAP and oxygen.

3. Feeling light headed / dizzy

- Light headed on standing after sitting occasionally lasting less than a minute.
- Can be light headed on standing quickly- once daily briefly. Can happen when turn quickly – briefly. But hard to say with vertigo.

4. Anxiety and Depression

Anxiety

Description of anxiety feelings (when, how often, under what circumstances):
Frustration with not being able to do tasks.

Depression

Description of depression feelings (when, how often, under what circumstances):
Frustration with not being able to do tasks.

5. Ischaemic Heart Disease

Pains in shoulder and neck when sitting and leaning forward, relieved on sitting back. Left arm and hand – mild to severe tingling in hand above wrist a lot of the time. Ache in elbow relieved by panadeine and position change, which returns, provoked with certain movements.

Tablets/spray; how frequently used: None.

Figure E2. Daily symptom diary for COPD and each of the relevant comorbid symptoms

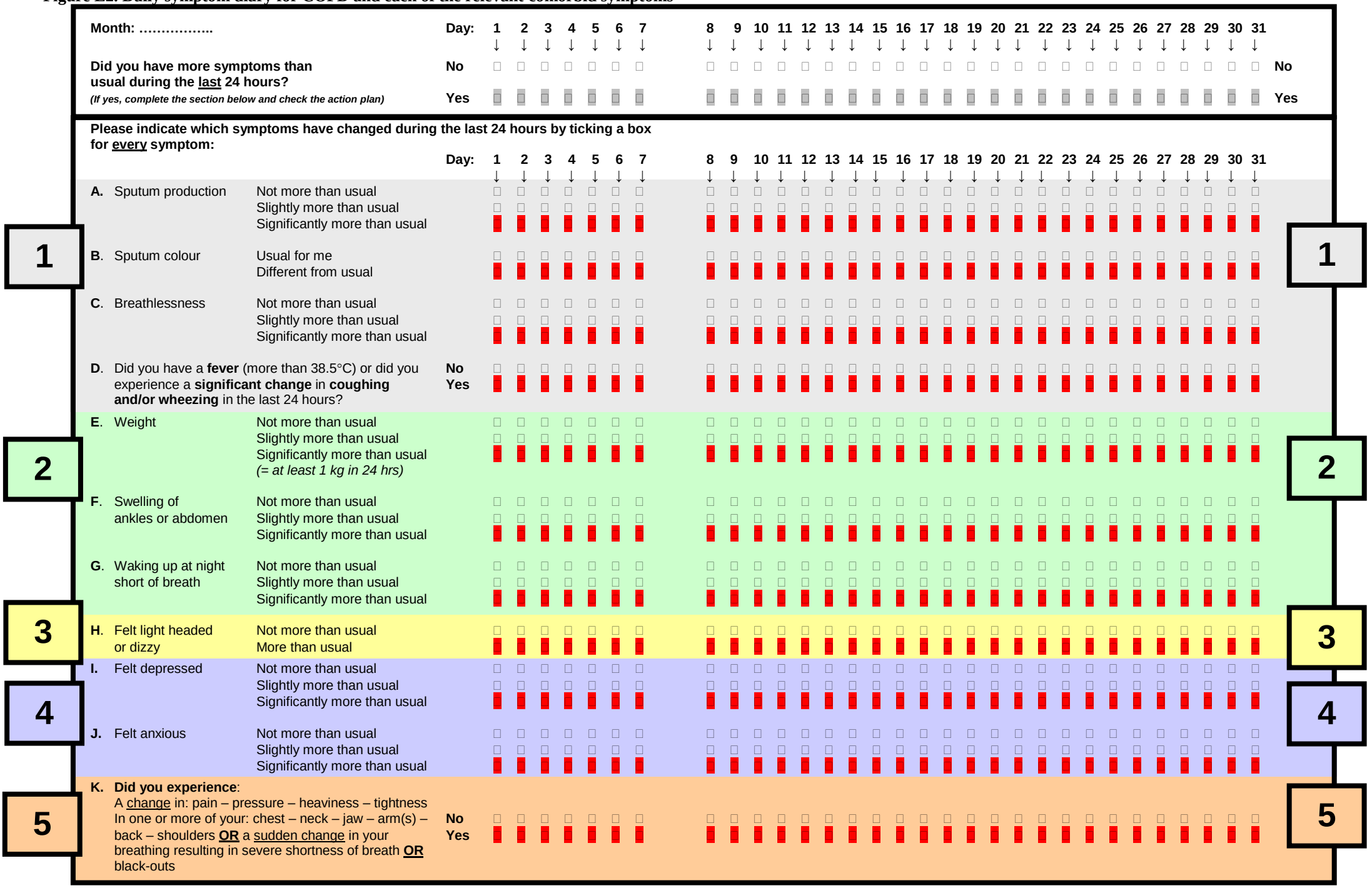
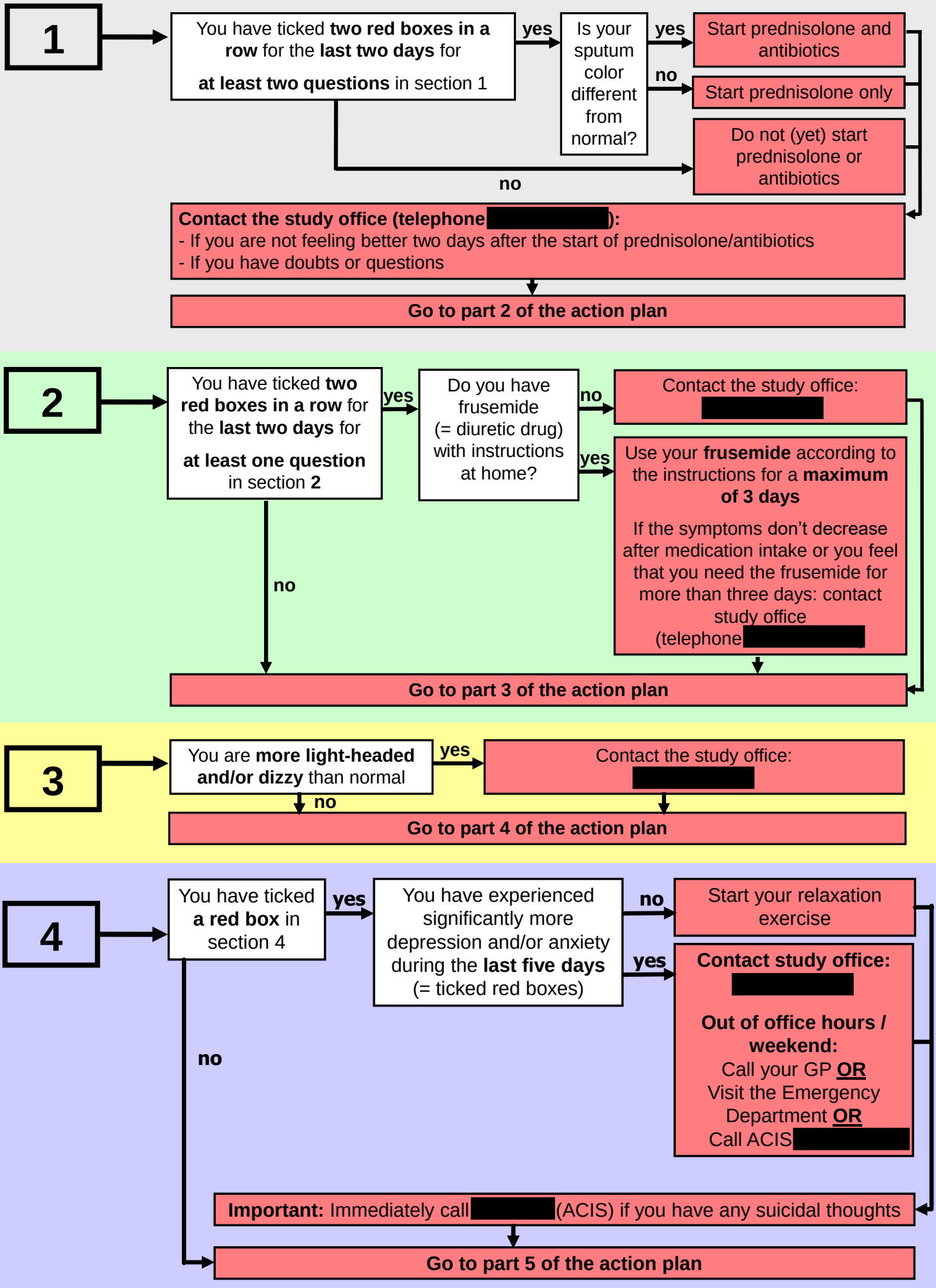
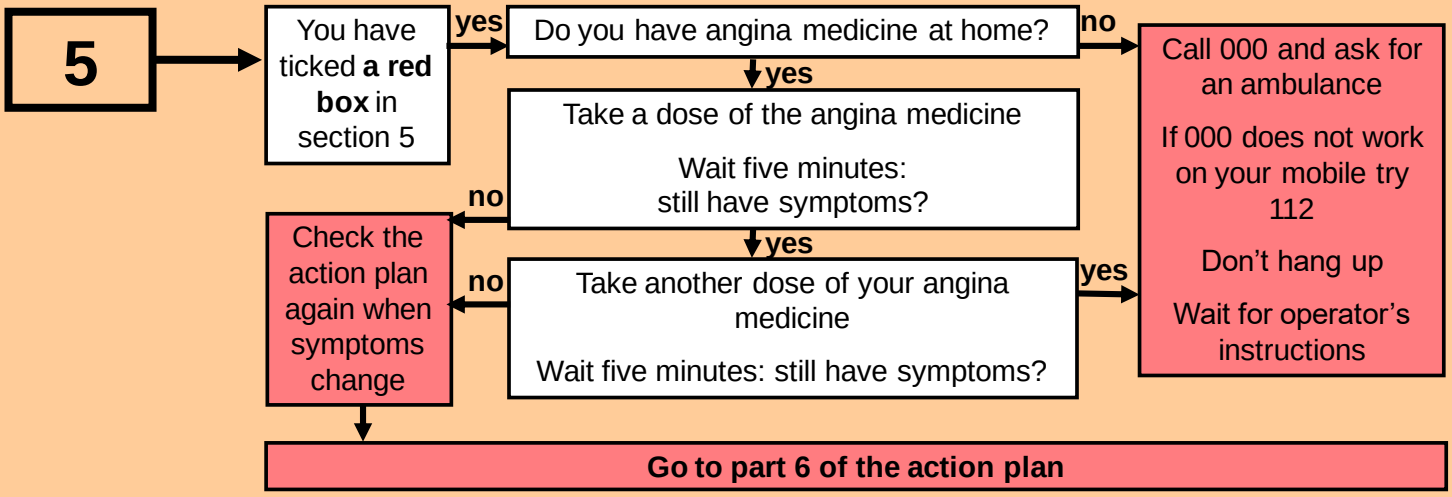
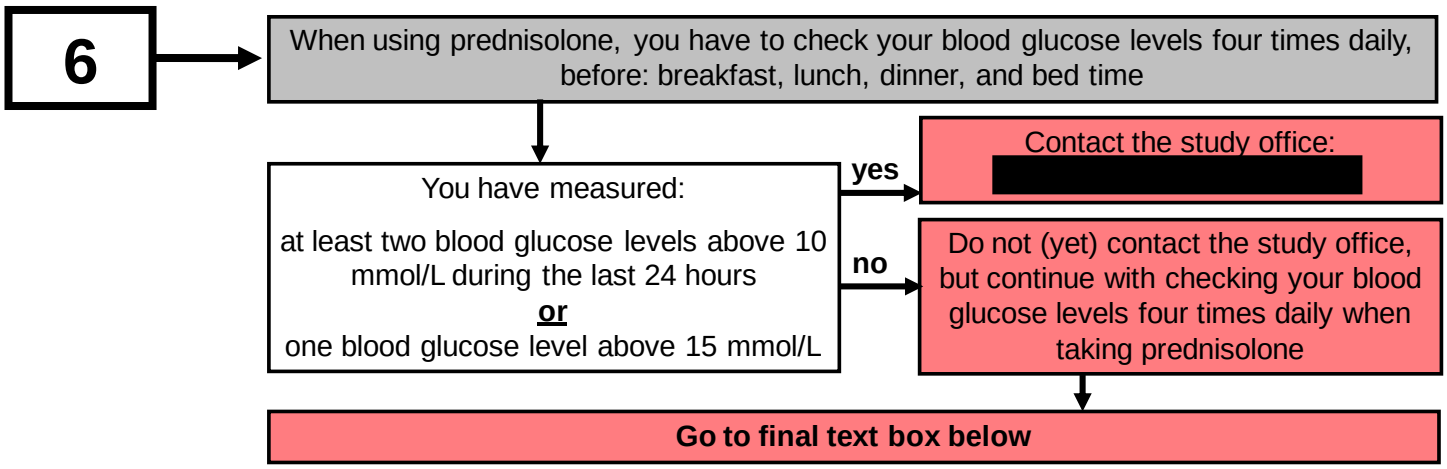


Figure E3. Patient-tailored action plan for COPD and each of the relevant comorbid symptoms







FINAL PART OF THE ACTION PLAN:

If you are not feeling better two days after the start of prednisolone/antibiotics
→ **Contact the study office**

If you have had a **fever** (more than 38.5°C) for **at least two days in a row** but you **did not** tick any red boxes for other symptoms
→ **Contact your GP**

PLEASE CHECK THE ACTION PLAN TOMORROW AGAIN

And remember: you can always contact the study office if you have any doubts or questions [redacted]

Table E1. Additional details on the self-management and the usual care sessions

In the first month, patients in the intervention group attended two to three small group (4-8 patients, 1-2 hours per session) and two individual hospital-based self-management sessions (1 hour per session) at weekly intervals (Table 2), depending on their comorbidities. These sessions were guided by a trained case-manager (experienced respiratory nurses) and supported by cardiac, mental health and/or diabetes nurses. Case-managers were trained specifically in the study methods and support of patients in two three-hour sessions before the study commenced. One, four, and eight months after completion of the self-management sessions, the case-manager checked and consolidated behaviours by phone to reinforce self-management skills. When symptoms significantly increased, patients were asked to consult their tailored action plans that consisted of colour-coded individualised actions for COPD and each comorbid symptom. Patients were taught when to self-initiate a course of oral prednisolone (and antibiotics) for a COPD exacerbation. Actions required for a change in comorbid symptoms included taking additional diuretic treatment for increased oedema, using specific relaxation strategies for anxiety, checking blood glucose levels when taking oral prednisolone, or calling an ambulance for severe or unresolving chest pain. When the cause of symptoms was unclear and additional advice was necessary, the research officer together with the case-manager acted as a triage. If new comorbidities were diagnosed during follow-up, patients received additional individual training and an adapted action plan that included the newly diagnosed comorbidities. Patients in the usual care control group attended two one-hour group sessions held on two consecutive weeks (Table 1). They were trained in diary completion and subsequently received 'usual care' (routine care provided at hospitals and in primary care). Patients were contacted by phone by the case-manager five times to confirm accurate completion of diaries during follow-up.

Table E2. Additional details on the patient recruitment

After one year of patient recruitment (July 2013), the observed withdrawal (8%) for randomised patients was lower than a-priori expected (30%). Therefore, we assumed that less patients needed to be included to achieve a significant effect for our primary outcome, and we revised the attrition rate to 10%. This adjusted attrition rate of 10% was approved by the Medical Ethical Committee Twente and the Southern Adelaide Clinical Human Research Ethics Committee. However, the observed attrition rate (15.9%) amongst all randomised patients was higher than 10%, and therefore reduced the power of the study to achieve a significant difference for the primary endpoint.

Table E3. Pre-defined algorithm for COPD exacerbation day severity scores

COPD exacerbation day severity scores

COPD exacerbation onset was defined as a 'clear negative change in two symptoms classified major (dyspnoea, sputum purulence, sputum volume) or one major and one minor symptom (coughing, wheezing, fever) from baseline, for at least two consecutive days'. The day that the exacerbation was resolved was defined as the first day of: 1) three consecutive successive days that the patient has returned to his normal baseline health state; or 2) seven consecutive days on which patients continuously reported no or only a slightly increase of COPD symptoms compared to baseline.

The severity of a COPD exacerbation day was determined by the sum of the individual relative change to baseline daily symptom scores (reported in the 'what are my usual symptoms' card) with a range of 0-10 points.

Major symptoms (breathlessness, sputum production, sputum colour) of a COPD exacerbation day scored as:

- Normal = 0 points
- Slightly increase = 1.4285 points
- Significantly increase = 2.8571 points
- Sputum colour different from usual = 2.8571 points

The major COPD symptom scores had a range of 0-8.5713 per COPD exacerbation day.

Minor symptoms (presence of fever and/or coughing and/or wheezing) of a COPD exacerbation day scored as:

- Normal = 0 points
- Presence of fever and/or coughing and/or wheezing = 1.4285 points

The minor COPD symptom scores had a range of 0-1.4285 per COPD exacerbation day.

When patients were hospitalised, a severity score of 20 points was assigned.

Table E4. Pre-defined algorithms for flare-ups of comorbid symptoms

Chronic Heart Failure exacerbation

Chronic Heart Failure (CHF) exacerbation onset was defined as a 'clear negative change in at least one symptom (fluid retention: weight, swelling of ankles or abdomen, wake up at night short of breath) from baseline, for at least two consecutive days'. The day that the CHF exacerbation was resolved was be defined as the first day of: 1) three consecutive successive days that the patient has returned to his normal baseline cardiac health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of CHF symptoms compared to baseline.

Anxiety flare-up

Anxiety flare-up onset was defined as a 'clear negative change in anxiety symptoms from baseline, for at least five consecutive days'. The day that the anxiety flare-up was resolved was defined as the first day of: 1) five consecutive successive days that the patient has returned to his normal baseline anxiety health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of anxiety symptoms compared to baseline.

Depression flare-up

Depression flare-up onset was defined as a 'clear negative change in depression symptoms from baseline, for at least five consecutive days'. The day that the depression flare-up was resolved was defined as the first day of: 1) five consecutive successive days that the patient has returned to his normal baseline depression health state; 2) seven consecutive days on which patients continuously reported no or only a slightly increase of anxiety symptoms compared to baseline.

Ischaemic Heart Disease events

An Ischaemic Heart Disease (IHD) event was defined as a 'clear negative change in IHD symptoms from baseline, for at least one day'. The day that the IHD event was resolved was defined as the first day of: one successive day that the patient has returned to his normal baseline cardiac health state.

Table E5. Analyses on the number of COPD exacerbation days and COPD exacerbations

The analyses on the number of COPD exacerbation days were conducted in three steps using imputed data in negative binomial regression models:

1) In the first step, we used negative binomial regression modelling to calculate predicted mean values for the number of COPD exacerbation days per patient per year for all patients, based on: I) the observed number of COPD exacerbation days per patient; II) individual patient data that correlated to exacerbation days; and III) variables that explained missing data including the number of missing days. A first negative binomial regression model (Table E6) was selected based on model fit (lowest Akaike information criterion);
2) In the second step, the predicted mean values from the first model were imputed for the patients with missing diary days. This was combined with the observed COPD exacerbation days to obtain an estimate of the number of COPD exacerbation days per patient per year. In a second negative binomial regression model this combination was used as outcome measure to calculate incidence rate ratios (IRR) for the self-management intervention group compared to the usual care group;
3) In the third step, we conducted a sensitivity analysis with observed diary data only (without any imputations) on the number of COPD exacerbation days per patient per year and an IRR was calculated.

The same steps were conducted to analyse the number of COPD exacerbations.

Table E6. Additional information imputation process: Final negative binomial regression model to calculate the predicted mean values for the number of COPD exacerbation days per patient per year, corrected for individual patient data that correlated to exacerbation days and variables that explained missing data

Model parameter	**Parameter estimate (95% CI)**	**Incidence Rate Ratio (95% CI)**
Group allocation		
Self-management	-0.57 (-0.94; -0.21)	0.56 (0.39; 0.81)*
Usual care	reference	
Number of missing days	-0.001 (-0.002; 0.00)	0.999 (0.999; 1.00)
Use of prednisolone	0.31 (0.22; 0.41)	1.37 (1.25; 1.50)
Number of CHF exacerbations	0.27 (0.03; 0.51)	1.31 (1.03; 1.66)
Respiratory-related hospitalisation days	0.02 (0.004; 0.03)	1.02 (1.00;1.03)
CRQ dyspnoea score at baseline	-0.19 (-0.31; -0.07)	0.83 (0.73; 0.93)

Δ Akaike Information Criterion: 1.3

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression modelling based on the observed number of COPD exacerbation days per patient per year and adjusted for the number of missing days, use of prednisolone, number of chronic heart failure (CHF) exacerbations, respiratory-related hospitalisation days, and the Chronic Respiratory Questionnaire (CRQ) dyspnoea domain score at baseline. In the second step, the corresponding predicted mean values from this model were imputed for patients with missing diary days.

Table E7. Additional information imputation process: Final negative binomial regression model to calculate the predicted mean values for the number of COPD exacerbations per patient per year, corrected for individual patient data that correlated to exacerbations and variables that explained missing data

Model parameter	**Parameter estimate (95% CI)**	**Incidence Rate Ratio (95% CI)**
Group allocation		
Self-management	-0.23 (-0.47; 0.02)	0.80 (0.61; 1.02)*
Usual care	reference	
Number of missing days	0.00 (0.00 - 0.001)	1.00 (1.00-1.001)
Use of prednisolone	0.17 (0.11; 0.24)	1.19 (1.12; 1.27)
Number of CHF exacerbations	0.09 (0.03; 0.16)	1.10 (1.03; 1.17)
Respiratory-related hospitalisation days	0.02 (0.01; 0.03)	1.02 (1.01; 1.02)
CRQ dyspnoea score at baseline	-0.15 (-0.25; -0.06)	0.86 (0.78; 0.95)

Δ Akaike Information Criterion: 1.9

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression modelling based on the observed number of COPD exacerbations per patient per year and adjusted for the number of missing days, use of prednisolone, number of chronic heart failure (CHF) exacerbations, respiratory-related hospitalisation days, and the Chronic Respiratory Questionnaire (CRQ) dyspnoea domain score at baseline. In the second step, the corresponding predicted mean values from this model were imputed for patients with missing diary days.

Table E8. Comorbid exacerbations and flare-ups: results from negative binomial regression and Mann-Whitney U analyses for between-group differences at 12 months of follow-up

	Self-management (n=102)	Usual care (n=99)	Treatment effect (self-management vs. usual care)*	
			IRR (95% CI) or difference in duration	p-value
Comorbid Chronic Heart Failure (CHF)	n=24	n=23		
CHF exacerbations	0 (0-4.0)	0 (0-2.0)	1.55 (0.67; 3.51)	0.290
CHF exacerbation days	0 (0-23.5)	0 (0-16.0)	1.63 (0.57; 4.69)	0.366
Duration per CHF exacerbation (days)	0 (0-6.3)	0 (0-8.0)	0	0.729†
Patients with ≥1 CHF exacerbation	n=11	n=11		
Duration per CHF exacerbation (days)	6.5 (2.5-14.3)	8.0 (5.0-10.5)	-1.5	0.532†
Comorbid anxiety	n=42	n=36		
Anxiety flare-ups, mean (SD)	0.33 (0.93)	0.25 (0.60)	1.33 (0.43; 4.17)	0.621
Anxiety flare-up days, mean (SD)	7.76 (30.1)	1.97 (6.21)	3.94 (0.84; 18.3)	0.081
Duration per anxiety flare-up (days), mean (SD)	4.22 (17.0)	1.24 (3.47)	2.98	0.742†
Patients with ≥ 1 anxiety flare-up	n=8	n=6		
Duration per anxiety flare-up (days)	8.5 (2.8-27.9)	6.0 (3.1-11.8)	2.5	0.604†
Comorbid depression	n=42	n=36		
Depression flare-ups, mean (SD)	0.21 (0.78)	0.19 (0.47)	1.10 (0.29; 4.20)	0.887
Depression flare-up days, mean (SD)	5.90 (24.0)	2.31 (7.72)	2.56 (0.51; 13.0)	0.256
Duration per depression flare-up (days), mean (SD)	3.48 (16.2)	1.76 (5.40)	1.72	0.408†
Patients with ≥1 depression flare-up	n=4	n=6		
Duration per depression flare-up (days)	21.1 (8.3-87.8)	2.8 (0-11.8)	18.3	0.201†

Data are presented as median (interquartile range) per patient per year, unless stated otherwise. Data on anxiety and depression flare-ups were skewed. Due to the low number of flare-ups for comorbid anxiety and depression, however, the medians of 0 (interquartile range 0-0) are not presented as they are less informative.

*Between-group difference results at 12 months of follow-up were obtained with negative binomial regression analyses.
†Non-parametric Mann-Whitney U test for data related to duration.
CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; IRR: Incidence Rate Ratio.

There were 24 COPD patients diagnosed with comorbid CHF in the self-management group and 23 in the UC group (Table E8). There was no effect of the self-management intervention on the number of CHF exacerbations, CHF exacerbation days, or duration per CHF exacerbation.

Comorbid anxiety or depression symptoms were diagnosed in 42 self-management and in 36 UC patients (Table E8). No between-group differences were observed for the number of anxiety or depression flare-ups or for the flare-up days/patient/year (medians for both groups 0 (0-0)). There was a trend towards a higher prevalence of anxiety flare-up days in the self-management group that did not reach statistical significance (IRR 3.94 (0.84; 18.3); p=0.081). However, this was mainly driven by two patients in the self-management group with >100 days of anxiety flare-ups. In addition, there was no between-group difference in the duration per anxiety or depression flare-up.

Patients in the self-management group (n=43) reported a total of 972 diary days with IHD events (e.g. pain/pressure in: arm(s), shoulder(s)) versus 983 in the UC group (n=50), with no significant between-group difference in the number of IHD events/patient/year (self-management: 0 (0-5); UC: 0 (0-11); p=0.228).

Comorbid DM was diagnosed in 39 self-management and 39 UC patients (Table E8). Fourteen patients in the self-management group instituted additional glucose-lowering treatment.