

**Short- and long-term efficacy of a community-based COPD management program in
less advanced COPD:
a Randomized Controlled Trial**

Running title: Efficacy of COPD management in less advanced COPD

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Abstract

Rationale: The effectiveness of pulmonary rehabilitation in advanced COPD is well established. Limited data is available in less advanced disease.

Methods: In a 2-year randomized, controlled trial, 199 patients with on average moderate airflow obstruction but impaired exercise capacity (FEV1: 60% (SD 16%), Wmax<70%) were randomized to the INTERdisciplinary COMMunity-based COPD management program (INTERCOM) or Usual Care. Intervention consisted of 4 months multidisciplinary rehabilitation followed by a 20-month maintenance phase. Outcomes (4, 12, 24 months): health related quality of life (St. George's Respiratory Questionnaire (SGRQ)), exacerbation frequency, Medical Research Council (MRC) dyspnea score, cycle endurance time (CET), 6 minute walking distance (6MWD), skeletal muscle strength and patients' and caregivers' perceived effectiveness.

Results: After 4 months between-group comparison (mean (SE)) revealed significant differences in favor of INTERCOM for SGRQ total score 4.06 (1.39) $p=0.04$, activity and impact sub scores ($p<0.01$), MRC score: 0.33 (0.13), $p=0.01$, W max: 6.0 (2.3) Watt, $p=0.02$, CET: 221 (104) seconds, $p=0.04$, 6 MWD: 13 (6) meter, $p=0.02$, hand grip force: 4.3 (1.5) pounds, $p<0.01$ and FFMI: 0.34 (0.13) kg/m², $p=0.01$. Between-group differences over two years: SGQR: 2.60 (1.3), $p=0.04$ and MRC: 0.21 (0.10), $p=0.048$, CET: 253 (104) seconds, $p=0.0156$, 6MWD: 18 (8) meter, $p=0.0155$. Exacerbation frequency was not different (RR 1.29 (95%CI 0.89-1.87)). Patients' and caregivers' perceived effectiveness significantly favored the INTERCOM program ($p<0.01$).

Conclusions: This study shows that a multidisciplinary, community-based disease management program is also effective in COPD patients with exercise impairment but less advanced airflow obstruction.

Clinical trial.gov: NCT00840892

Introduction

In patients with advanced COPD beneficial effects of pulmonary rehabilitation programs on exercise capacity, dyspnea and quality of life are well established.[1-3] Limited information is available about pulmonary rehabilitation in physically impaired COPD patients with less advanced disease stages, although the majority of diagnosed COPD patients have mild or moderate COPD as defined by the GOLD guidelines.[4-6] Until recently, limited attention has been given to exercise intolerance and systemic impairment in COPD patients in earlier disease stages. COPD patients are markedly inactive and not FEV₁ but functional exercise capacity showed the strongest correlation with physical activities in daily life.[7] A high proportion of patients with muscle atrophy in mild to moderate COPD, independent of body mass index.[8,9] No difference in the prevalence of muscle atrophy between moderate and severe COPD was shown. Commonly used GOLD stages do not adequately reflect exercise impairment, systemic impairment and the potential need for pulmonary rehabilitation. In a previous paper we indeed showed that not only in severe and very severe patients but also in moderate COPD impaired exercise capacity was a significant determinant of disease burden.[10] These findings provided the rationale to study the efficacy of pulmonary rehabilitation in COPD patients whose exercise capacity is impaired while at the same time their lung function obstruction is less advanced. To be able to provide tailored care to these patients close to their home and enable access for a large and rapidly growing population of COPD patients, we designed the INTERdisciplinary COMMunity based COPD management program (INTERCOM). The program consisted of a 4-month rehabilitation phase and a 20-month active maintenance phase. Here we present the results of a two-year randomized controlled trial evaluating the efficacy of the INTERCOM program relative to Usual Care.

Methods

Setting and Participants

The INTERCOM trial recruited COPD patients that were under supervision of the department of respiratory medicine of two general hospitals in the Netherlands. Patients were recruited when 1) having an impaired exercise capacity, defined as peak work load (Wmax) during incremental cycle ergometry of less than 70 percent of the predicted normal value, 2) having GOLD stage 2 or 3 COPD and 3) being able and willing to participate in a community-based program.[11] Patients who had had prior rehabilitation and patients with serious co-morbidity that precluded exercise therapy were excluded. Patients were judged to be clinically stable at inclusion by their respiratory physician and pharmacotherapy was optimized. All patients gave written informed consent for participation in the study. Ethical approval was granted by the Medical Ethics Committee from Máxima Medical Centre.

Randomization and Interventions

Patients were randomized to the INTERCOM program or to Usual Care using a computerized procedure with concealed patient allocation. Outcomes were assessed at enrolment and 4, 12 and 24 months after the start of the trial, except for exacerbations which were recorded continuously and peak exercise capacity which was measured at baseline and 4 months only. All measurements were assessed single-blinded.

INTERCOM program

The intervention consisted of an intensive four-month, standardized, supervised rehabilitation phase and a 20-month active maintenance phase. The program was designed to improve and subsequently maintain exercise capacity, to promote self-management skills and improve knowledge on COPD. Nutritional intervention and smoking cessation support were provided upon indication. The program was offered by local physiotherapists and dieticians in the proximity of the patient's home and by respiratory nurses from the hospital. Local care-givers were supervised by colleagues from the hospital. During the first four months, the patients visited the physiotherapists twice a week (30 min. per visit) for intensive exercise training consisting of endurance training (cycling and walking) and four specific exercises for upper and lower extremities to improve both strength and endurance without the use of special equipment. Patients were instructed to perform the same exercises twice a day during 30 minutes in their home environment in addition to walking and cycling outside. Furthermore all patients participated in an individualized education program that was structured using a patient education book. All smokers were assigned to the respiratory nurse for standardized smoking cessation counseling according to the Minimal Intervention Strategy for Lung patients.[12] Nutritionally depleted patients received scheduled counseling (4 visits) by a dietician and nutritional supplements (Respifor®, Nutricia, Netherlands).[13]

During the 20-months active maintenance phase, patients visited the physiotherapist once a month to monitor exercise capacity and adherence to the training and to provide encouragement to continue the exercise training at home. After a patient had experienced an exacerbation, he/she was allowed to start six extra training sessions in three weeks at the physiotherapy practice. Nutritionally depleted patients visited the dietician four times in the maintenance phase i.e. after 6, 9, 12 and 24 months. The visits to the respiratory nurse were scheduled upon indication or request.

The Usual Care group received pharmacotherapy according to accepted guidelines, a short smoking cessation advice by their chest physician, and if they were nutritionally depleted, a recommendation by their respiratory physician to eat more.

Outcomes and Follow-up

Primary outcomes were change from baseline in disease specific quality of life as assessed with the St. George's Respiratory Questionnaire (SGRQ) total score and the total number of exacerbations (moderate plus severe).[14, 15]. A moderate exacerbation was defined as a visit to the general practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient was related to a worsening of COPD symptoms. A severe exacerbation was defined as a hospitalization for a COPD exacerbation.

Secondary outcomes were change from baseline in sub-scores of the SGRQ (symptom, activity and impact scores), dyspnea (modified Medical Research Council (MRC) dyspnea scale)[16], exercise performance (Peak exercise capacity (Wmax)) Cycle Endurance test (CET) at 50% Wmax for maximal 10 minutes and thereafter at 70% Wmax until exhaustion[13], six minute walking test (6MWD), muscle strength (handgrip force (HGF), isometric quadriceps peak torque (QPT) maximal inspiratory mouth pressure (Pi-max))[17] body composition (Fat-free mass (FFM))[18] and lung function. Details of the methods are provided in the online supplement.

After 24 months, both patients and caregivers were asked for a global assessment of perceived effectiveness on a 5-point Likert scale: much improved, slightly improved, no change, slightly worse and much worse.

Statistical analyses

All reported data analyses were pre-specified in the statistical analyses plan. P-values less than 0.05 indicate statistical significance. The analysis was performed according to an intention-to-treat (ITT) approach. All randomized patients who started the treatment (applies to the INTERCOM group) and completed at least one post-randomization outcome measurement (applies to both the INTERCOM group and Usual Care group) were included in the statistical analysis.

Differences in baseline characteristics between patients who completed the trial and patients who prematurely discontinued the trial were statistically tested using independent sample T-tests for continuous, normally distributed data, Wilcoxon Mann-Whitney U tests for continuous, non-normally distributed data and Chi-square tests for categorical variables. Repeated measurement analysis was performed to analyze the change from baseline in all continuous outcome variables using the SAS procedure PROC MIXED with the co-variance among repeated measures modeled as "unstructured". The model included treatment, time (i.e. the measurement at 4, 12 and 24 months), treatment by time interaction, baseline SGRQ score, smoking status at baseline, FEV₁% pred. at baseline and the self-reported number of exacerbations during the 12 months preceding the trial. Differences in perceived effectiveness were tested using Chi-Square tests. The total number of exacerbations was compared between treatment groups using negative binomial regression, with treatment, smoking status at baseline, FEV₁% pred. at baseline and the self-reported number of exacerbations during the 12 months preceding the trial as factors, and the natural logarithm of the length of the observation period as offset variable. The duration of the exacerbations were subtracted from the length of the observation period.

Based on a SGRQ score of 59 (12.5) and an improvement of 5 units, 98 patients were required in each group ($\alpha=0.05$, $\beta=0.20$).

Results

Patients

Between January 2002 and December 2004 199 patients were enrolled into the trial. The patient disposition and the reasons for drop out are described in figure 1. Table 1 shows that baseline characteristics of the INTERCOM and Usual Care group were comparable. At baseline 39 (20%) patients were depleted (23 in the INTERCOM group and 16 in the Usual Care group) and qualified for the nutritional intervention. Thirteen of the 199 randomized patients did not start the treatment. The total drop-out rate was 24.5 % (25 patients) in the INTERCOM group and 16.5 % (16 patients) in the Usual Care group. This difference was not statistically significant ($p=0.22$). In the INTERCOM group drop-outs were older than completers, while in the Usual Care group drop-outs were younger than completers.

Table 1: Baseline characteristics of the randomized study population.

	Randomized patients (n=199)	
	INTERCOM (n=102)*	Usual Care (n=97)*
Gender (% male)	71%	71%
Age (years)	65.9 (8.8)	67.2 (8.9)
Number of co-morbidities	1.6 (1.6)	1.5 (1.4)
Number of exacerbations in 12 months before trial	1.2 (1.4)	1.0 (1.5)
Number of COPD hosp. admissions in 12 months before trial	0.24 (0.52)	0.23 (0.50)
Current smokers (%)	33%	24%
Smoking (PY)	38.5 (25.2)	36.1 (26.4)
FEV ₁ %pred	58 (17)	60 (15)
FEV ₁ /FVC, %	49 (11)	51 (12)
% pat FEV ₁ > 50% pred	72%	65%
% pat FEV ₁ ≤ 50% pred	28 %	35%
SGRQ Total score [#]	39 (15)	38 (15)
SGRQ-Activity score	55 (18)	56 (19)
SGRQ-symptom score	45 (19)	41 (22)
SGRQ-Impact score	27 (16)	25 (16)
Total MRC score ^{\$}	1.7 (1.0)	1.5 (0.9)
6-min walk test % pred	80 (13)	83 (12)
Wmax % pred	60 (19)	61 (17)
HGF % pred	77 (17)	78 (18)
QPT % pred	95 (21)	92 (23)
Fat Free Mass (kg/m ²)	17.1 (2.0)	17.6 (1.9)
BMI (kg/m ²)	26.1 (4.4)	27.3 (4.7)

*Data are n (%), or mean (SD)

[#] St. George's respiratory questionnaire: a higher score indicates a worse quality of life

^{\$} modified Medical Research Council (MRC) dyspnea score

PY, pack years; FEV₁, Forced expiratory volume in one second. FVC, Forced Vital Capacity; SGRQ total, St. George's Respiratory Questionnaire total score; SGRQ activity, St. George's Respiratory Questionnaire activity sub score; SGRQ symptom, St. George's Respiratory Questionnaire symptom sub score; SGRQ impact, St. George's Respiratory Questionnaire impact sub score; MRC dyspnoe score, modified Medical Research Council dyspnea score; 6 MWD, six minute walking distance; Wmax, peak exercise capacity; HGF, handgrip force; QPT, isometric quadriceps peak torque; FFM, fat-free mass; BMI, body mass index;

Outcomes at 4 months

Primary outcomes

Table 2 shows the results of the four-month intensive part of the intervention. The SGRQ total score improved in the INTERCOM group and remained stable in the Usual Care group (mean difference in change from baseline: 4.06 (SE 1.39) (p=0.004) units. The number of exacerbations after 4 months did not differ between the two groups (RR 1.01 (95% CI: 0.57-1.79).

Secondary outcomes

The difference between the two groups in mean change from baseline in SGRQ activity and SGRQ impact score were 5.17 (SE 2.00) (p=0.01) and 4.26 (SE 1.56) (p=0.007) units, respectively. The between-group difference in mean change from baseline in MRC score was 0.33 (SE 0.13) (p=0.01). Cycle endurance time improved with 234 (SE 79) seconds in the INTERCOM group compared to 29 (SE 77) seconds in the Usual Care group, a difference of 221 (SE 104) seconds (p=0.04). Significant differences in favor of the INTERCOM group were also found for the change from baseline in Wmax, walking distance, HGF and FFMI, but not for SGRQ symptom score, QPT, Pimax and BMI (Table 2).

Table 2: Outcomes of INTERCOM compared with Usual Care after 4 months

Health outcome	Mean (SE) change from baseline		Mean (SE) difference in change from baseline as observed	Adjusted difference in change from baseline [#]	P value
	Usual Care (n=88)	INTERCOM (n=87)			
SGRQ total	0.3 (1.0)	- 3.9 (1.1)	4.2 (1.5)	4.1 (1.4)	0.04
SGRQ activity	0.9 (1.4)	- 3.9 (1.5)	4.8 (2.1)	5.2 (2.0)	0.01
SGRQ symptom	- 1.4 (1.8)	- 3.0 (1.9)	1.6 (2.6)	1.1 (2.3)	0.64
SGRQ impact	0.5 (1.3)	- 4.1 (1.2)	4.6 (1.8)	4.3 (1.6)	< 0.01
MRC dyspnoe score	0.1 (0.1)	- 0.3 (0.1)	0.4 (0.1)	0.33 (0.13)	< 0.01
CET (sec)	29 (77)	234 (79)	205 (108)	221 (104)	0.04
6 MWD (m)	-15.3 (3.9)	-1.4 (3.9)	13.8 (5.5)	13.3 (5.6)	0.02
Wmax (Watt)	- 0.4 (1.7)	5.2 (1.6)	5.6 (2.3)	6.0 (2.3)	0.01
HGF (pounds)	- 1.2 (1.2)	2.9 (1.1)	4.1 (1.5)	4.3 (1.5)	< 0.01
QPT (Nm)	2.4 (2.3)	- 1.0 (2.2)	3.4 (3.1)	2.1 (3.1)	0.51
Pimax (kPa)	0.06 (0.17)	0.23 (0.16)	0.16 (0.23)	0.27 (0.21)	0.21
FFMI (kg/m ²)	- 0.23 (0.10)	0.15 (0.08)	0.38 (0.13)	0.34 (0.13)	0.01
BMI(kg/m ²)	0.02 (0.10)	0.28 (0.1)	0.26 (0.15)	0.23 (0.15)	0.13
FEV ₁ %pred	-1.74 (1.04)	0.87 (0.72)	2.61 (1.27)	2.75 (1.28)	0.03

[#] Difference in change from baseline adjusted for the baseline value of the parameter, smoking status, FEV₁ % predicted and the self-reported number of exacerbations during the 12 months preceding the trial.

SGRQ total, St. George's Respiratory Questionnaire total score; SGRQ activity, St. George's Respiratory Questionnaire activity sub score; SGRQ symptom, St. George's Respiratory Questionnaire symptom sub score; SGRQ impact, St. George's Respiratory Questionnaire impact sub score; MRC dyspnoe score, modified Medical Research Council dyspnea score; CET, Cycle Endurance test; 6 MWD, six minute walking distance; Wmax, peak exercise capacity; HGF, handgrip force; QPT, isometric quadriceps peak torque; Pimax, maximal inspiratory mouth pressure; FFMI, fat-free mass index; BMI, body mass index; FEV₁, Forced expiratory volume in one second.

Outcomes at 24 months

Primary outcomes

Figure 2A shows the change over time in SGRQ total score. The SGRQ total score initially improved in the INTERCOM group and remained stable in the Usual Care group. At 12 months the SGRQ score in the INTERCOM group had almost returned to baseline, whereas in the Usual Care group it remained stable up to twelve months and worsened thereafter. Over the total two-year period there was a statistically significant difference of 2.60 (SE 1.3) units ($p=0.045$) in change from baseline between the two groups. The two-year exacerbation frequency was not significantly different between the groups (RR 1.29; 95% CI: 0.89-1.87).

Secondary outcomes

Over the two-year period a significant difference between the groups in change from baseline MRC dyspnea score of 0.21 (SE 0.10) units ($p=0.048$) was found in favor of the INTERCOM group (figure 2B). The difference between the INTERCOM group and the Usual Care group in exercise capacity increased over time. Over two years time CET significantly increased in the INTERCOM group with 172 (SE 73) seconds ($p=0.02$) and decreased in the Usual Care group with 81 (SE 73) seconds ($p=0.27$) resulting in a difference of 253 (SE 104) seconds over two years time, which was statistically significant ($p=0.02$) (figure 3A). In contrast, functional exercise capacity reflecting habitual walking speed decreased in both groups, but significantly less in the INTERCOM group. The 6MWD score decreased over 24 months in the INTERCOM group with 15.1 (SE 5.4) meter ($p<0.01$) and in the Usual Care group with 33.4 (SE 5.2) meter ($p<0.001$) resulting in a difference of 18.3 (SE 7.5), which was statistically significant ($p=0.016$) (figure 3B).

Over the total two-year period HGF decreased in the Usual Care group with 1.9 (SE 0.8) pound ($p=0.02$) and in the INTERCOM group with 0.08 (SE 0.8) pound (NS) resulting in a non significant difference of 1.8 (SE 1.5) pound ($p=0.12$). Over two years time Pimax significantly improved in the INTERCOM group with 0.37 (SE 0.14) kPa ($p=0.008$), while Pimax in the Usual Care group did not change (0.004 (SE 0.13)). This resulted in a difference of 0.37 (SE 0.19) kPa over two year time ($p=0.06$). BMI in the INTERCOM group significantly increased with 0.31 (SE 0.12) kg/m^2 compared to baseline ($p=0.01$). In the Usual Care group BMI increased with 0.14 (SE 0.12) kg/m^2 ($p=0.24$), resulting in a non-significant difference of 0.18 (SE 0.17) kg/m^2 ($p=0.30$). Over the total 24 months the FEV₁ in the Usual Care group decreased significantly with 2.9 (SE 0.7) % predicted ($p<0.001$). In the INTERCOM group the decrease of 1.6 (SE 0.8) % predicted was not significant. The difference between the two groups of 1.3 (SE 1.1) was also not significant. The change from baseline in SGRQ sub scores, QPT and FFMI was not significantly different between or within the two groups.

Results on perceived effectiveness showed that both for patients (figure 4) and respiratory physicians the perceived effectiveness was statistically significantly better for the INTERCOM group with p -values of $p<0.001$ and $p=0.01$, respectively.

Discussion

To the best of our knowledge this is the first randomized controlled trial showing that community-based pulmonary rehabilitation is feasible and effective, even for patients with less advanced airflow obstruction. The intensive four-month rehabilitation resulted in significant improvements in health related quality of life, breathlessness, exercise performance, muscle strength and body composition. In the following 20 months patients participated in an active maintenance program. Quality of life, functional exercise capacity, and breathlessness remained significantly different between INTERCOM and Usual Care over the entire two year evaluation. The positive results in terms of functional outcomes were not reflected in a decreased exacerbation frequency. The influence of pulmonary rehabilitation on exacerbations and the appropriateness as primary outcome variable is still debated.[19] Improved early recognition of exacerbations has been suggested[20, 21] to explain a similar or even increased exacerbation frequency after rehabilitation.

Community-based pulmonary rehabilitation programs for COPD patients have been studied before and significant improvements in exercise capacity, dyspnea and health related quality of life have been reported.[22-25]. However, mean FEV₁% predicted in former studies was substantially lower, around 40-45%, compared to 60% in our study. Two other Dutch studies reported the outcome of community based programs in COPD patients with comparable airflow obstruction.[20, 26] The COPE study evaluated a COPD self management program consisting of fitness, education and self-treatment of exacerbations and reported no significant effect on health related quality of life and 6 MWD after 6 and 12 months.[20] Campbach reported that rehabilitation in local physiotherapy practices improved exercise tolerance and quality of life after 6 months but the study group consisted of both asthma patients(35%) and patients with less severe COPD (65%).[26] Most of the community-based programs studied previously focused particularly on physical exercise training without providing a comprehensive, multidisciplinary approach comparable to the INTERCOM program.[22-26] Furthermore, since no data are available on cost-effectiveness of out-patient or home based pulmonary rehabilitation in less severe COPD patients, we conducted a full economic evaluation of the INTERCOM program that is reported elsewhere [27].

The physiotherapy sessions focused on behavioral changes towards a more physically active lifestyle including walking, cycling, gardening and any form of physical activity tailored to the preferences and possibilities for each individual patient.[28] This approach has already been proven effective to increase physical activity in healthy elderly persons but, at the time we designed this study in 2001, had not been applied in COPD before.[29, 30]

The within-group change in cycle endurance time that we observed over 24 months of 278 seconds can be considered as clinically relevant according to other studies.[31-32] Recent guidelines advice to use a sub maximal cycle ergometer test instead of peak exercise capacity as outcome measure.[25, 33]. While CET significantly improved after 4 months and was maintained in the active maintenance phase, no improvement was observed in 6 MWD. This response pattern may indicate that the 6 MWD is a less sensitive outcome measure of pulmonary rehabilitation programs as was indeed recently reported and discussed by Laviolette.[31] A remarkable finding was that the 6 MWD did not improve in the INTERCOM group. Rather, it declined progressively in both groups, although less so in the INTERCOM group. A potential explanation could be that, in contrast to most other test protocols, we deliberately chose not to encourage patients during the walking test but allowed them to choose their own walking speed. We hypothesize that this observation is indicative

for a progressive decline in physical activity pattern. Recently, Pitta quantified physical activities in daily life in healthy control subjects and in patients with COPD with a wide range in disease severity.[34] Patients indeed showed lower walking time and movement intensity during walking. Interestingly and in line with our hypothesis, walking time assessed by accelerometry was highly correlated with the 6 MWD and more modestly correlated to maximal exercise capacity, lung function and muscle force.

In contrast with the improvements in cycle endurance time no effect was seen on quadriceps muscle strength. Lack of effects on this outcome measure is most likely related to the fact that mean quadriceps muscle strength at baseline was within normal limits.

Drop-out rate was 24.5% in the INTERCOM group of whom only 19% actually started the program. Considering the two-year duration of the study, this drop-out rate is not unusual. Most patients dropped out because they died or because of serious co-morbidity. It is important to note that only 9% of the patients of the INTERCOM intervention group dropped out because of unwillingness to continue their participation. This low proportion illustrates the feasibility of the community-based program. Drop-out was 16.5% the Usual Care group. Moreover while in the INTERCOM-group drop-outs were older than completers, drop-outs were younger in the Usual Care group. To adjust for potential differences in disease severity between the groups, the statistical analyses were adjusted for baseline SGRQ score, smoking status, FEV₁% pred. and self-reported number of exacerbations during the 12 months preceding the trial.

In conclusion, our interdisciplinary, community-based COPD management program proved to be a feasible approach to improve disease-specific quality of life, dyspnea and functional exercise capacity during a 2 year follow-up period in patients with impaired exercise capacity but less advanced airflow obstruction.

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Figure legends

Figure 1: Patient enrollment scheme.

Figure 2: Change from baseline over 24 months in disease specific quality of life and dyspnea.

A: SGRQ total score, $p = 0.045$

B: MRC score, $p = 0.048$

Figure 3: Change from baseline over 24 months in cycle endurance time and 6 minute walking distance.

A: Cycle endurance time, $p = 0.020$

B: 6 Minute walking distance, $p = 0.016$

Error bars represent standard errors.

P-values are based on repeated measurement analysis adjusting for baseline SGRQ score, smoking status, FEV₁% pred. and self-reported number of exacerbations during the 12 months preceding the trial.

Figure 4: Perceived effectiveness by patients and chest physicians

A: Patients: $p < 0.001$

B: Chest physicians: $p = 0.010$

Outcomes and Follow-up

Primary outcomes were change from baseline in disease specific quality of life as assessed with the St. George's Respiratory Questionnaire (SGRQ) total score and the total number of exacerbations (moderate plus severe) (15). A moderate exacerbation was defined as a visit to the general practitioner or respiratory physician in combination with a prescription of antibiotics and/or prednisolone or a visit to the emergency department or day care of a hospital, which according to the patient was related to a worsening of COPD symptoms. A severe exacerbation was defined as a hospitalization for a COPD exacerbation.

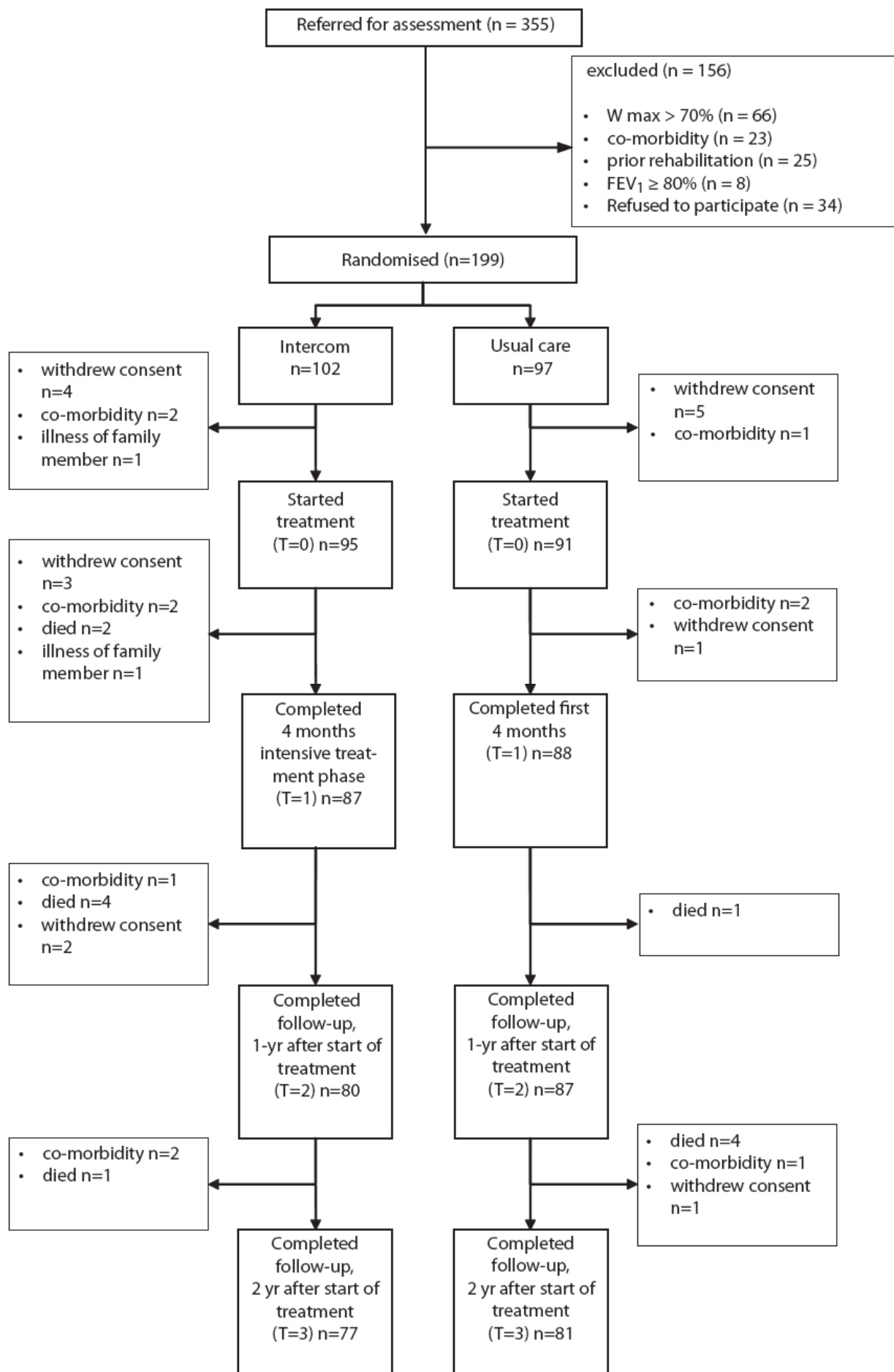
Secondary outcomes were change from baseline in sub-scores of the SGRQ (symptom, activity and impact scores), dyspnea, exercise performance, skeletal muscle strength, body composition and lung function. The degree of dyspnea was measured with the modified Medical Research Council (MRC) dyspnea scale (16, 17). The Cycle Endurance test (CET) started at 50% of the peak work rate (CET 50%) during a maximum of 10 minutes and continued thereafter at 70% of peak work rate (CET 70%) until exhaustion (14). Functional exercise capacity was assessed during a six minute walking test in a 50-meter corridor in the hospital. The test was deliberately performed without encouragement, to allow patients to choose their own walking speed as a reflection of physical activity level in daily life.

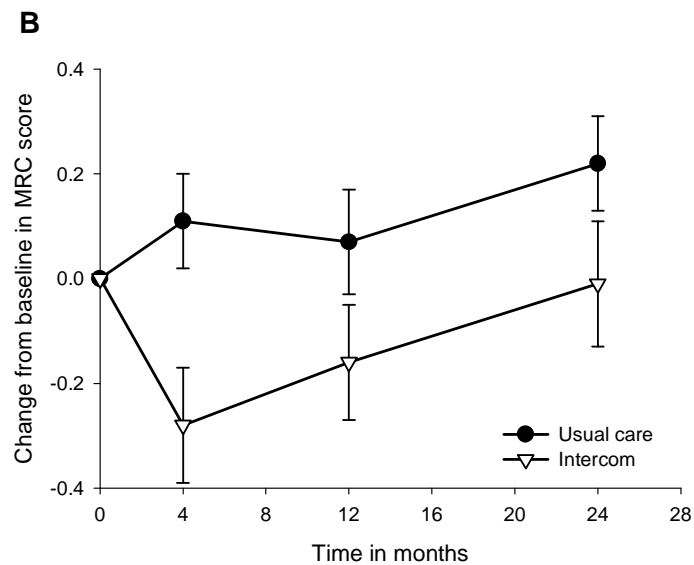
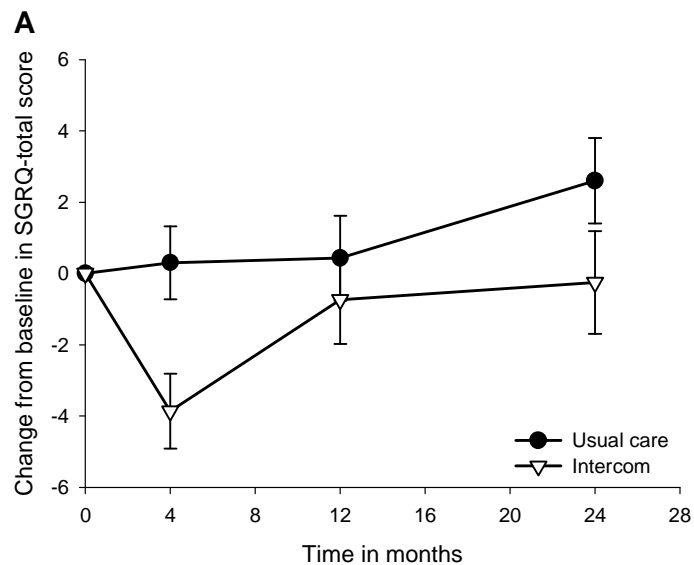
Peak exercise capacity (W_{max}) was measured using an incremental cycle ergometer test (Corival 1, Lode, Groningen, The Netherlands). Peripheral muscle strength was assessed by handgrip force (HGF) (Yamar Preston, U.S.A.) and isometric quadriceps peak torque (QPT) (Biodex system 3 dynamometer, Biodex Corporation, Shirley, /New York, U.S.A.). Inspiratory muscle strength was assessed by measuring maximal inspiratory mouth pressure (P_{i-max}) according to the method of Black and Hyatt (Masterlab, Jaeger, Wurzburg, Germany) (18). Body composition was assessed using single-frequency (50 kHz) bioelectrical impedance analysis (Bodystat 1500, Bodystat Ltd. Douglas, Isle of Main, Britain). Fat-free mass (FFM) was calculated with a disease-specific regression equation (19). The FFM index (FFMI) was calculated as the fat free mass divided by height². Forced expiratory volume in one second (FEV_1) was derived from the flow volume curve.

After 24 months, both patients and caregivers were asked for a global assessment of perceived effectiveness on a 5-point Likert scale: much improved, slightly improved, no change, slightly worse and much worse.

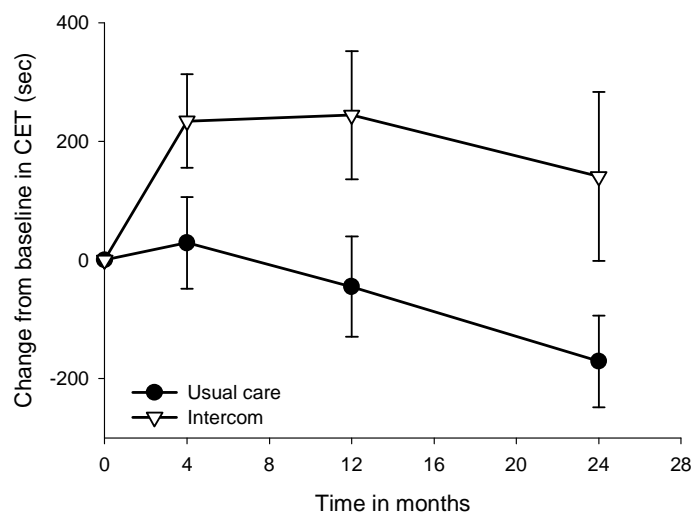
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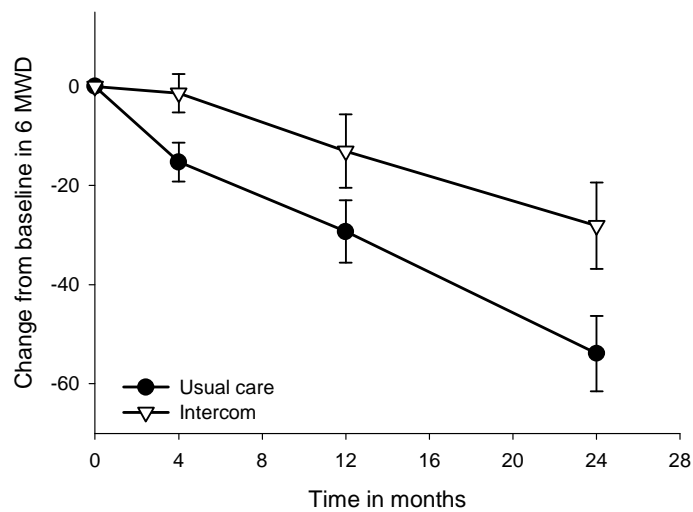




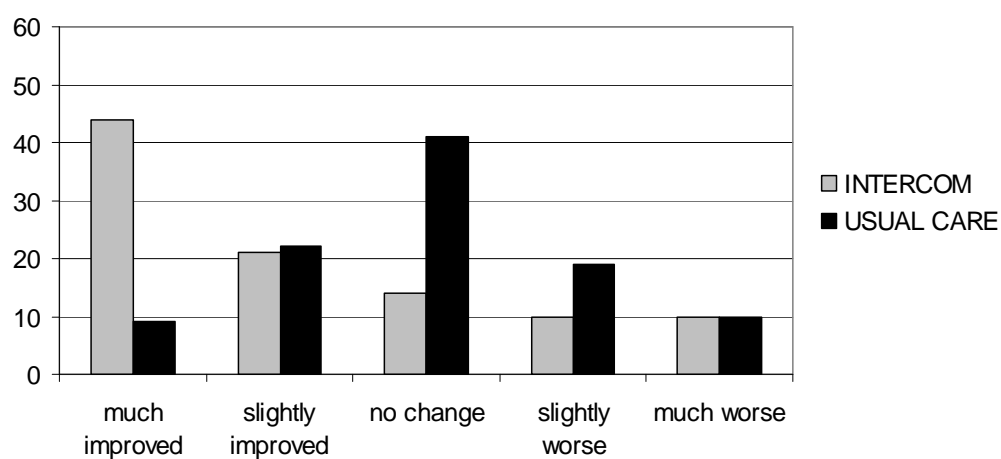
A



B



A



B

