Program of Integrated Care for Patients with Chronic Obstructive Pulmonary Disease and Multiple Comorbidities (PIC COPD^{+}): a randomised controlled trial

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Multicomponent, case manager-led intervention led to fewer ED and hospital admissions and almost halved risk of death http://ow.ly/J6Y730fM2GC

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ABSTRACT We sought to evaluate the effectiveness of a multi-component, case manager-led exacerbation prevention/management model for reducing emergency department visits. Secondary outcomes included hospitalisation, mortality, health-related quality of life, chronic obstructive pulmonary disease (COPD) severity, COPD self-efficacy, anxiety and depression.

Two-centre randomised controlled trial recruiting patients with ⩾2 prognostically important COPD-associated comorbidities. We compared our multi-component intervention including individualised care/action plans and telephone consults (12-weekly then 9-monthly) with usual care (both groups). We used zero-inflated Poisson models to examine emergency department visits and hospitalisation; Cox proportional hazard model for mortality.

We randomised 470 participants (236 intervention, 234 control). There were no differences in number of emergency department visits or hospital admissions between groups. We detected difference in emergency department visit risk, for those that visited the emergency department, favouring the intervention (RR 0.74, 95% CI 0.63–0.86). Similarly, risk of hospital admission was lower in the intervention group for those requiring hospital admission (RR 0.69, 95% CI 0.54–0.88). Fewer intervention patients died (21 *versus* 36) (HR 0.56, 95% CI 0.32–0.95). No differences were detected in other secondary outcomes.

Our multi-component, case manager-led exacerbation prevention/management model resulted in no difference in emergency department visits, hospital admissions and other secondary outcomes. Estimated risk of death (intervention) was nearly half that of the control.

Introduction

Chronic obstructive pulmonary disease (COPD) is a multi-factorial systemic disease [1]. Most COPD patients have numerous comorbidities [2] including cardiovascular and metabolic disorders that not only affect COPD prognosis, but also are themselves affected by COPD exacerbations. Optimal COPD management includes identification and treatment of its comorbidities [3]. As a nonreversible disease, primary treatment goals aim to relieve symptoms and limit exacerbations while maximising functional ability and wellbeing [4]. A fundamental problem in COPD exacerbation prevention and management is that patients often present late resulting in delayed treatment, longer exacerbation duration, exacerbation of comorbid disease, presentation to the emergency department and hospital admission [5]. Poor ability to recognise signs and symptoms of exacerbation are a core knowledge gap of COPD patients [6] Therefore, the key objective for any programme designed to facilitate disease management for this highly comorbid population is early recognition of exacerbation symptoms combined with prompt self-management and timely and easy access to appropriate healthcare providers [7].

Current evidence regarding multi-component self-management models for COPD is equivocal likely due to variation in the intensity, duration, delivery and content [8]. For the most part, trials exclude COPD patients with significant comorbid disease or do not prioritise management of treatable comorbid disease. Additionally, previous trials do not specifically evaluate models of health service delivery that integrate care between hospitals, primary care and community services. COPD patients are particularly vulnerable to care fragmentation due to significant comorbidity, the need to access care from various healthcare disciplines and professions and the potential for conflicting health advice to manage these comorbidities. We aimed to evaluate a multi-component, case manager-led disease management model targeting patients with moderate-to-severe COPD and significant comorbid disease. Our intervention focused on early exacerbation recognition and self-management as well as care integration across hospital and community sectors. Specifically, our primary objective was to evaluate the effect of the intervention on subsequent emergency department visits in the 12 months following randomisation. Secondary objectives included to evaluate the intervention's effect in the 12 months following randomisation on hospital admission and length of stay, mortality, disease severity, health-related quality of life (HrQoL), anxiety, depression, self-efficacy, satisfaction, caregiver burden, and adherence to chronic disease management measures.

Methods

Study design, setting and participants

We conducted a parallel group, two centre, randomised controlled trial (RCT). Centres are large community teaching hospitals; one serves a diverse urban population, the other regional and rural. Eligibility criteria were: COPD diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [3] and published Canadian reference values [9] confirmed by a respirologist or internist, ⩾50 years of age, ⩾1 emergency department visit or hospital admission for COPD exacerbation in previous 12 months, and ⩾2 prognostically-important COPD associated comorbidities (as defined by GOLD and Canadian Thoracic Society Guidelines) identified *via* medical record screening [2, 3]. Exclusion criteria were: primary diagnosis of asthma (action plans differ substantially); terminal diagnosis; dementia; uncontrolled psychiatric illness; inability to understand English; no telephone access; inability to attend follow up; resident in a long-term care facility; enrolled in the provincial tele-home monitoring programme; and no family physician. Participants were recruited on emergency department presentation and/or hospital admission for COPD exacerbation, or during attendance at respirology outpatient clinic.

Intervention

In addition to usual care described below, our intervention group received a multi-component, case manager-led intervention including: 1) case-manager delivered 40-min standardised education session based on Living Well with COPD [10] on study enrolment; 2) individualised care and action plans for

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This study was approved by the research ethics boards of the Michael Garron Hospital and Southlake Regional Health Centre (#0033 1213), and was registered as a clinical trial at ClinicalTrials.gov (NCT01648621).

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COPD exacerbation recognition, self-management and management of comorbidities (see the online supplementary material); 3) case manager-initiated telephone consultations (12 weekly, and monthly for the subsequent 9 months; 21 sessions) comprising standardised reinforcement/motivational interviewing focusing on health behaviours; action plan teach-back sessions; assessment of symptoms/symptom monitoring, problems and problem solving strategies; 4) ongoing case manager communication with family physicians and with hospital specialists including respirologists; and 5) priority access to ambulatory outpatient clinics. Exacerbation management prescriptions were provided with the action plan either directly to the participant or to their pharmacy.

Case managers received standardised training focused on the Living Well with COPD programme [10]. We developed "road maps" for family physicians that established how to contact case managers including a dedicated telephone line and priority access to respirologist/internal medicine consultation if required.

Usual care

Usual care comprised: 1) 3-monthly outpatient clinic visits with dictated patient summary sent to family physician; 2) referral to an 8-week in-hospital rehabilitation programme for clinically stable patients experiencing recent exacerbation at the discretion of the treating specialist; and 3) an individualised action plan and referral to educational materials again at the discretion of the treating specialist. Smokers were referred to smoking cessation resources.

Randomisation and blinding

Randomisation was performed according to a centralised, computer generated 1:1 randomisation schedule stratified by study site. Because of the nature of the intervention and co-location of research staff within the respiratory clinics, healthcare providers, patients and outcome assessors were not blinded, though treating respirologists were not informed of study allocation.

Outcomes

Our primary outcome was number of emergency department visits at 1 year after randomisation. Secondary outcomes included: number of hospital admissions and number of hospitalised days at 1 year; mortality; time to first emergency department presentation; change in BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index [11] generic (EQ-5D-3L [12]) and disease-specific (St. George's Respiratory Questionnaire [13]) HrQoL, Hospital Anxiety and Depression Scale (HADS) [14] COPD Self-Efficacy Scale (SES) [15] Client Satisfaction Questionnaire-8 (CSQ8) [16] and Caregiver Impact Scale [17] measured at baseline and at 3, 6 and 12 months. We evaluated adherence to chronic disease management measures; smoking cessation and vaccination status (influenza and pneumonia) at 1 year.

Research ethics and trial registration

The study was approved by the Research Ethics Boards of the Michael Garron Hospital (Toronto, ON, Canada) and Southlake Regional Health Centre (Southlake, NS, Canada). Written informed consent was obtained from all participants. Prior to participant recruitment, the trial was registered with at ClinicalTrials.gov5 (NCT01648621).

Statistical analyses

We based our sample size estimates using a standard Poisson distribution with a rate of one emergency department visit per year considered standard treatment and an estimated 12-month mortality of 10%. We considered a clinically significant reduction as 0.75 emergency department visits per year. Simulations indicated 235 participants per group would achieve 80% power with an alpha level of 0.05.

We conducted an intention-to-treat analysis according to a pre-specified analysis plan. Baseline characteristics were summarised for each group. Due to data overdispersion from many participants not requiring an emergency department visit or hospitalisation in the 12 months subsequent to randomisation, we analysed these outcomes using zero-inflated Poisson models. We performed an adjusted analysis including variables *a priori* considered to affect the primary outcome based on published data available at the time of study design. Variables comprised determinants of COPD exacerbation and subsequent hospital readmission [18] as well as determinants of self-management efficacy [19]. To assess any heterogeneity of treatment effect between sites, we used the likelihood ratio test comparing the full model, with an interaction term between site and treatment group, to a reduced model without this term. We generated Kaplan–Meier curves and developed a Cox proportional hazard model examining the effect of group assignment on mortality. For secondary outcomes measured repeatedly over time, we generated linear mixed effects models to examine effect of group assignment, time and interaction between group assignment and time including a random effect for subject. For binary secondary outcomes such as smoking cessation and vaccination status we used logistic regression. All analyses were two-tailed (with a

p-value of 0.05 considered statistically significant). An independent statistician conducted all analyses using R Version 3.2.4.

Results

Baseline characteristics

From August 2012 to March 2015, we screened 8696 patients of whom 2100 had a documented COPD diagnosis, and recruited 470 participants: 234 usual care and 236 intervention group (figure 1). Mean±SD age was 71±9.5 years; 53% female. Mean±SD emergency department visits 12 months before randomisation was 2.3±2.0; hospital admissions was 1.3±1.3. No participants participated in pulmonary rehabilitation in the year prior to enrolment; only 3% had an up-to-date action plan on study enrolment (table 1).

Most common co-morbidities were cardiovascular disease, including coronary artery disease, hypertension and congestive heart failure (76%), diabetes (20%) and depression (19%) (table 2). Most common medications were inhaled bronchodilator (95%), inhaled steroid (91%) and anti-hypertensives (65%) (supplementary table S1).

Primary outcome

There was no difference in the mean±SD rate of emergency department visits between groups (1.9±3.1 usual care *versus* 1.5±2.3 intervention group (RR 0.76, 95% CI 0.47–1.23; p=0.76). Of the 234 participants randomised to usual care, 134 (57%) visited the emergency department in the 12 months following randomisation, 140 (59%) out of 236 in the intervention group. Of those with ⩾1 emergency department visit, mean±SD visits was 3.4±3.5 usual care and 2.6±2.4 intervention group. A zero-inflated Poisson model showed a difference in risk ratio for an emergency department visit for those that visited the emergency department, favouring the intervention group (RR 0.74, 95% CI 0.63–0.86; p=0.0001). In our multivariate model, younger age reduced risk (RR 0.99, 95% CI 0.98–1.00; p=0.04) whereas previous history of emergency department visits presented increased risk of further visits to the emergency department in the 12 months after study randomisation (RR 1.14, 95% CI 1.11–1.16; p<0.0001) (table 3). In our analysis examining the effect of study site, for those participants at risk of an emergency department visit, we found evidence of a difference in risk for those in the intervention group by site (p=0.03, RR 1.18).

Secondary outcomes

There was no difference in time to first emergency department visit between groups (see supplementary figure). There was no difference in the number of hospital admissions between groups in the 12 months following randomisation (0.9±1.8 usual care *versus* 0.8±1.5 intervention group). A zero-inflated Poisson model showed a difference in risk ratio for hospital admission, for those that required admission, favouring the intervention group (RR 0.69, 95% CI 0.54–0.88; p=0.003). Of participants with ⩾1 hospital visit, median (interquartile range) length of stay was 11 (4–22) days (usual care) and 8 (4–15) days (intervention group) with a difference in risk ratio of hospitalised days for those at risk of 0.84 (95% CI 0.78–0.90; p<0.0001) favouring the intervention group.

Of those in usual care, 36 died compared with 21 in the intervention group (figure 2). Of those who died, palliative care was received by 39% (usual care) and 43% (intervention group). A Cox proportional hazards model demonstrated a difference in survival favouring the intervention group (hazard ratio 0.56, 95% CI 0.32–0.95; p=0.03).

We found no evidence that treatment assignment changed scores of any of our secondary outcomes measured across time (table 4; supplementary table S2 for scores). Due to missing responses, we did not evaluate the difference in COPD SES or Caregiver Impact Scale scores. Of the 112 active smokers, five in each treatment arm ceased smoking (estimate −0.26, 95% CI −1.60–1.08). Vaccination for influenza and pneumonia was up-to-date 12 months after randomisation for 90 (66%) out of 136 usual care and 114 (60%) out of 189 intervention group participants that provided these data (estimate −0.26, 95% CI −0.26–0.21).

Process measures

Respiratory rehabilitation

More intervention group participants than usual care met eligibility criteria for respiratory rehabilitation but were unable to attend due to unavailability of classes (38% *versus* 20%). 12% of intervention group compared with 5% of usual care were referred to respiratory rehabilitation. Of these 16 (55%) (intervention group) attended all eight classes compared with 2 (18%) (usual care).

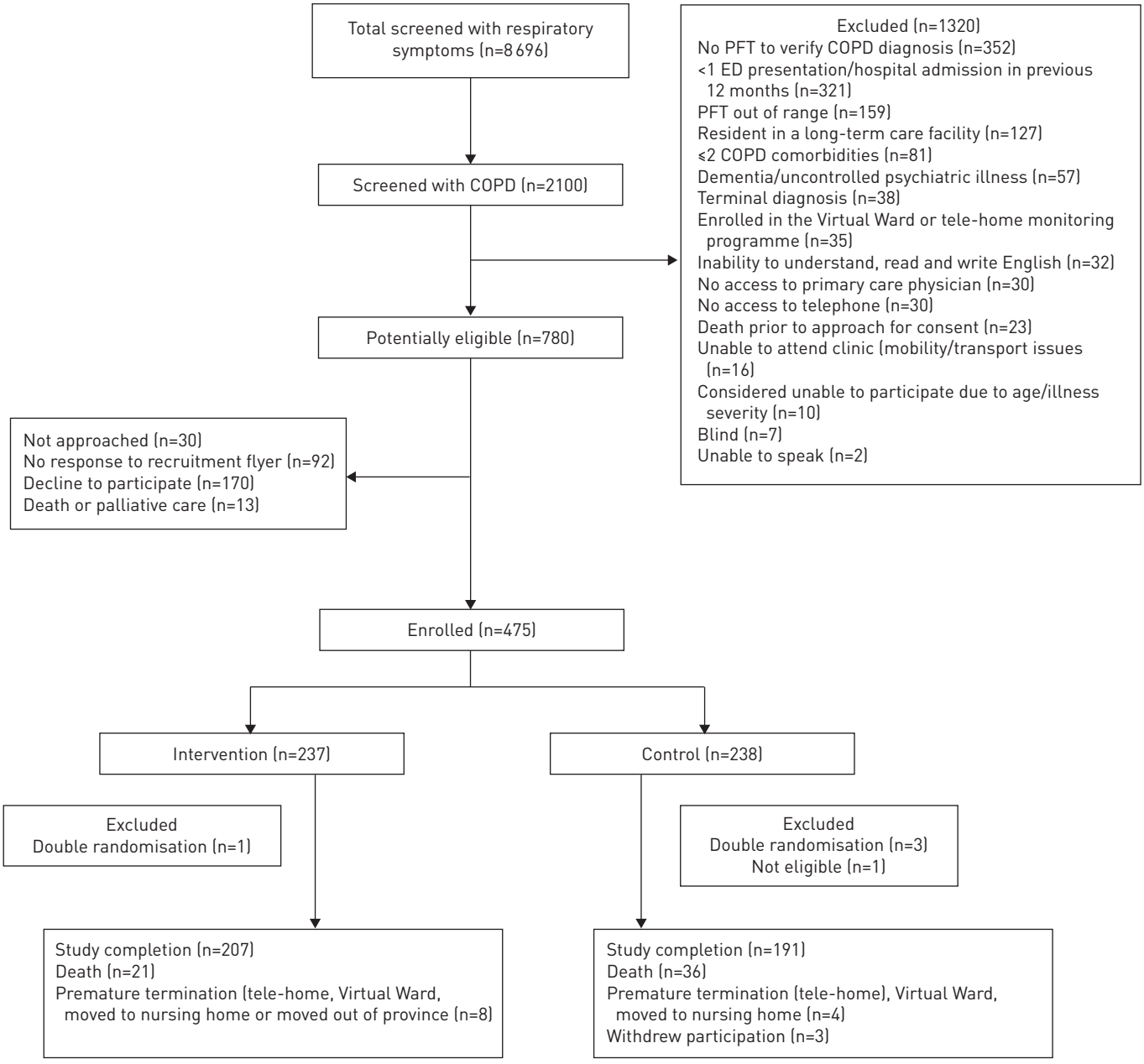

FIGURE 1 Consort diagram. PFT: pulmonary function test; COPD: chronic obstructive pulmonary disease; ED: emergency department.

Intervention group

Of the 221 participants with case manager contact for all 12 weekly calls, 29% were 100% compliant, 62% 50–99% compliant, and 22% <50% compliant *i.e.*, completed call activities. Of the 203 participants with case manager contact for all nine monthly calls, 31% were 100% compliant, 47% 50–99% compliant, and 22% <50% compliant. Most (65%) participants did not refuse any calls; 20% refused two, 5% refused three, and 1% refused ⩾4 calls. Most common reason for refusal was being too busy (69% of refused calls), other reasons were too fatigued or ill (20%), or not interested in talking when called (6%). Case managers made 162 unscheduled calls to 56 participants. 53% met with their family physician to discuss their action plan within 2 weeks of enrolment. Family physicians communicated action plan validation to the case manager for 35% of participants. Only five participants required non-scheduled outpatient clinics, two participants required referral to four separate specialists.

During case manager initiated telephone consultations, an exacerbation was reported a mean±SD of 20 ±18% proportion of times. Participants could complete action plan teach-back during a mean±SD of 83

TABLE 1 Baseline characteristics

	Usual care	Intervention group
Subjects n	234	236
Age	71±9.7	71±9.2
Male sex	103 (44)	117 (50)
Active smoker	59 (26)	53 (23)
Former smoker	159 (69)	176 (75)
Married	95 (42)	94 (40)
Education less than high school	86 (39)	89 (39)
Limited or simple reading level	55 (24)	46 (20)
Emergency department presentations in previous 12 months	2.4±2.1	2.3±1.9
Hospital admissions in previous 12 months	1.4±1.3	1.3±1.3
Most recent FEV_1 % predicted [#]	45±17.8	43±17.0
Most recent FEV_1/FVC	52±13	50±12.6
Influenza immunisation in last 12 months	54 (25)	74 (32)
Pneumonia immunisation in last 12 months	84 (39)	83 (37)
Up-to-date action plan	4 (2)	9 (4)
Home oxygen	62 (27)	79 (33)

Data are presented as n (%) or mean±SD, unless otherwise stated. No statistically significant differences were detected in baseline variables. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: based on Canadian prediction equations of spirometric lung function for Caucasian adults aged 20–90 years [9].

±24% of calls; reported adherence to inhaled medication was 100%, adherence to oral COPD medication 73±37%, and adherence to oral medications for comorbidities 98±6%.

Discussion

In this two-centre RCT, we demonstrate that, for patients with moderate-to-severe COPD and at least two prognostically significant COPD related comorbidities, a multi-modal case manager led intervention integrating acute and community care and including an action plan for management of exacerbation of COPD and specific comorbidities, did not reduce frequency of emergency department visits or hospital admissions but resulted in a reduction in mortality of almost half that compared with the usual care group. However, we did not detect differences in disease progression, HrQoL, anxiety, depression or COPD self-efficacy. For those participants that did require an emergency department visit or hospitalisation there were reductions in these outcomes for those randomised to the intervention group.

TABLE 2 Baseline co-morbidities

	Usual care	Intervention group
Subjects n	234	236
Cardiovascular disease	177 (76)	177 (75)
Diabetes	51 (22)	43 (18)
Depression	47 (20)	41 (17)
Osteopenia and osteoporosis	68 (29)	70 (30)
Gastro-oesophageal reflux disease	28 (12)	34 (14)
Hypothyroidism	22 (9)	21 (9)
Osteoarthritis	22 (9)	21 (9)
Glaucoma and cataracts	20 (9)	21 (9)
Cachexia and malnutrition	19 (8)	24 (10)
Chronic kidney disease	16 (7)	17 (7)
Anxiety	16 (7)	14 (6)
Peripheral muscle dysfunction	15 (6)	15 (6)
Obstructive sleep apnoea	13 (6)	12 (5)
Lung cancer	13 (6)	14 (6)
Cerebrovascular accident	9 (4)	6 (3)

Data are presented as n (%), unless otherwise stated.

TABLE 3 Variables associated with emergency department visits for those at risk of an emergency department visit

Variable	RR (95% CI)	p-value
Emergency department visits in prior 12 months	1.14 (1.11–1.16)	<0.0001
Intervention arm	0.80 (0.68–0.95)	0.01
Age	0.99 (0.98–1.00)	0.04
Male	0.98 (0.83–1.15)	0.78
Not married	1.06 (0.90–1.26)	0.48
Active smoker	1.01 (0.83–1.24)	0.90
Education less than high school diploma	0.93 (0.79–1.09)	0.35
Number of baseline co-morbidities	0.96 (0.88–1.04)	0.28
Up-to-date action plan at baseline	1.10 (0.63–1.93)	0.74
Home oxygen at baseline	1.03 (0.86–1.24)	0.73
Steroids at baseline	0.93 (0.71–1.23)	0.63

Our trial essentially combined an action plan for COPD and comorbidity exacerbation combined with a comprehensive case manager reinforced self-management programme without respiratory rehabilitation or formal exercise programme. Understanding evidence regarding the most efficacious and cost-effective intervention(s) to change health behaviours to prevent COPD exacerbation and slow disease progression; and to recognise and manage exacerbations as they occur, remains challenging. Many studies, including ours, evaluate a combination of complex interventions that address both these objectives. In a 2014 systematic review evaluating complex self-management interventions that included 29 trials with 3688 participants, 74% also included an action plan [20]. Self-management interventions decreased respiratory and all-cause hospital admissions, improved disease-specific HrQoL and reduced dyspnoea but had no effect on mortality or exercise capacity. Differences in effect on outcomes of interventions with or without an action plan were not examined due to limited studies without an action plan [20]. A systematic review of COPD action plans *without* a comprehensive self-management programme that included seven RCTs recruiting 1550 participants also found reduced frequency of hospital admission and likelihood of an ED visit, plus a small difference in disease specific HrQoL for participants using an action plan [21]. Conversely, the largest trial to date of a COPD self-management programme, with variable inclusion of an action plan, involving 1086 patients and 40 general practices in the Netherlands found no effect of their intervention on days of hospital admission or HrQoL using a number of disease-specific and generic measures [22]. These authors attributed the lack of effect primarily to implementation at the provider as opposed to patient level resulting in substantial variation in, and likely suboptimal intensity of, interventions [23].

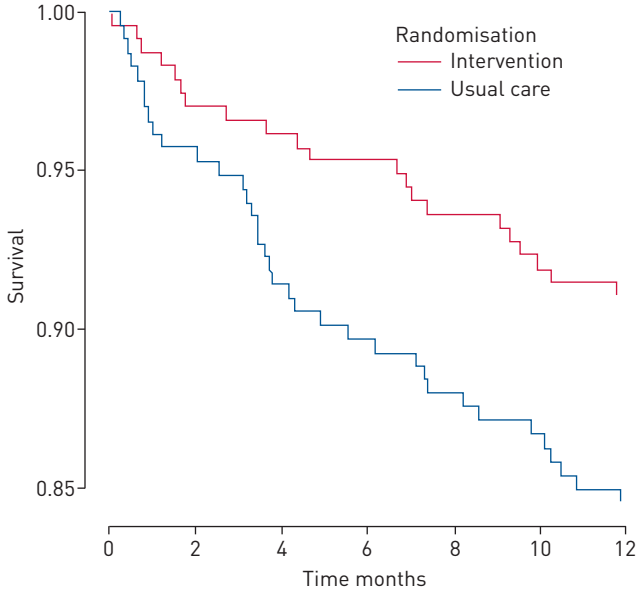

FIGURE 2 Kaplan–Meier curves of time to death.

TABLE 4 Secondary outcomes measured across time

Outcome	Baseline n	3 months n	6 months n	12 months n	Estimate (95% CI)
BODE index	433		321	319	0 (−0.002–0.000)
EQ-5D-3L	350	269	239	232	0.007 (−0.005–0.018)
St. Georges Respiratory Questionnaire	347	270	242	236	−0.001 (−0.01–0.009)
HADS depression	349	271	246	242	−0.004 (−0.002–0.002)
HADS anxiety	345	271	246	240	0 (−0.002–0.002)
CSQ8	344	280	257	247	0.002 (−0.001–0.004)

n: number of participants completing sufficient items of the questionnaires to calculate a score; BODE: body mass index, airflow obstruction, dyspnoea and exercise capacity; HADS: Hospital Anxiety and Depression Scale; CSQ8: Client Satisfaction Questionnaire-8.

Only 34 (7%) of our study participants attended respiratory rehabilitation despite being a component of usual care. During study recruitment, hospital funding for respiratory rehabilitation was withdrawn completely at one centre and substantially reduced at the second. Individually tailored exercise plans are central to respiratory rehabilitation which also may include education regarding behaviour change [24]. High-quality evidence indicates respiratory rehabilitation improves HrQoL when commenced after exacerbation [25] and when commenced in patients not immediately experiencing exacerbation [26]. Omission of tailored exercise in our intervention may be one reason why there was no effect on HrQoL though our results must be interpreted with caution due to missing data at the 12 month follow up.

Our study unexpectedly found the estimated risk of death for participants receiving our intervention was nearly half that of usual care. Reasons for this mortality reduction are unclear but may relate to the targeted inclusion of COPD patients with moderate-to-severe disease and a minimum of two prognostically-important COPD related comorbidities [2, 27]. Four studies of action plans without a comprehensive self-management programme include mortality as an outcome with meta-analysis demonstrating no difference in all-cause mortality at 12 months [21]. Interestingly, few previous RCTs of self-management programmes evaluate mortality as an outcome [20], with only one other to our knowledge reporting a reduced mortality favouring the intervention [28]. This trial reporting a 9% reduction in mortality, recruited 8217 participants with COPD in all stages, with an intervention comprising health management education without a specific action plan.

To our knowledge, ours is the first trial to evaluate an action plan that addresses exacerbation of both COPD and individual-specific comorbidities. The presence of ⩾2 chronic conditions, frequently affects COPD patients and increases exacerbation frequency [29] as well as hospital admissions, length of stay, and costs [30, 31]. We did not find evidence of an association between comorbidity number and emergency department visits frequency in the 12-month follow-up in our multivariable model. Evidence of the influence of comorbidity on outcomes when receiving self-management or respiratory rehabilitation is equivocal. In a retrospective cohort of 2622 COPD patients undergoing respiratory rehabilitation, Crisafulli *et al.* [32] found comorbidity resulted in worse outcomes in terms of exercise tolerance, dyspnoea and HrQoL. Conversely, a more recent prospective study objectively measuring 13 individual comorbidities found no association for any comorbidity, or five clusters of comorbidity [33] with exercise tolerance or HrQoL [34].

Our trial has limitations. First, we were unable to blind participants, personnel, and outcome assessors. However, our primary outcome and several secondary outcomes such as hospitalisation and mortality are unlikely to be biased due to lack of outcome assessor blinding. Second, missing data for secondary outcomes that required return of questionnaires means results may be open to bias and should be interpreted with caution. Third, we are unable to compare the frequency of exacerbation that did not result in an emergency department visit or hospitalisation in the control arm as these participants were not contacted weekly or monthly to collect these data.

Conclusion

Our multi-component, case manager-led exacerbation prevention/management model resulted in no difference in the frequency of emergency department visits and hospital admissions in the 12 months following randomisation. However, estimated risk of death (intervention) was nearly half that of the control. No differences were detected in HrQoL or other secondary outcomes but caution is required in interpreting this finding due to missing data at 12 months of follow up. Based on findings from our trial

and recent meta-analyses, we recommend self-management programmes that include an individualised action plan become standard of care for COPD patients with moderate-to-severe disease.

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Author contributions: L. Rose, I. Fraser and R. Shafai designed and supervised the study. L. Carriere, A. Thomas, S. Rezaie and H-B. Lee recruited subjects. L. Istanboulian and L. Carriere performed the case manager role. A. Thomas, S. Rezaie and H-B. Lee collected outcome data. L. Rose and I. Fraser analysed the data. All authors contributed to writing of the manuscript.

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