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Early View

Research letter

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Efficacy and costs of telehealth for the management of COPD:

The PROMETE II trial

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INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is a significant, and largely under-diagnosed cause of morbidity and mortality worldwide.[1] More long-term survivors with advanced disease led to an ageing COPD population profile with an increased level of acute exacerbations, hospitalisations and polymorbidity.[2]

Attention has been placed on identifying and validating innovative COPD care models, particularly for high cost patients with severe COPD and/or frequent acute exacerbations, such as telehealth.[3] Early intervention during an exacerbation has been shown to reduce severity, duration and hospitalisation rates and may lead to a slower decline in lung function and reduced clinical or social care costs.[4]

Remote patient monitoring is often a key element of new care programs as it permits the regular collection of physiological and symptomatic data from patients at home which can be used to promptly identify exacerbations and initiate treatment.[5]

Previously, the PROMETE I study, confirmed the practicality of a telehealth intervention for severe COPD patients, and produced directional cost and clinical benefit data.[6] As a development and refinement of this study, the larger and longer PROMETE II project was designed. The primary objective was to reduce the number of COPD exacerbations leading to ER visits/hospital admissions with telehealth.

METHODS:

The study design of this second Madrid-based Project on Managing Chronic Obstructive Pulmonary Disease with Remote Patient Management (PROMETE II) study, was a multicentre, non-blind, randomised controlled trial of 12-months duration (**Figure 1**). Patients were recruited in five hospitals, and randomized by block allocation within each centre: H. U. La Paz, H. U. La Princesa, Fundación Jiménez Díaz, H. U. 12 de Octubre, and H.U. Rey Juan Carlos. The study protocol and procedures were approved by the Institutional Review Boards of each hospital, and all patients were required to provide their written informed consent to participate. The trial was registered at ClinicalTrials.gov NCT02499068. The research protocol of the PROMETE II trial is available upon request from the authors.

Inclusion criteria for study subjects were: patients aged 50 to 90 yrs. old, diagnosed with COPD,[7] with severe airflow obstruction defined as the forced expiratory volume in the first second (FEV_1) below 50% of the predicted level, treated with chronic home oxygen therapy, and suffering two or more moderate or severe exacerbations in the previous year (with or without hospitalization), but currently clinically stable (defined as 6 weeks without clinical symptoms since the last COPD exacerbation and separated by at least 4 weeks after finalising treatment for the previous exacerbation).[16]

Exclusion criteria were standard for COPD telelehealth trials.

Our principal objective was to estimate the effectiveness of a Home Telemonitoring (HTM) Strategy in managing patients with severe-very severe COPD when compared to

Routine Clinical Practice (RCP). The main variable was changes in the number of severe exacerbations, defined as those resulting in a hospital admission or a visit to the hospital emergency services.

The RPM program started with a nurse from the Monitoring Centre (MC) registering the participant in a dedicated data management portal. Once this was completed, the MC scheduled a home visit. The equipment given to each patient was a modem 2Net Hub, a pulsioximeter Onyx II (Nonin), a blood pressure gauge (A&D), a spirometer Spirotel® (MIR) and a respiratory rate and oxygen therapy compliance monitor VisionOx® (The Linde Group). After the first visit, the participant was given an aide memoire instruction sheet detailing how to correctly measure the required physiological parameters.

Blood pressure, oxygen saturation, heart rate and spirometry were actively measured by the patient at home as per instructions whilst respiratory rate (and oxygen adherence) data was passively collected by the Visionox® device[8] connected to the oxygen feed from their main oxygen source. The information was sent to secure servers by a 3G modem which was provided free to the patient as part of the study equipment. The patient took measurements at the same time daily, at rest and after having taken their prescribed medication and with the oxygen therapy.

On their first day in the study, patients were required to perform the initial measurements of all the parameters under the supervision of the nursing staff. The values obtained over the first four days of the program, were taken as reference values (basal parameters) for each participant and titrated each alert configuration.

The information was received by the MC, which used a triage application to grade into a stop light system according to severity: Red: one or more measurements exceeded the pre-established limits. Yellow: The measurements were missing either through not being performed or not being received. and Green: all measurements made and within the limits predefined as acceptable.

Statistical analysis:

Following CONSORT guidance,[9] a sample size was estimated *a priori* of 240 patients to be recruited in the trial, that is 120 in each branch, to obtain 108 completers in each arm after 12 months of follow-up. Comparisons between proportions were made using X^2 or Fisher's exact tests as appropriate. For selected outcomes, the 95% confidence intervals were calculated. All analyses are presented intention-to-treat, unless otherwise stated. A p value <0.05 was considered statistically significant.

RESULTS:

Overall, 237 COPD patients were recruited, and 229 (96.6%) were randomized to TH (n=115) or RCP (n=114). Given that only 8 (3.4%) of all initially recruited participants were lost, it was considered unnecessary to conduct a CONSORT non-response study.

Participants had a mean±SD age of 71±8 years and 80% were men, and all demographic and clinical characteristics were evenly distributed by group, including education level, having a caretaker, dyspnoea mMRC, or number of COPD hospitalizations in the last year (all p>0.05).

There were no statistically significant differences in the primary efficacy analysis of the proportion of participants who had a severe exacerbation leading to a hospital admission or a visit to the hospital ER over the 12-month period (60% in TH vs. 53.5% in RCP (p=0.321) (**Table 1**). Similarly, the mean number of exacerbations over the 12-month period was comparable between groups, 1.1 vs. 0.9 (p=0.1810); mean total duration of hospitalization in the TH group (18.9±16.1 days) compared to the RCP group (22.4±19.5 days), p=0.308, and days in the ICU, 6.0±4.6 vs.13.3±11.1 days, p=0.3490.

When Kaplan-Meier analysis of time to a first exacerbation was performed, like in the primary analysis above, these differences were not statistically significant (p=0.4195).

There were no differences by group in anxiety, depression, daily activity, EQ5D or COPD symptoms at 12 months (**Table 1**), or throughout the study follow-up.

At month 12, the number of deaths was comparable between groups (12 vs. 13). However, when “Time To Death” was measured in days, on average, participants in the

TH group stayed alive for 240.14 days during the follow-up period compared to those in the RCP group (157.13 days, p=0.2170) which is approximately 83 days longer.

DISCUSSION:

Meta-analyses have produced conflicting results on the use of telehealth in severe COPD: the Cochrane review of ten RCTs concluded telehealth did not significantly improve quality of life, but could significantly reduce the risk of emergency department attendance and hospitalisation,[10] whereas a more recent meta-analysis of 18 trials found no statistically significant quality of life benefits.[11]

The original PROMETE study,[6] showed a significant reduction in ER visits, hospitalisation, length of stay and mechanical ventilation rates. PROMETE II, as a validation of the first study, was larger and of longer duration. This required multiple recruiting hospitals which made direct Primary Care management challenging from a resource and coordination standpoint. Whilst patient demographics and interventions remained comparable between the two studies, the reasons for this inconclusive findings in PROMETE II can only be speculative. Overall, our core results are nearly identical to a number of studies, including Pinnock H, et al.[12]

PROMETE II was a pragmatic trial designed as an intervention study to answer the question of effectiveness of telehealth in COPD management in the real world. Our study highlights the limitation of using telehealth as a stand-alone with physiological monitoring in the management of exacerbations of COPD. The main interpretation of our study results is that having only telehealth physiological monitoring of COPD patients will unlikely be of benefit. To date, no physiological measurements taken alone have been shown to assist in early recognition of disease worsening. These physiological changes (decrease in O_2 saturation, increases in respiratory rate, blood

pressure, and else) mostly reflect an exacerbation being severe and/or complicated, as opposed to an exacerbation being in an early stage. This consequently does not allow the patient or the health care professional being alert to intervene early and promptly preventing further aggravation and/or complications such as hospital admissions

In countries like Spain, where a well-developed health system ensures COPD patients have rapid, effective access to appropriate care, it may well prove challenging to demonstrate that telehealth further improves outcomes.

To conclude, remote patient management using this monitoring protocol in PROMETE II did not reduce the COPD-related ER visits or hospital admissions compared to RCP within 12 months.

Figure 1. PROMETE II trial study design

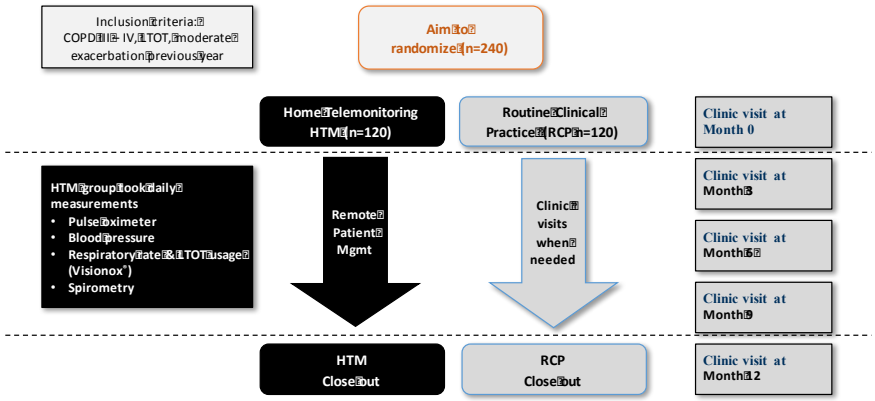

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Table 1. Primary and Secondary End Points Analyses

	Telehealth (TH) (n=115)	**Routine Clinical Practice (RCP)** (n=114)	**P value**
Primary:			
Participants who have at least one exacerbation (ER or H) in the 12 months -all participants ITT	69 (60.0)	61 (53.5)	0.321
Number of exacerbations in the 12 months -all participants ITT	1.1 ± 1.13	0.9 ± 1.04	1.181
Participants who have at least one exacerbation (ER or H) in the 12 months -only patients who reached Month 12 PP	49 (56.3)	43 (52.4)	0.612
number of exacerbations in the 12 months (ER or H) -only patients who reached Month 12 PP	1.0 ± 1.13	0.9 ± 1.09	0.472
Secondary:			
Mean duration of hospitalisation in days	18.9 ± 16.05	22.4 ± 19.52	0.308
Number of ICU Admissions (%)	3 (2.6)	3 (2.6)	0.991
Number of days in ICU	6.0 ± 4.6	13.3 ± 11.1	0.349
Presence of non-invasive ventilation (%)	15 (13.0)	16 (14.0)	0.781
Presence of orotracheal ventilation (%)	2 (1.7)	3 (2.6)	0.628
COPD symptoms at 12 months. CAT Index Score	21.5± 5.6	21.4± 6.1	0.855
Goldberg Anxiety Subscale Score at 12 months	0.9 ± 1.9	1.0 ± 2.0	0.911

Goldberg Depression Subscale Score at 12 months	1.8 ± 2.21	2.2 ± 2.64	0.316
Daily activity at 12 months. Barthel Index	95.3± 8.4	96.3 ± 9.1	0.460
Quality of life. EQ5D Index Score (EuroQoL)	0.80±0.2	0.79±0.2	0.895

Table footnote: TH: Telehealth; RCP: Routine Clinical Practice; ITT: Intention to treat; PP: Per protocol; Groups compared by Student's t-test for continuous variables and Chi ^{2} test for categorical variables.

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