Home-based maintenance tele-rehabilitation reduces the risk for AECOPD, hospitalizations and emergency department visits

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Summary of findings: Home-based tele-rehabilitation reduces the risk for AECOPD and constitutes an effective alternative strategy to hospital-based, outpatient, rehabilitation.

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Abstract

Pulmonary rehabilitation (PR) remains grossly underutilized by suitable patients worldwide. We investigated whether home-based maintenance tele-rehabilitation will be as effective as hospital-based maintenance rehabilitation and superior to usual care in reducing the risk for acute COPD exacerbations (AECOPD), hospitalizations and emergency department (ED) visits.

Following completion of an initial 2-month PR program this prospective, randomized controlled trial (between 12/2013 and 07/2015) compared 12-months of home-based maintenance tele-rehabilitation (n=47) to 12-months of hospital-based, outpatient, maintenance rehabilitation (n=50) and also to 12-months of usual care treatment (n=50) without initial PR.

In a multivariate analysis during the 12-month follow-up, both home-based tele-rehabilitation and hospital-based PR remained independent predictors of a lower risk for: i) AECOPD [incidence rate ratio (IRR) 0.517 (95% CI:0.389-0.687) and IRR 0.635 (95% CI:0.473-0.853)], respectively, and ii) hospitalizations for AECOPD [IRR 0.189 (95% CI:0.100-0.358) and IRR 0.375 (95% CI:0.207-0.681)], respectively. However, only home-based maintenance tele-rehabilitation and not hospital-based, outpatient, maintenance PR was an independent predictor of ED visits [IRR 0.116 (95% CI: 0.072-0.185).

Home-based maintenance tele-rehabilitation is equally effective to hospital-based, outpatient, maintenance PR, in reducing the risk for AECOPD and hospitalizations. In addition, it encounters a lower risk for ED visits, thereby constituting a potentially effective alternative strategy to hospital-based, outpatient, maintenance PR (Clinical Trials.Gov. ID: NCT02618746).

Introduction

The benefits of pulmonary rehabilitation (PR) in terms of improvement in functional capacity, limb muscle function, chronic dyspnea and emotional function are well documented [1]. However, these benefits are often lost over the subsequent 12 months without the implementation of a maintenance strategy [1, 2]. Few investigations have explored maintenance strategies to sustain the benefits of PR over the longer term; these results remain equivocal in regard to the duration that functional capacity and quality of life are preserved [3-6]. The effect of these long-term strategies to reduce the risk for acute exacerbations of COPD (AECOPD), hospitalizations, and emergency department visits (ED) also remains inconclusive [3, 4, 6, 7]. A recent meta-analysis of ten randomized controlled trials (including both short- and long-term PR maintenance strategies) [7] demonstrated that PR, when compared to usual care, is associated with lower overall rates of hospitalizations attributable to AECOPD.

Despite the well documented benefits of PR [1], long-term access and utilization of PR by eligible COPD patients remains low due to insufficient funding, resources, reimbursement and other patient-related barriers limiting long-term access to PR [8]. Accordingly, alternative approaches (such as tele-rehabilitation) to extend the initial benefits of PR for a longer term, were recently recommended by the Official ATS/ERS Policy Statement [8].

Tele-rehabilitation involves the use of information and communication technologies to provide rehabilitation services remotely to people in their homes [9]. In contrast to traditional centre-based programs, undertaking PR within the home environment might promote more effective, longer term integration of exercise routines into daily life [10]. Whilst there is still little evidence of the benefits of tele-

rehabilitation [1], initial small-scale studies, most of which uncontrolled, demonstrate some feasibility. These data suggest that clinical benefits such as compliance, patient empowerment to physical training, improved health status and quality of life might be achieved [10-14]. Although these look promising, these interventions had numerous limitations such as a short duration intervention (2-6 months), high dropout rates (up to 45%), small patient numbers ($n \leq 10$) or poor adherence to different components of tele-rehabilitation [10-13, 15-17].

Consequently, more evidence is needed to ascertain the effectiveness of home-based maintenance tele-rehabilitation in reducing the risk for AECOPD, hospitalizations and ED visits, whilst maintaining the functional benefits of primary PR. In the present prospective study we hypothesized that regular home monitoring of vital signs, in combination with tele-consultation sessions encouraging patient adherence to physical training regimes, would be as effective as hospital-based, outpatient, maintenance rehabilitation and superior to usual care in reducing the risk for AECOPD, hospitalizations and ED visits over a 12-month period.

Methods and Materials

Study design

As shown in Figure 1, 150 COPD patients were randomized into three groups using a set of computer-generated random numbers to either home-based maintenance tele-rehabilitation (group A, n=50), hospital-based, outpatient, maintenance rehabilitation (group B, n=50) or usual care treatment (group C, n=50), (Clinical Trials. Gov. ID: NCT02618746). During the period spanning from December 2013 to

July 2015, patients in groups A and B initially completed a multidisciplinary intense hospital-based, outpatient, PR program lasting for 2 months (see online supplement [18]) that was followed by a 12-month maintenance rehabilitation program at home (Group A) or at Hospital (Group B). Patients in group C followed the usual care treatment throughout the 14 month period, without participation to either the 2-month primary or the 12-month maintenance programs (Figure 1). In Greece only few University Medical Departments deliver PR. Hence, the majority of COPD patients follow usual care only, which is associated with high costs for treating AECOPD. The present study was designed to investigate the value of delivering and maintaining the benefits of initial PR in comparison to usual care. Thus, in order to balance the observation period between the three groups, we performed all measurements in group C at the same time points as in the other two groups (i.e. months 0, 2 and 14).

Study subjects

One hundred and fifty (150) clinically stable patients that regularly attending the Outpatient Clinic (1st Department of Respiratory Medicine at Athens University Medical School based at Sotiria General Chest Hospital) were recruited. Patients (n=150) were included in the study if they were older than 40 years; with a diagnosis of COPD (post-bronchodilation $FEV_1/FVC<0.7$) with moderate to very severe airflow obstruction (post-bronchodilator FEV_1 <80% pred.); with optimal medical treatment according to GOLD [19] without regular use of systemic corticosteroids; and a history of AECOPD one year prior to entering the study. Patients were excluded from the study based on the diagnosis of orthopedic, neurological and other conditions that significantly impair exercise tolerance, or respiratory disorders other than COPD. Patients were also excluded on grounds of cognitive impairment and/or difficulties to managing electronic devices that precluded interactions with the tablet, as judged by

the investigator. More details on the exclusion criteria are provided in the online supplement. The majority of patients were referred to the PR program because of persistent respiratory symptoms, but also following hospitalization for AECOPD (4 patients in Group A and 6 patients in Group B). These patients were included in the study at least 8 weeks after the hospitalization [19]. None of these patients had previously participated in a PR program. The Scientific Board of Clinical Studies at Sotiria Hospital approved the study protocol (approval number: 22964).

Description of interventions

Home-based maintenance tele-rehabilitation program (Group A)

The home-based maintenance tele-rehabilitation program consisted of 144 sessions performed over 12 months. The program included the following components: a) individualized action plan; b) physical exercise sessions to remote monitoring; c) access to the call center 5 days/week - 10 hrs/day; d) psychological support; and e) dietary and self-management advice via scheduled weekly contacts with a physiotherapist, an exercise scientist, a dietician and a physician through telephone or a video conference. During the course of the 2-month initial PR program, patients were trained to appropriately use the multimodal apparatus (MIR Spirodoc, Spirodoc®, Spiro+Oxi, Roma, Italy), that was subsequently used to make measurements at home. Training enabled the patients to take their own spirometry and vital sign measurements using a wireless apparatus fitted with Bluetooth technology. Patients were also taught to successfully transfer the data to a tablet placed in their home (Lenovo Smart Tab II[7], Bratislava, Slovakia) and transmit the data from the tablet to a secured web-based platform via a mobile communications network. The home-based exercise program was comprised of arm and leg exercises, as well as walking drills. Exercises were individually tailored to address each patient's specific

requirements and adapted as required by an exercise scientist. A video demonstration of the home exercises was installed on to the tablet to provide patients with a resource to correctly execute the exercises. Exercise vital sign data (heart rate and oxygen saturation) along with ratings relating to the symptoms of dyspnea and leg discomfort, were recorded by patients immediately after completion of the home exercise program. These data were transmitted to the web-based platform on three specific days every week for 12 months. The remainder of the data, namely daily steps captured by a pedometer, spirometry, oximetry and responses to questionnaires (HRQoL, CAT, HADS, mMRC) were recorded and transmitted twice weekly for 12 months. Patients were asked to complete the HADS questionnaire once every month. Data were transmitted from the tablet to a secure web-based server platform [(TELECARE (version 2.2.13): Linkcare Health Services SL, Barcelona, Spain; incorporated and adapted by Singularlogic Integrator S.A., Athens, Greece)] [20]. Data were stored on the web-based platform and reviewed regularly (three to four times per week) by the different health care professionals (see online supplement for further details).

Hospital-based, outpatient, maintenance rehabilitation program (Group B)

Patients assigned to the hospital-based PR program visited the hospital twice weekly for 12 months in order to participate to a multidisciplinary maintenance rehabilitation program including exercise training, physiotherapy, dietary and psychological advice [18] (see online supplement). The hospital-based maintenance rehabilitation program consisted of 96 sessions performed over 12 months.

Usual care

Usual care, included optimal pharmacotherapy oxygen therapy in the presence of respiratory failure, vaccination for S. pneumoniae, annual vaccination for

influenza, and regular follow up by a respiratory physician according to the guidelines [19]. Furthermore, patients were trained on the early recognition of an AECOPD in order to be able to seek for timely medical care.

Study Procedures

For groups A and B outcome assessment was conducted at baseline, immediately after completion of the primary 2-month PR program and 12 months later. For group C outcomes were assessed at the respective time points as groups A and B (Figure 1). The primary end point was the rate of moderate to severe AECOPD, hospitalizations due to AECOPD and ED visits, which were compared among the 3 groups over a period of 12 months following completion of the primary 2-month period. Additional analyses included the rate of severe exacerbations (hospitalizations) and the rate of ED visits due to AECOPD that did not require hospital admission. Decision for hospital admission was based on the judgment of the consultant physicians in accordance with the criteria suggested in the GOLD document [19], including the marked increase in symptom intensity (e.g. sudden development of resting dyspnea), severe underlying COPD, onset of new physical signs (e.g. cyanosis, peripheral edema), failure of an exacerbation to respond to initial medical management, presence of serious comorbidities (e.g. heart failure or new arrhythmias), frequent exacerbations, older age, and insufficient home support [19]. In regards to the ED visits, they were based on the patients' judgment and the availability of care at the timing of the worsening of the symptoms. Secondary end points included i) functional capacity, ii) daily physical activity and iii) health-related quality of life outcomes.

Definitions of AECOPD

AECOPD were defined according to the GOLD definition [19] as acute events characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leaded to a change in medication. Moderate to severe AECOPD were events where patients received antibiotics, systemic corticosteroids or both. Hospitalizations (severe exacerbations) and emergency department visits (ED) due to AECOPD were also assessed. A respiratory physician with expertise in COPD (acted as case manager) was able to recognize symptom deterioration using the study web-based platform and communicated with the patients assigned to the home-based maintenance tele-rehabilitation group when needed. Patients in the other two groups (hospital-based, outpatient, maintenance and usual care) received training to be able to recognize the onset of an AECOPD and contact the study chest physicians in case of symptom deterioration. Monthly telephone contacts with the patients in all groups ensured that no AECOPD event was missing. In case patients needed hospital admission the study medical case manager was able to contact the patients' physicians and get all information needed for the patient and the type of AECOPD. Drug prescription could be found in the electronic prescription system used by the Greek medical registration system.

Outcome measures

Lung function and functional capacity assessment

Post-bronchodilation dynamic spirometry, diffusing capacity of the lung and evaluation of static lung volumes (see online supplement) [21] were assessed. Incremental exercise tests were performed on an electronic ergometer bicycle with breath-by-breath gas exchange measurements and cardiac output recordings, using

impedance cardiography, to the limit of tolerance (see online supplement). Functional capacity was assessed by the 6MWT [22].

Daily physical activity

Daily physical activity measurements were performed by using a validated for COPD patients activity monitor (Actigraph GT3X, Actilife, Pensacola, FL) [23, 24] (see online supplement).

Health Related Quality of life (HRQoL) and respiratory symptoms

HRQoL and respiratory symptoms were evaluated by the following questionnaires [1, 19]: a) St. George's Hospital Respiratory Questionnaire (SGRQ), b) COPD assessment questionnaire (CAT) and c) modified Medical Research Council dyspnea scale (mMRC).

Analysis of adherence rates (compliance)

Adherence to the home-based maintenance tele-rehabilitation and hospital-based, outpatient, maintenance programs were assessed by the adherence rate (actual number of sessions/total expected number of session*100). Adherence to measurements of vital signs, home exercises, responses to questionnaires and daily steps were recorded by the number of registrations entered divided by the number of those recommended, for each participant (see online supplement for more details).

Sample size calculations

The calculation of sample size was based on ANOVA repeated measurements between the three groups. The minimum detectable difference in the number of hospitalizations for AECOPD was used for the power calculation, which was obtained from a previous study [25]. This previous work evaluated the effect of a PR program on the frequency of hospitalization during 1 year after completion of the initial PR program compared with 1 year before PR. An effect size of 0.42, based on a mean

difference (1.37) and SD (3.26) of AECOPD/year [25], estimated a sample size of 116 patients was required to achieve a power of 0.90 using an alpha significance level of 0.05 (2-sided). To compensate for a potential dropout rate of 20%, a total sample size of 138 patients (46 patients in each group) was determined to be sufficient. Sample size calculation was performed by GPower 3.1.7 software. During the 2-month primary PR program, 3 patients from group A were discontinued from the study due to transport barriers.

Statistical Analysis

The Shapiro-Wilk test revealed that all data were normally distributed. One-way ANOVA was utilized to detect differences among the 3 groups at baseline for all variables. Group differences were investigated by two-way ANOVA with repeated measurements at different time points, namely baseline, 2 months and 14 months after patient enrolment to the study. Where necessary, significance differences were followed up with pair-wise Tukey's post-hoc analyses. Time to first AECOPD, hospitalization for AECOPD and ED visit for each group were evaluated by Kaplan-Meier survival curves and log-rank tests. Poisson regression univariate and multivariate analyses were performed in order to evaluate the influence of the participation in hospital-based, outpatient, PR or home-based tele-rehabilitation programs, AECOPD, hospitalizations for AECOPD and visits to emergency department (ED) in the 1-year of follow-up. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Poisson regression univariate and multivariate analyses were additionally performed in order to account for variability in exacerbation rates between patients. Skewed data were logarithmically transformed for regression analyses. P-values $\leq$0.05 were considered statistically significant. Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

AECOPD, hospitalizations and ED visits

Patients' demographic and clinical characteristics at baseline are shown in Table 1. Both the home-based maintenance tele-rehabilitation group and the hospital-based group showed a lower rate $p<0.001$ of AECOPD and hospitalizations for AECOPD in the 12 months of follow-up compared to the usual care group [(mean±SD) 1.7±1.7 vs 1.8±1.4 vs 3.5±1.8; respectively]. Similarly, the rates of hospitalizations for AECOPD were lower in the home-based tele-rehabilitation group and the hospital-based group compared to usual care (0.3±0.7, 0.3±0.6 vs 1.2±1.7, respectively, $p<0.001$). Finally, the home-based tele-rehabilitation group showed lower rate of ED visits in the 12 months of follow-up compared to both the hospital-based group and the usual care group (0.5±0.9 vs 1.8±1.5 vs 3.5±1.8, respectively, $p<0.001$).

Kaplan-Meier survival curves evaluating the time to next AECOPD and hospitalizations for AECOPD in the 12 months of follow-up are presented in Figure 2. In the univariate Poisson regression analysis, significant predictors of AECOPD were smoking status, FEV_1 (% predicted), number of AECOPD in the preceding year and PR (either home-based maintenance tele-rehabilitation or hospital-based, outpatient, maintenance rehabilitation; Table 2). Accordingly, significant predictors of hospitalizations for AECOPD were gender, FEV_1 (% predicted), number of AECOPD in the preceding year, and PR (either hospital-based, outpatient, maintenance PR or home-based maintenance tele-rehabilitation; Table 2). In multivariate analysis, PR (both home-based tele-rehabilitation and hospital-based, outpatient rehabilitation) remained an independent predictor of a lower risk for AECOPD in the 12-month follow up [incidence rate ratio (IRR) 0.517 (95%CI 0.389-0.687), $p<0.001$] and [IRR

0.635 (95%CI 0.473-0.853), p=0.003] for the home-based maintenance tele-rehabilitation and hospital-based, outpatient, maintenance PR groups, respectively. In addition, PR (both home-based maintenance tele-rehabilitation and hospital-based maintenance rehabilitation) remained an independent predictor of a lower risk for hospitalizations for AECOPD [IRR 0.189 (95%CI 0.100-0.358), p<0.001] and [IRR 0.375 (95%CI 0.207-0.681), p=0.001] for home-based maintenance tele-rehabilitation and hospital-based maintenance PR, respectively. However, only home-based maintenance tele-rehabilitation and not hospital-based maintenance PR was an independent predictor of visits in the ED [IRR 0.116 (95% CI 0.072-0.185), p<0.001; Table 2).

Functional capacity

Home-based maintenance tele-rehabilitation was equally effective to hospital-based, outpatient, maintenance PR in preserving for 12 months the initial statistical and/or clinically meaningful improvements in peak work rate (p=0.011) and the distance covered during the 6MWT, respectively and were superior to usual care (Table 3). The magnitude of improvement induced by the primary 2-month PR program in the aforementioned variables was not different between groups A and B. Following the initial PR program the fraction of patients who improved beyond the MCID (>25 m) the 6MWT was for Group A: 53%, Group B: 60% and Group C: 4%.

HRQoL, respiratory symptoms and chronic dyspnea

Home-based maintenance tele-rehabilitation was equally effective to hospital-based, outpatient, maintenance rehabilitation in preserving the initial clinically meaningful improvement in SGRQ, CAT and mMRC scores over a period of 12-months and was superior to usual care exhibiting deterioration in the questionnaire scores over the same period (Table 4). The magnitude of improvement induced by the

primary 2-month PR program in the aforementioned parameters was not different between the two rehabilitation groups.

Daily physical activity

Home-based maintenance tele-rehabilitation was equally effective to hospital-based maintenance, outpatient, PR in preserving the initial improvement in time spent in sedentary, light, lifestyle and moderate daily physical activities over the 12-month period, and was superior to usual care exhibiting an increase in time spent in sedentary, and decrease in lifestyle, and moderate daily activities over 12 months follow up (Figure 3: on line supplement).

Adherence/Compliance

The overall compliance to the different components of the home-based maintenance tele-rehabilitation intervention (Figure 4: online supplement) over 12-months follow up was 93.5%.

Discussion

The main finding of the study was that home-based maintenance tele-rehabilitation via monitoring of vital signs was as effective as hospital-based, outpatient, maintenance PR and superior to usual care in terms of reducing the risk for AECOPD and hospitalizations, whilst preserving the functional and HRQoL benefits of a primary PR program over a period of 12 months. Moreover, only home-based maintenance tele-rehabilitation and not hospital-based, outpatient, maintenance PR was an independent predictor of reduced risk for ED visits.

Recently an international task force commissioned by the ATS and ERS delivered policy recommendations to improve access and delivery of PR services to suitable patients [8]. It was recognized that although traditional models of outpatient

PR are suitable for many patients, several barriers prevent the vast majority of eligible patients to access or adhere to these programs, particularly in regions or healthcare systems where traditional models of PR are not feasible [8]. It was, thus, recommended that research should focus on the effectiveness of alternative models of PR such as tele-rehabilitation [26].

In the present study we have included a population of high-risk patients with a history of exacerbations as the majority of them experienced ED visits and hospitalizations during the study, in accordance with previous observations in similar populations in Greece [47]. Our findings on the reduction of the risk for AECOPD for both home-based maintenance tele-rehabilitation and hospital-based maintenance strategies are consistent with previous RCT studies [27, 28] employing comparable protocols of initially intense PR programs followed by home maintenance sessions. In addition, our results on the reduction of risk for hospitalizations for AECOPD concur with those [27-29] applying long-term follow-up maintenance strategies. Importantly, our findings on the reduction of the overall rate of hospitalizations for AECOPD per person/year at risk for the home-based maintenance tele-rehabilitation group [by 0.19 (0.10-0.35)] as well as for the hospital-based, outpatient, maintenance program [by 0.38 (0.21-0.68)], compare favorably with the overall rate recently reported form the meta-analysis of 10 RCT studies [by 0.62 (0.33-1.16)] [7]. Furthermore, the effectiveness of home tele-rehabilitation in reducing the risk for ED visits provides evidence that early patient and physician recognition of AECOPD followed by prompt treatment initiation prevent COPD-related health worsening [27-30]. The home-based tele-rehabilitation group had the advantage of spirometry and physical signs monitoring that may have further supported the early recognition of AECOPD. Indeed, a more prompt recognition of symptom and/or lung function deterioration

may have resulted in the prompt intervention for medical care and decreased the need for an ED visit.

The economic burden of COPD increases with increasing disease severity, whilst it is substantially augmented by exacerbations and hospitalizations. A study conducted in Greece has estimated that the mean cost per severe COPD exacerbation is €1711; range: €1357 to €2614, depending on the severity [31]. These findings highlight the importance of reducing the frequency of AECOPD and hospitalizations. This is particularly important in light of findings indicating that a significant proportion of COPD patients in Greece experience two or more AECOPD/year and that the majority of these exacerbations are moderate or severe, frequently leading to hospitalizations [32]. Collectively, these findings emphasize the importance of decreasing the number of AECOPD per patient/year, in order to alleviate the disease burden as well as the economic cost of the disease. In regards to cost savings for delivering the present home-based maintenance tele-rehabilitation program over a period of 12 months, the calculated total cost per patient including equipment, development of the ICT platform, use of 3G network, and cost for personnel was approximately €1800. This figure is equivalent to approximately 60% of the total estimated cost (€2908) spared by reducing the frequency of AECOPD (by 1.7 AECOPD per patient/year x €1711= €2908) [31]. In addition, this figure is approximately 40% of the estimated cost for one year of hospital-based maintenance rehabilitation sessions including twice-weekly outpatient respiratory department visits.

Remote monitoring of vital signs allows clinicians to monitor a patient remotely with reference to physiological signs, respiratory symptoms and activity levels using a wide range of technological devices [10, 33-36]. In this study, we have

implemented patient tele-consultation based on vital sign data (recorded by patients using portable devices) transmitted to an ICT web based platform via patients' tablets. In addition, patients were provided with feedback to maintain progress in respect to executing home exercise drills and enhancing daily activity levels. Accordingly, we have described a novel home-based maintenance tele-rehabilitation approach to reduce the risk for AECOPD and hospitalizations for AECOPD to a similar extent of a hospital-based maintenance rehabilitation program.

The home-based maintenance tele-rehabilitation program was not by any means inferior to the supervised hospital-based, outpatient, maintenance PR program in preserving true physiological training effects, respiratory symptoms, daily activity levels and aspects of quality of life over a period of 12 months. Previous studies have also reported positive effects of hospital-based maintenance PR programs on exercise capacity and quality of life [6]. However, insufficient funding, resources, and reimbursement limit the implementation of such hospital-based programs worldwide [8]. To the best of our knowledge, this is the first study to show that home-based rehabilitation with the use of ICT is effective in preserving the long-term physiological training effects initially acquired by a comprehensive hospital-based PR program. Nevertheless, future studies by healthcare professionals are required to inform and disseminate information on the costs, clinical- and cost-effectiveness of maintenance rehabilitation programs to payers [8]. Patients assigned to the usual care group not undertaking the initial 2-month outpatient PR program and subsequently the 12-month maintenance program experienced significant deterioration in functional capacity and quality of life, further highlighting the beneficial effects of PR maintenance strategies [27-29].

449 The finding that home-based maintenance tele-rehabilitation preserved the
450 initial physiological benefits deserves further analysis to justify these findings.
451 Potential factors may include [36]: i) excellent patient adherence to regular vital sign
452 recordings (Figure 4), ii) very good compliance to home exercise drills, iii) patient
453 empowerment in the promotion of high levels of daily physical activity, iv) regular
454 feedback on patient's progress through motivation messages to tablets or via
455 telephone contacts and v) adherence to sufficient exercise training loads and self-
456 management techniques. Indeed, regular investigators-patient communications
457 facilitated their empowerment in the promotion of increased levels of physical activity
458 and raised their awareness to comply with the measurement and physical activity
459 requirements of the protocol.

460 Incomplete implementation of the aforementioned factors as well as
461 inadequate sample size power [37-39] most likely explains why previously
462 implemented tele-rehabilitation studies did not demonstrate such long-term benefits
463 [38, 40, 41]. Combining self-management techniques, regular exercise training and
464 contact with the PR personnel has likely contributed to reinforce behavioral changes
465 towards a more active lifestyle [42]. Our findings support this notion since the
466 combination of home physical training, physical activity consultation and
467 personalized feedback on weekly physical activity levels decreased the time spent in
468 sedentary activities and improved the time spent in light and moderate lifestyle
469 activities [43]. Given that low levels of daily physical activity is a independent risk
470 factor for AECOPD [42], it is plausible that maintenance of enhanced daily physical
471 activity over a period of 12 months could have contributed to the reported reduced
472 risk for AECOPD. This is an important outcome since earlier studies including a
473 recent systematic review with meta-analyses [15-17] highlight the finding that tele-

healthcare interventions have minimal impact on patients' physically active time.

Our findings are in tandem with those of Hoaas *et al.* who showed that following completion of an initial (4-week) supervised PR program, improvements in 6MWT and quality of life were preserved for one year when a home tele-rehabilitation program was implemented [13]. These outcomes are justified by the high adherence rate for vital sign measurements and training sessions. Indeed, our multimodal home-based tele-rehabilitation and tele-consultation program, in contrast to other studies [36, 44], resulted in very good adherence without dropouts over a period of 12 months.

Study limitations

Our study design was not blinded, and as such the investigators were aware of the allocation of patients into the different maintenance rehabilitation groups. Importantly, patients were given general information about their participation in the study and details on the interventions related only to their intervention arm. Moreover, the choice of objective endpoints that were related to healthcare resource use (moderate or severe AECOPD, hospitalizations and ED visits) minimizes to the best possible extent potential biases.

Another potential limitation of the study is that the usual care group (C) of our study did not participate in a PR program. PR in Greece is delivered only by few University Medical Departments. Hence, the majority of COPD patients follow usual care only, which unfortunately does not include access to PR. This is due to the lack of specialized rehabilitation centers and trained personnel. This is why our study was designed to represent the reality in the local community and provide evidence to health authorities of the major advantages of PR, in order to allocate an infrastructure (personnel and resources) to establish PR programs in the community or at home

across the nation. Lack of access for the usual care group to the initial 2-month PR program may therefore constitute a limitation as one could argue that maintenance of benefits might be, at least in part, related to the conduction of initial PR, which brought benefits to only those patients who undertook PR. However, it is well documented that benefits of PR are often lost over a period of 12 months without implementation of a maintenance strategy [1-6]. Hence, an important aspect of our study was to identify the best maintenance strategy to preserve the initial benefits of PR for an extended period.

The hospital-based, outpatient, maintenance program was conducted at the hospital's gymnasium using specialized equipment (e.g. stationary bicycles and weight lifting apparatus), whilst the home-based exercise program was comprised by arm and leg exercises, as well as walking drills without use of any specialized equipment. This is the reason why we offered three weekly sessions at home (as opposed to two sessions during the outpatient hospital-based maintenance program) in an attempt to ensure adequate weekly physical exercise in this group. This difference in the total number of maintenance sessions between the two maintenance strategies over the 12-month follow up period could have potentially introduced bias. Nevertheless, our finding that the home-based maintenance tele-rehabilitation program was equally effective to the hospital-based, outpatient, maintenance PR in preserving for 12 months the initial statistical and/or clinically meaningful improvements in peak work rate and the 6MWT, respectively suggest that the applied overall training load was well matched between the hospital-based and the home-based groups.

The incidence of AECOPD is often related to multiple factors, including appropriate care by the attending physicians, adherence to treatment [45, 46], and co-

morbidities that include anxiety and depression [47] and cardiovascular comorbidities [48]. However, we have attempted to delimit the impact of such confounding factors during the study, as all patients were prescribed optimal treatment for COPD and co-existent conditions, received appropriate training on the use of inhaled medication and were optimally followed-up by respiratory physicians.

Clinical implications

Application of home-based maintenance tele-rehabilitation programs may lead to significant reductions of healthcare resource use for patients with COPD compared to usual care, with potential benefits on patients' outcomes and quality of life.

Conclusions

Home-based maintenance tele-rehabilitation is equally effective to hospital-based, outpatient, maintenance PR, in reducing the risk for AECOPD and hospitalizations and encounters a lower risk for ED visits, thereby potentially constituting an effective alternative strategy to hospital-based, outpatient, maintenance rehabilitation.

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549 **Table 1.** Patients' demographic and clinical characteristics at baseline

	Group A (n=47)	Group B (n=50)	Group C (n=50)
Men/women, n/n	44/3	38/12	37/13
Age, years	66.9±9.6	66.7±7.3	64.0±8.0
FEV_1, L	1.55±0.80	1.41±0.48	1.42±0.66
FEV_1, % pred	49.6±21.9	51.8±17.3	51.7±21.0
FVC, L	3.07±0.90	2.70±0.65	2.77±0.81
FVC, %pred	80.7±20.2	78.4±18.4	80.0±20.3
FEV_1/FVC, %	47.0±14.1	49.0±12.7	51.9±12.4
VC, %pred	83.6±20.6	85.5±14.6	82.6±21.9
IC, %pred	81.7±33.0	77.3±30.0	76.9±31.0
TLC, %pred	118.8±30.3	120.7±25.7	119.9±28.8
FRC, %pred	158.5±60.5	154.5±43.0	154.4±56.6
RV, %pred	184.6±80.6	180.2±59.9	182.0±70.9
DL_{CO}, %pred	53.5±19.9	57.0±20.4	55.9±28.4
SpO_2,%	93.0±3.0	94.0±2.9	94.0±3.0
6MWT, m	389.1±91.3	385.1±80.3	384.8±80.2
Body mass index, kg/m^2	28.0±5.3	27.5±5.0	26.4±5.0
BODE index	3.5±2.7	3.2±2.1	3.3±2.3
mMRC	2.3±1.0	2.5±1.0	2.2±1.1
Oxygen therapy (LTOT)	13	9	15
Smoking status (cur. vs ex.)	7/40	4/46	3/47
Drug therapy			
LAMA	36	37	35
LABA	22	26	24
ICS	32	37	41
Comorbidities			
≥1 comorbidity			
Cardiovascular	14	15	13
Number of AECOPD	3.3±1.3	3.4±1.4	3.3±1.6

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551 Values are mean±SD. Abbreviations: FEV_1: forced expiratory volume in 1 s; FVC: forced
552 vital capacity; FEV_1/FVC: forced expiratory volume (FEV_1)/forced vital capacity (FVC);
553 VC(%predicted): vital capacity; IC(%predicted): inspiratory capacity; TLC(%predicted): total
554 lung capacity; FRC(%predicted): residual capacity; RV(%predicted): reserve volume;
555 $DL_{,CO}$(%predicted): diffusion capacity; SpO_2(%): oxygen saturation; 6MWT: six minute walk
556 test. mMRC: modified Medical Research Council dyspnea scale; LAMA: Long-Acting

Muscarinic Agonists; LABA: Long-Acting Beta-Agonists; ICS: inhaled corticosteroids. Group A: home-based maintenance tele-rehabilitation; Group B: hospital-based, outpatient, maintenance rehabilitation and Group C: usual care.

583 **Table 2.**Predictors of AECOPD, hospitalizations and ED visits

	Univariate analysis			Multivariate analysis		
	IRR	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
AECOPD						
Age	1.001	0.987-1.014	0.069			
Gender (female)	1.225	0.942-1.595	0.131			
Smoking status (ex-smoker)	1.727	1.170-2.550	0.006	1.045	0.694-1.573	0.833
FEV_1 (%pred)	0.985	0.979-9.991	<0.001	0.992	0.986-0.999	0.016
n AECOPD/preceding year	1.164	1.125-1.203	<0.001	1.148	1.098-1.201	<0.001
Group A	0.562	0.429-0.737	<0.001	0.517	0.389-0.687	<0.001
Group B	0.498	0.375-0.660	<0.001	0.635	0.473-0.853	0.003
Group C (indicator)						
Hospitalizations for AECOPD						
Age	1.002	0.975-1.030	0.877			
Gender (female)	0.497	0.248-0.997	0.049	0.475	0.208-0.871	0.019
Smoking status (ex-smoker)	1.523	0.732-3.170	0.261			
FEV_1 (%pred)	0.979	0.960-0.986	<0.001	0.981	0.967-0.995	0.008
n AECOPD/preceding year	1.171	1.096-1.251	<0.001	1.160	1.051-1.280	0.003
Group A	0.268	0.149-0.482	<0.001	0.189	0.100-0.358	<0.001
Group B	0.292	0.165-0.518	<0.001	0.375	0.207-0.681	0.001
Group C (indicator)						
ED visits for AECOPD						
Age	0.990	0.975-1.005	0.191			
Gender (female)	1.536	1.162-2.031	0.003	1.051	0.772-1.431	0.752
Smoking status (ex-smoker)	1.964	1.242-3.105	0.004	0.815	0.504-1.318	0.404
FEV_1 (%pred)	0.987	0.980-0.994	<0.001	0.992	0.984-0.994	0.027
n AECOPD/preceding year	1.156	1.113-1.201	<0.001	1.244	1.175-1.316	<0.001
Group A	0.151	0.099-0.232	<0.001	0.116	0.072-0.185	<0.001
Group B	0.501	0.380-0.661	<0.001	0.750	0.555-1.015	0.062
Group C (indicator)						

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585 Abbreviations: AECOPD: Acute exacerbation of COPD; ED: Emergency Department; FEV_1:
586 forced expiratory volume in 1 s; n: Number. Group A: home-based maintenance tele-
587 rehabilitation; Group B: hospital-based, outpatient, maintenance pulmonary rehabilitation and
588 Group C: usual care.

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Table 3. Changes in functional capacity

	Baseline	2-months	14-months
WR_{peak} (Watt)			
Group A	63±33	74±35*	76±35*
Group B	67±25	79±32*	79±31*
Group C	65±24	63±27	58±24*
6MWT (m)			
Group A	389.1±91.3	422.1±70.5†	420.2±74.9†
Group B	385.1±80.3	423.0±70.5†	427.5±63.0†
Group C	384.8±80.2	382.4±80.3	339.9±110.1†

Values are mean±SD. Abbreviations: WR_{peak}: peak work rate; 6MWT: the distance covered during the six minute walking test. Asterisks indicate statistically significant differences from baseline. Crosses indicate clinically meaningful differences from baseline. Group A: home-based maintenance tele-rehabilitation; Group B: hospital-based, outpatient, maintenance rehabilitation and Group C: usual care.

Table 4. Changes in HRQoL, respiratory symptoms and chronic dyspnea

	Baseline	2-months	14-months
SGRQ			
Group A	46.2±19.7	42.2±19.2†	38.4±20.5†
Group B	43.5±16.7	35.4±15.7†	33.6±16.5†
Group C	44.1±16.6	44.7±16.9	50.2±17.7†
CAT			
Group A	17.6±8.1	12.9±7.5†	13.0±7.3†
Group B	15.7±5.6	13.2±5.8†	11.8±5.6†
Group C	15.8±4.9	16.1±6.2	20.9±6.7†
mMRC			
Group A	2.3±1.0	1.8±0.9†	1.6±1.0†
Group B	2.5±1.0	1.5±0.9†	1.3±0.9†
Group C	2.2±1.1	2.5±1.0	3.1±0.8†

Values are mean±SD. Abbreviations: SGRQ: Saint George Respiratory Questionnaire; CAT: COPD Assessment Test; mMRC: modified Medical Research Council. Crosses indicate clinically meaningful differences from baseline. Group A: home-based maintenance tele-rehabilitation; Group B: hospital-based, outpatient, maintenance rehabilitation and Group C: usual care.

Figure legends

Figure 1. Patient flow chart providing information in regards to the study protocol.

Figure 2. Percentage (%) of patients with AECOPD (Figure 2A) hospitalizations (Figure 2B) and emergency department visits (Figure 2C) during the 12 months follow up. Group A: home-based maintenance tele-rehabilitation, Group B: hospital-based, outpatient, rehabilitation and Group C: usual care treatment. Note that AECOPD refers to all kind of AECOPD regardless of the place where they were treated (home, hospital or ED).

Figure 3. Changes in daily physical activity levels defined by the time spend in sedentary (A), light (B), lifestyle (C) and moderate (D) activities. Values are mean±SD. Asterisks indicate statistically significant differences from baseline for the home-based maintenance tele-rehabilitation (dark grey bars) and hospital-based, outpatient, rehabilitation (light grey bars) groups. Two asterisks indicate statistically significant differences from the 2-month time point for the usual care group (white bars).

Figure 4. Patient's compliance to the different components of monitoring and home-based maintenance tele-rehabilitation maintenance program over a 12-month period (Group A, n=47).

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