

## **Angiotensin-Converting Enzyme Inhibition as an Adjunct to Pulmonary Rehabilitation in COPD**

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*At a glance commentary:*

Evidence associates the renin-angiotensin system in the control of skeletal muscle bulk and function, and suggests angiotensin II is implicated in the skeletal muscle dysfunction seen in

individuals with COPD. Thus manipulation of this pathway may allow greater response to exercise interventions such as pulmonary rehabilitation. We report on the first placebo-controlled, double-blind, randomised controlled trial to investigate if angiotensin-converting enzyme (ACE) inhibition, without a conventional existing clinical indication, could enhance the impacts of pulmonary rehabilitation on exercise capacity in patients with COPD.

Contrary to expectation, ACE-inhibition mediated by enalapril administration actually attenuated the increase in exercise capacity resulting from pulmonary rehabilitation in COPD.

"This article has an online data supplement, which is accessible from this issue's table of content online at [www.atsjournals.org](http://www.atsjournals.org)".

## **ABSTRACT**

**Rationale:** Epidemiological studies in older individuals have found an association between use of ACE-inhibition (ACE-I) therapy and preserved locomotor muscle mass, strength and walking speed. ACE-I therapy might therefore have a role in the context of pulmonary rehabilitation.

**Objectives:** We investigated the hypothesis that enalapril, an ACE-inhibitor, would augment the improvement in exercise capacity seen during pulmonary rehabilitation.

**Methods:** We performed a double-blind, placebo-controlled, parallel-group randomised controlled trial. COPD patients, with at least moderate airflow obstruction and taking part in pulmonary rehabilitation, were randomised to either 10 weeks therapy with an ACE-inhibitor (10mg enalapril) or placebo.

**Measurements:** The primary outcome measurement was the change in peak power (assessed using cycle ergometry) from baseline.

**Main Results:** Eighty patients were enrolled, seventy-eight randomised (age  $67\pm 8$  years,  $FEV_1$   $48\pm 21\%$  predicted), and sixty-five completed the trial (34 placebo, 31 ACE-inhibitor). The ACE-inhibitor treated group demonstrated a significant reduction in systolic blood pressure ( $\Delta$ -16mmHg, 95% CI -22 to -11) and serum ACE activity ( $\Delta$ -18IU/L, 95% CI -23 to -12) versus placebo (between group differences  $p<0.0001$ ). Peak power increased significantly more in the placebo group (placebo  $\Delta$ +9 Watts, 95% CI 5 to 13 vs. ACE-I  $\Delta$ +1 Watt, 95% CI -2 to 4, between group difference 8 Watts, 95% CI 3 to 13,  $p=0.001$ ). There was no significant between group difference in quadriceps strength or health-related quality of life.

**Conclusion:** Use of the ACE-inhibitor enalapril alongside a programme of pulmonary rehabilitation, in patients without an established indication for ACE-inhibition, reduced the response to exercise training in COPD patients.

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Key words: COPD, renin-angiotensin system, exercise, rehabilitation

## INTRODUCTION

Skeletal muscle dysfunction is a common and important extra-pulmonary complication of COPD, associated with reduced endurance exercise capacity (1), impaired healthcare status (2) and greater mortality (3). Whilst pulmonary rehabilitation (PR) is a high value treatment modality (4-6), its effects begin to decline towards baseline at 12-18 months (7, 8) and some patients with skeletal muscle dysfunction may be responding sub-optimally to this intervention (9). There is thus a need for adjunctive agents to ensure that patients gain the greatest response from rehabilitation programs and maintain this for as long as possible.

As components of circulating and tissue renin-angiotensin systems, the enzyme angiotensin-converting enzyme (ACE) plays a key role in the synthesis of angiotensin II and degradation of vasoactive kinins, most notably bradykinin. Evidence suggests a role for chronic activation of the intramuscular renin-angiotensin system (RAS) in regulating skeletal muscle phenotype, contributing to the skeletal muscle dysfunction seen in COPD (10). There are several potential levels of action of ACE-inhibition in promoting effective skeletal muscle function, including attenuation of the activity of angiotensin II which contributes to pro-inflammatory pathways, impaired glucose handling and promotes skeletal muscle atrophy (10). Bradykinin activity is also known to influence insulin sensitivity (11), protect against oxidative damage (12) and promote angiogenesis (10), all essential components of skeletal muscle function.

Epidemiological studies in older populations have shown ACE-inhibitor therapy to be associated with preserved locomotor muscle mass (13), leg strength (14) and walking speed (14) and thus could be predicted to affect exercise capacity, although these are observational findings and the exact mechanisms behind these associations have not been fully investigated. In line with this, individuals with genetically low serum and tissue ACE levels, associated with a polymorphism of the human ACE gene, have improved exercise characteristics both healthy and athletic populations (15, 16) and improved mechanical efficiency in response to training (17). Following this, COPD patients possessing the same genotype demonstrated greater peak workload during incremental cardiopulmonary exercise testing than those with higher intrinsic levels of ACE activity (18). Observational work has also shown that the bradykinin receptor polymorphism leading to reduced activity at the bradykinin receptor (+9/+9 BK<sub>2</sub>R) to be associated with both reduced fat-free mass and quadriceps strength in COPD (19).

In an elderly population with restricted mobility, ACE-inhibition was associated with an improvement in six minute walking distance (20). Furthermore, in COPD patients pharmacological reduction in angiotensin II has been associated with improvements in both quadriceps strength (21) as well as exercise capacity as assessed by incremental cardiopulmonary exercise testing, with a 7% increase in peak workload achieved following four weeks therapy with enalapril in those with moderate to severe airflow obstruction (22). However, in another study in COPD patients stratified on the basis of quadriceps weakness (quadriceps maximal volitional contraction strength <120% BMI), the use of the ACE-inhibitor fosinopril did not improve either quadriceps strength or endurance (23). Animal

studies have, however, suggested a potential synergistic role for ACE-inhibition and exercise in ensuring a more favourable skeletal muscle phenotype to promote greater exercise capacity (24). This raises the possibility that a training stimulus may be required to ensure maximal benefit from reduced angiotensin II activity.

Thus the aim of this study was to investigate the effects of therapy with an ACE-inhibitor as an adjunctive therapy to a standardised programme of pulmonary rehabilitation in a COPD population, with focus on the effects on exercise capacity, strength, health-related quality of life and daily physical activity.

## **MATERIALS AND METHODS**

### **Patient Selection**

All participants provided written informed consent prior to enrolment in the study which was approved by the London Bloomsbury Research Ethics Committee (REC reference 12/LO/0331) and registered prospectively on a publicly accessible database ([www.controlled-trials.com/ISRCTN79038750](http://www.controlled-trials.com/ISRCTN79038750)).

Stable COPD patients of GOLD stage II-IV (25) referred for pulmonary rehabilitation, and with an MRC dyspnoea score of at least 3, or 2 with functional limitation (26), were considered for inclusion. Individuals already using ACE-inhibitors or angiotensin-receptor blockers or with other reason to benefit from these medicines (including ischaemic heart



disease, impairment of ventricular function and diabetes mellitus) were excluded from the study. Other principle exclusion criteria were renovascular disease or significant renal impairment (defined as an eGFR  $<50\text{ml/min}/1.73\text{m}^2$ ), pulmonary exacerbation within one month, recent (less than 3 months) prior pulmonary rehabilitation course or other comorbid factors which either significantly impaired exercise capacity or ability to participate in rehabilitation, including significant musculoskeletal, neurological and aortic valve disease. Individuals with hypotension (defined as a systolic blood pressure less than 100mmHg) were excluded from participation.

### **Study design**

The study was a double-blind, placebo-controlled, parallel-group randomised trial. The primary outcome measure was the between group difference in the absolute change in peak power achieved on incremental cycle ergometry. This measure is a validated endpoint in COPD and provides an effective evaluation of whole body exercise capacity, taking into consideration both cardiorespiratory and skeletal muscle function, having been used in large trials such as the National Emphysema Treatment Trial (NETT) study (27). Leg fatigue has been shown to be more likely to limit cycle-based tasks than walking exercise (28). Hence, cycle ergometry may be more discriminatory in the assessment of interventions that influence skeletal muscle function. Both genotype based studies (18) and clinical research (22) have shown reduced angiotensin II activity to be associated with improved peak power achieved during incremental cardiopulmonary exercise testing in COPD. Secondary outcome measures included the between group differences in the change in quadriceps

maximal volitional contraction force, health-related quality of life and daily physical activity level.

### **Intervention and randomisation**

Patients were randomly allocated to receive either ACE-inhibitor (10mg enalapril once daily) or placebo (microcrystalline cellulose) for 10 weeks in a 1:1 manner using block randomisation and a block size of 4. Randomisation was performed by Imperial College Trials Unit using a stratified approach, based on the baseline peak power achieved on incremental cycle ergometry (using 50 Watts as a cut-off) and ACE genotype (II, ID or DD; I representing the insertion allele and D the deletion allele; the I allele is associated with lower ACE activity (19, 29, 30)). ACE genotype was assessed by polymerase chain reaction on DNA isolated from a saliva sample, the method for which is included in the online supplemental material. Both subjects and the assessor were blind to treatment allocation.

### **Study conduct**

Subjects were assessed at baseline and started enalapril/placebo treatment one week prior to the initiation of pulmonary rehabilitation. The pulmonary rehabilitation programme was 8 weeks in duration with a combination of educational and exercise sessions, incorporating both aerobic and strength training individualised to the patient as per national and international guidelines (4, 26). The programme delivered 3 exercise sessions per week, 2

under direct supervision and 1 for the patient to undertake independently at home. The sessions were delivered in a circuit style programme with a goal-setting and progressive approach. Aerobic training included treadmill and cycle exercise, with individuals prescribed exercise at an intensity of 85% of their predicted VO<sub>2</sub> peak. Strengthening exercises included upper and lower limb resistive exercise with weights. Blood pressure and renal function were checked one week after starting treatment and if symptomatically hypotensive (systolic blood pressure less than 100mmHg, or fall from baseline of greater than 10mmHg, with accompanying symptoms) or with evidence of significant decline in renal function (serum creatinine increase >30% beyond baseline) subjects were withdrawn from the study.

Subjects reattended for assessment within one week of completion of the PR programme and continued therapy until completion of the study. Patient assessments performed at baseline and following completion of rehabilitation included blood pressure, full pulmonary function, maximal symptom-limited incremental cycle ergometry, fat free mass assessed by bioelectrical impedance analysis, health-related quality of life assessment, quadriceps maximal volitional contraction, mid-thigh computed tomography scan and physical activity monitoring using a triaxial accelerometer. Further details of these assessments are available in the on-line supplement.

### **Data analysis and statistics**

The primary endpoint selected in this study was peak workload achieved on incremental cycle ergometry. Sample size was determined based on previous data showing an increase in peak power following rehabilitation, from  $55\pm 19$  to  $63\pm 9$  Watts (31). To show an additional 10% improvement with ACE-inhibition, at an 80% statistical power with a significance level of 0.05, 54 individuals would need to complete the study. Allowing for a 10% withdrawal rate and individuals with genetically low ACE levels (II genotype, expected prevalence 25%) potentially responding to a lesser degree, led to a sample size of 80. Data are presented as mean  $\pm$  standard deviation or 95% confidence interval, and compared using two-sided paired (for comparison pre and post rehabilitation) or unpaired (comparing treatment groups) t-tests. Categorical data are presented as percentages and comparisons performed using the Chi-squared test. Analysis was performed on a per protocol basis using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego, California, USA). A p-value  $<0.05$  was considered to be statistically significant.

## **RESULTS**

### **Subjects**

80 patients were enrolled into the study, of whom 65 completed the full study protocol.

There were five withdrawals in the placebo group and eight in the treatment group, further explanation of which is provided in the CONSORT diagram (figure 1).

### **Baseline characteristics**

The baseline characteristics of the group are presented in table 1. The participants were representative of COPD subjects referred for pulmonary rehabilitation with a mean age  $67\pm 8$  years, FEV<sub>1</sub>  $48\pm 21\%$  predicted, systolic blood pressure  $137\pm 18$ mmHg, MRC dyspnoea score  $3\pm 1$ , quadriceps strength  $73\pm 22\%$  predicted and daily average step count of  $5428\pm 3633$ . 79% of the subjects displayed evidence of ventilatory limitation at baseline (as assessed by the ratio of peak ventilation to the estimated maximal ventilation of  $\geq 0.9$  (32)). The groups were well-matched for age, gender, lung function and exercise capacity at baseline. Although the difference in BMI reached statistical significance, it would not be considered to be a clinically important difference. The ACE genotypes were consistent with Hardy-Weinberg equilibrium in both groups, and the distribution did not differ between the treatment arms.

### **Effect of ACE-inhibition on blood pressure parameters**

In the placebo arm, systolic blood pressure was unchanged from baseline ( $\Delta$ -1mmHg, 95% CI -5 to 4,  $p=0.78$ ), whereas it was significantly reduced in the ACE-I arm ( $\Delta$ -16mmHg, 95% CI -22 to -11,  $p<0.0001$ ) with a significant between group difference (-15mmHg, 95% CI -21 to -9,  $p<0.0001$ ) (figure 2). Similar changes were also noted with diastolic blood pressure (placebo  $\Delta$ +1mmHg, 95% CI -3 to 4,  $p=0.71$  vs. ACE-I  $\Delta$ -9mmHg, 95% CI -11 to -6,  $p<0.0001$ ; between group difference -10mmHg, 95% CI -14 to -5,  $p=0.0001$ ; figure 2).

### **Effect of ACE-inhibition on serum ACE levels**

There was a significant reduction in serum ACE levels in the ACE-I arm that was not seen in the placebo arm (placebo  $\Delta+4$  IU/L, 95% CI 0 to 8,  $p=0.05$  vs. ACE-I  $\Delta-18$  IU/L, 95% CI -23 to -12,  $p<0.0001$ ; between group difference -22 IU/L, 95% CI -29 to -15,  $p<0.0001$ ; figure 3).

### **Effect of ACE-inhibition on exercise capacity**

The peak power achieved on incremental cycle ergometry increased in both groups following pulmonary rehabilitation but the change was only significantly greater in the placebo group (placebo  $\Delta+9$  Watts, 95% CI 5 to 13,  $p<0.001$  vs. ACE-I  $\Delta+1$  Watt, 95% CI -2 to 4,  $p=0.62$ ; between group difference 8 Watts, 95% CI 3 to 13,  $p=0.001$ ; figure 4). A similar pattern was seen in the change in peak pulmonary oxygen uptake (placebo  $\Delta+1.37$  ml/min/kg, 95% CI 0.79 to 2.02,  $p=0.0001$  vs. ACE-I  $\Delta+0.33$  ml/min/kg, 95% CI -0.41 to 1.08,  $p=0.45$ ; between group difference 1.04 ml/min/kg, 95% CI 0.08 to 2.01,  $p=0.035$ ).

There were no significant between group differences in the change in the VE/VCO<sub>2</sub> slope from baseline to post pulmonary rehabilitation (placebo  $\Delta-1.25$ , 95% CI -3.21 to 0.72,  $p=0.45$  vs. ACE-I  $\Delta-0.87$ , 95% CI -2.17 to 0.43,  $p=0.18$ ; between group difference 0.38, 95% CI -2.02 to 2.78,  $p=0.57$ ). The oxygen uptake efficiency slope altered from baseline to post pulmonary rehabilitation more in the placebo group, although the between group difference failed to reach statistical significance (placebo  $\Delta 151$ , 96% CI 40 to 261,  $p=0.009$  vs. ACE-I  $\Delta 29$ , 95% CI -109 to 167,  $p=0.67$ ; between group difference 122, 95% CI -49 to 292,  $p=0.08$ ).

### **Effect of ACE-inhibition on quality of life, lung function variables and strength**

Health-related quality of life scores, as assessed by the St. George's Respiratory Questionnaire for COPD (SGRQ-C), improved in both treatment arms following pulmonary rehabilitation but there were no significant between group differences (table 2). Lung function variables, measures of quadriceps strength and muscle bulk showed no significant between group differences (table 2). Daily physical activity as assessed by the physical activity level (PAL) increased in the placebo arm but actually reduced in the treatment arm, producing a significant between group difference (table 2).

### **Effect of ACE-inhibition on rate of adverse events, rehabilitation and drug compliance**

There was no difference in the rate of either pulmonary exacerbations or other adverse events comparing the study arms. Although there was a statistically significant difference in the number of supervised rehabilitation sessions attended (placebo 13, 95% CI 12 to 14 vs. ACE-I 11, 95% CI 10 to 12;  $p=0.002$ ), the actual difference was small and unlikely to have provided a more favourable training stimulus in the placebo group. Drug compliance was excellent in both arms (placebo 96% compliance, 95% CI 93 to 98 vs. ACE-I 96% compliance, 95% CI 94 to 99;  $p=0.45$ ).

Two patients in the ACE-inhibitor arm showed significant decline in renal function (>30% increase in serum creatinine) and were withdrawn from the study. Only one patient, in the ACE-I treated arm, described a persistent cough, outside the context of a pulmonary exacerbation, but this did not lead to cessation of therapy.

## DISCUSSION

The main finding of this study was that enalapril, rather than enhancing the improvement in maximal exercise capacity seen with pulmonary rehabilitation in COPD, in fact reduced it. Enalapril did lower both blood pressure and serum ACE activity, confirming that a biologically relevant dose had been administered. The current data therefore do not support the use of ACE-inhibitors to help ameliorate the skeletal muscle dysfunction in COPD when assessed through incremental cardiopulmonary exercise testing, and indeed suggest caution should be applied in this context. Clinically it is important to note that this conclusion applies only to individuals who do not have a clinically established reason for being on an ACE-I.

### *Significance of the findings*

Studies of molecular pathways have suggested that the renin-angiotensin system is an important component of the skeletal muscle dysfunction seen in COPD (10), and previous experimental work has suggested a potential beneficial effect from ACE-inhibition on skeletal muscle phenotype so the results of the current study were unexpected. This is, however, the first randomised controlled trial of ACE-inhibition as an adjunct to pulmonary rehabilitation. Our findings emphasise the important role of prospective blinded randomised trials particularly as much previous work on both epidemiological cohorts (13, 14) and ACE genotype polymorphisms (15, 18) suggesting ACE-inhibition might have beneficial effects was observational in nature.



Previous randomised controlled trials had suggested that manipulation of the RAS would produce favourable effects on exercise capacity in COPD subjects. Andreas *et al.* showed that use of the angiotensin receptor blocker irbesartan for four months in severe COPD led to numerical improvements in quadriceps strength (21), and a small pilot study using enalapril for four weeks in 21 moderate to severe COPD subjects improved peak power achieved on incremental cycle ergometry (22). However, our own group studied the administration of the ACE-inhibitor fosinopril to a group of moderate to severe COPD patients selected for quadriceps weakness, showing no improvement in either quadriceps strength, endurance or functional outcomes as measured by the incremental shuttle walk test (33). In fact, despite exercise training not being administered in that study, an increase in quadriceps maximal volitional force of contraction (QMVC) was seen in both groups, but to a lesser extent in the ACE-inhibitor treated group than the placebo group, consistent with the current findings. Recognised limitations of that study included the failure to stratify by ACE genotype and lack of a training stimulus, both issues that were addressed in this present study.

We specifically excluded subjects with ischaemic heart disease, ventricular failure and diabetes, and thus although we cannot support use of ACE-inhibitors for targeting skeletal muscle dysfunction in COPD, many such patients will have other indications for ACE-inhibitor therapy. In fact it is well recognised that cardiovascular comorbidities are of a higher prevalence in COPD (34), and we would not support avoidance or cessation of ACE-inhibitors when comorbidities known to benefit from such therapy are present.

### *Possible mechanism of action of ACE-inhibitors*

Despite epidemiological evidence suggesting ACE-inhibition should improve skeletal muscle function, the molecular basis for this remains unclear although several mechanisms have been proposed, including improved glucose sensitivity, promotion of hypertrophic pathways, reduction in local inflammation and enhancement of the effects of bradykinin (10). There are several possible mechanisms by which ACE-inhibition may have attenuated the acute response to pulmonary rehabilitation, although the exact basis for the attenuation of gain in maximal exercise capacity in the current study remains unclear. It could be hypothesised that reductions in total peripheral vascular resistance may divert blood flow away from actively exercising muscle and reduce perfusion pressure to the muscle vascular bed, impeding effective matching of blood flow to metabolic demand, although evidence suggests that, at least in the resting state, ACE-inhibition improves skeletal muscle blood flow by reducing vascular resistance (35, 36).

Interestingly there is increasing evidence that tissue capillarity is reduced in COPD and associated with muscle contractile fatigue (37), and that increased capillarity is one mechanism through which rehabilitation is beneficial (9). The RAS is implicated in angiogenesis and reactivity of the microvasculature of the skeletal muscle, with the administration of captopril in a rat model associated with reduced arteriolar density, diameter (38) and response to vasodilator stimuli (39), associated with reduced exercise tolerance (40). The RAS is a complicated pathway and angiotensin (1-7), itself a breakdown

product of angiotensin II, is known to have muscle anti-atrophic effects (41), thus it is possible that ACE-inhibition is having several counter-regulatory effects.

Although angiotensin II is recognised to have adverse effects on skeletal muscle, as with cardiac muscle, angiotensin II is important for tetanic strength and hypertrophy in response to mechanical loading (42). It is recognised that COPD subjects with high intrinsic levels of angiotensin II (ACE DD genotype) have maintained strength (29). In addition, peripheral muscle strength is known to be an important contributor to endurance capacity in COPD patients attending pulmonary rehabilitation (1), and it may be that by reducing angiotensin II activity we attenuated strength capacity, which in turn affected exercise performance. Thus it may be that the impact of high angiotensin II levels on strength and hypertrophy outweighs the impact of lower levels on exercise capacity in this context.

It was interesting to note the reduced physical activity of those treated with ACE-inhibition in comparison to the rise seen in response to training in the placebo group. Although it might be possible to speculate this was because of hypotension, in fact only two subjects in the ACE-inhibitor group reported symptomatic dizziness but this was transient, settled spontaneously and did not require cessation of therapy. In addition, the change in symptom scores was comparable between treatment arms, suggesting the ACE-inhibitor treated group did not subjectively feel worse. It is difficult to comment further on why this effect was seen, although the quality of life questionnaires employed understandably focussed on respiratory disability and may have not detected other relevant symptoms, although

patients in the treatment group did not report adverse effects that would explain the differences noted.

### *Methodological issues*

This study was prospectively stratified by ACE genotype which is important as previous work has shown a greater response to exercise training in the II ACE genotype group (43). A strong primary endpoint was selected and the groups were well-matched at baseline, lending confidence to the findings.

We chose to use an ACE-inhibitor to ensure effects on both angiotensin II and bradykinin activity. Bradykinin receptor polymorphisms have been shown to impact on skeletal muscle phenotype in COPD (19, 30), and previous experimental work has shown bradykinin to have positive effects on skeletal muscle metabolism, including through the generation of nitric oxide, reduced oxidative stress and improved skeletal muscle insulin sensitivity (11, 12). Thus we chose an agent that would not only reduce angiotensin II activity but also enhance bradykinin activity. Previous beneficial effects in COPD have been shown in trials with perindopril (20) and enalapril (22), although not with fosinopril (33). Given that enalapril has previously been noted to improve peak work rate in COPD subjects (22), which was our selected primary outcome measure, this seemed an appropriate agent to select. There was physiological evidence of adequate dosing, manifest by reduced blood pressure and serum ACE activity, although it is impossible to determine the effects on the skeletal muscle RAS without direct sampling. This study does not exclude the possibility that the same effects

would be seen with all ACE-inhibitors but is in line with our previous work (33), suggesting this is likely a class effect. It also remains unclear the time period over which ACE-inhibitors should be administered to influence the skeletal muscle phenotype, although shorter periods of treatment than we provided in this study have been associated with changes in exercise capacity (22).

### *Potential study Limitations*

There are several possible limitations of the current study that deserve further mention. The enalapril treated group attended a lower number of physiotherapist led training sessions than the placebo treated group. Whilst we believe this is unlikely to have been sufficient to account for the differences seen in outcomes, it is possible that this assumption is incorrect. It is also possible that beneficial effects might have been noted had different exercise tests, such as endurance capacity during constant rate submaximal exercise, been used and this cannot be resolved without further study.

It is also possible that certain subgroups of COPD patients may experience benefit from ACE-inhibition whereas others may experience detrimental effects. The current study was not sufficiently powered to allow effective subgroup analysis beyond the chosen stratification variables, and we cannot therefore address this point.. We recognise that we used quality of life questionnaires that focussed on respiratory disability. While this was appropriate given the nature of the study, and different questionnaires might have been more effective

at detecting symptomatic changes induced by ACE-inhibition that could have influenced physical activity levels and exercise capacity.

### *Conclusion*

Our results suggest that ACE-inhibition actually reduced the response to exercise training compared to placebo in patients with COPD, and thus ACE-inhibitors cannot be recommended for this indication. The biological mechanisms underlying this unexpected finding may warrant further scrutiny. We caution that our study specifically excluded patients with an established indication for ACE inhibition and therefore our data do not support withdrawing ACE inhibition from such patients during PR.

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## FIGURE LEGENDS

Figure 1: CONSORT recruitment diagram for enrolment and study completion.

Abbreviations: ACE-I - angiotensin-converting enzyme; A<sub>2</sub>RB – angiotensin II receptor blocker; GOLD – global initiative for chronic obstructive lung disease; PR – pulmonary rehabilitation.

Figure 2: Alterations in blood pressure parameters (systolic blood pressure sBP and diastolic blood pressure dBP) from baseline to post pulmonary rehabilitation in the placebo (PL) and ACE-inhibitor (ACE-I) treatment arms. Comparisons were made using unpaired t-tests, \*p value <0.0001; †p value=0.0001.

Figure 3: Change in serum ACE levels from baseline to post pulmonary rehabilitation in the placebo (PL) and ACE-inhibitor (ACE-I) treatment arms. Comparison was made using an unpaired t-test, \*p<0.0001.

Figure 4: Change in peak workload achieved during incremental cycle ergometry from baseline to post pulmonary rehabilitation in the placebo (PL) and ACE-inhibitor (ACE-I) treatment arms. Comparison was made using an unpaired t-test, \*p =0.001.



## TABLES

Table 1: Demographic and baseline clinical characteristics of the subjects.

|                                       | Placebo group (n=34) | ACE-I group (n=31) | p value |
|---------------------------------------|----------------------|--------------------|---------|
| Sex (% female)                        | 41                   | 55                 | 0.27    |
| Age (years)                           | 68 (7)               | 66 (10)            | 0.28    |
| ACE genotype (II, ID, DD) %           | 21, 47, 32           | 23, 42, 35         | 0.92    |
| BMI (kg/m <sup>2</sup> )              | 26.9 (5.9)           | 24.0 (4.6)         | 0.033*  |
| Systolic BP (mm Hg)                   | 139 (17)             | 133 (15)           | 0.10    |
| Diastolic BP (mm Hg)                  | 79 (11)              | 78 (9)             | 0.73    |
| LAMA (%)                              | 71                   | 84                 | 0.20    |
| LABA-ICS (%)                          | 79                   | 71                 | 0.43    |
| MRC dyspnoea score                    | 3 (1)                | 3 (1)              | 0.52    |
| CAT score                             | 18 (7)               | 17 (7)             | 0.65    |
| SGRQ-C total                          | 46.25 (18.59)        | 46.78 (17.68)      | 0.91    |
| Average daily step count <sup>†</sup> | 4883 (2668)          | 6685 (4234)        | 0.15    |
| Average PAL <sup>†</sup>              | 1.39 (0.20)          | 1.49 (0.19)        | 0.10    |
| FEV <sub>1</sub> (L)                  | 1.31 (0.53)          | 1.10 (0.54)        | 0.12    |
| FEV <sub>1</sub> % predicted          | 51.6 (20.2)          | 48.2 (22.5)        | 0.37    |
| FVC (L)                               | 3.25 (0.67)          | 2.96 (0.88)        | 0.15    |
| TLC <sub>c</sub> % predicted          | 54.2 (22.7)          | 51.1 (23.1)        | 0.59    |
| RV/TLC ratio (%)                      | 52.8 (8.5)           | 56.5 (9.0)         | 0.09    |
| PaO <sub>2</sub> (kPa)                | 10.4 (1.6)           | 10.4 (1.6)         | 0.87    |
| PaCO <sub>2</sub> (kPa)               | 4.7 (0.6)            | 4.9 (0.6)          | 0.22    |
| Peak power on cycle (watts)           | 51 (22)              | 54 (29)            | 0.62    |
| Peak VO <sub>2</sub> (ml/min/kg)      | 14.1 (3.1)           | 16.1 (5.4)         | 0.19    |
| VE/VCO <sub>2</sub> slope             | 31.26 (7.84)         | 30.16 (7.59)       | 0.38    |
| OUES                                  | 1686 (485)           | 1658 (520)         | 0.73    |
| FFMI (kg/m <sup>2</sup> )             | 17.1 (2.3)           | 15.7 (1.8)         | 0.0089* |
| QMVC (kg)                             | 30.4 (11.0)          | 28.9 (10.1)        | 0.58    |
| MTMCSA (mm <sup>2</sup> )             | 9969 (2012)          | 9120 (2417)        | 0.12    |
| Quadriceps CSA (mm <sup>2</sup> )     | 4348 (950)           | 4027 (1277)        | 0.27    |

Data shown are mean (SD). Abbreviations: ACE – angiotensin converting enzyme; I – insertion allele; D – deletion allele; BMI – body mass index; BP – blood pressure; LAMA – long-acting muscarinic antagonist; LABA-ICS – long-acting beta-agonist and inhaled corticosteroid; MRC – Medical Research Council; CAT – COPD assessment test; SGRQ-C – St.

George's respiratory questionnaire for COPD; PAL - physical activity level; FEV<sub>1</sub> – forced expiratory volume in 1 second; FVC – forced vital capacity; TLC<sub>c</sub> – carbon monoxide diffusion capacity; RV – residual volume; TLC – total lung capacity; PaO<sub>2</sub> – arterial partial pressure of oxygen; PaCO<sub>2</sub> – arterial partial pressure of carbon dioxide; VO<sub>2</sub> – pulmonary oxygen uptake; VE – minute ventilation; VCO<sub>2</sub> – pulmonary carbon dioxide production; OUES – oxygen uptake efficiency slope; FFMI – fat free mass index; QMVC – quadriceps maximal volitional contraction; MTMCSA - mid-thigh muscle cross-sectional area.

\*p<0.05; † Data is analysed from 53 subjects (29 placebo, 24 treatment arm) who recorded an adequate period for physical activity assessment.

Table 2: Change in outcome measures from baseline to post pulmonary rehabilitation.

|                                    | Placebo group (n=34) | ACE-I group (n=31) | p value |
|------------------------------------|----------------------|--------------------|---------|
| ΔCAT score                         | -1 (3)               | 1 (4)              | 0.05    |
| ΔSGRQ-C Symptoms                   | -0.55 (12.48)        | -3.00 (11.43)      | 0.56    |
| ΔSGRQ-C Activity                   | -6.51 (13.30)        | -9.03 (15.65)      | 0.49    |
| ΔSGRQ-C Impacts                    | -1.83 (7.82)         | -2.62 (10.63)      | 0.52    |
| ΔSGRQ-C Total                      | -3.14 (6.10)         | -4.66 (8.71)       | 0.42    |
| ΔFEV <sub>1</sub> (L)              | -0.02 (0.10)         | -0.01 (0.13)       | 0.91    |
| ΔFEV <sub>1</sub> % predicted      | 0.02 (3.77)          | -0.10 (6.68)       | 0.93    |
| ΔTLC <sub>c</sub> % predicted      | -1.45 (4.82)         | -1.96 (5.61)       | 0.70    |
| ΔRV/TLC ratio (%)                  | 0.39 (2.67)          | 0.09 (3.65)        | 0.70    |
| ΔPaO <sub>2</sub> (kPa)            | -0.02 (1.16)         | 0.00 (1.12)        | 0.95    |
| ΔPaCO <sub>2</sub> (kPa)           | 0.08 (0.38)          | 0.02 (0.41)        | 0.60    |
| ΔFFMI (kg/m <sup>2</sup> )         | -0.31 (0.87)         | -0.18 (0.54)       | 0.58    |
| ΔQMVC (kg)                         | 2.09 (4.70)          | 0.37 (5.29)        | 0.17    |
| ΔMTMCSA (mm <sup>2</sup> )         | 53 (498)             | -52 (601)          | 0.45    |
| ΔQuadriceps CSA (mm <sup>2</sup> ) | 81 (284)             | 69 (223)           | 0.86    |
| ΔDaily step count <sup>†</sup>     | 561 (2528)           | -382 (2082)        | 0.30    |
| ΔPAL <sup>†</sup>                  | 0.04 (0.15)          | -0.06 (0.16)       | 0.030*  |

Data shown are mean (SD). Abbreviations: ACE-I - ACE-inhibitor; CAT – COPD assessment test; SGRQ-C – St. George’s respiratory questionnaire for COPD; FEV<sub>1</sub> – forced expiratory volume in 1 second; TLCO<sub>c</sub> – carbon monoxide diffusing capacity; RV – residual volume; TLC – total lung capacity; PaO<sub>2</sub> – arterial partial pressure of oxygen; PaCO<sub>2</sub> – arterial partial pressure of carbon dioxide; FFMI – fat free mass index; QMVC – quadriceps maximal volitional contraction; MTMCSA - mid-thigh muscle cross-sectional area; PAL - physical activity level.

\*p<0.05; †Data is analysed from 40 subjects (22 placebo, 18 treatment arm) who recorded an adequate period for physical activity assessment both at baseline and following rehabilitation.

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