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BMJ Open Respiratory Research

Bisoprolol versus celiprolol on dynamic hyperinflation, cardiopulmonary exercise and domiciliary safety in COPD: a single-centre, randomised, crossover study

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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) is frequently associated with cardiovascular disease. The utility of beta-blockers for treating patients with COPD may be beneficial, but their safety remains uncertain, including worsening of dynamic hyperinflation (DH) during exercise. We hypothesised that among cardioselective beta-blockers celiprolol, due to its partial beta-2 agonist activity, may be safer than bisoprolol on exercise DH.

Methods We measured isotime inspiratory capacity (IC) during cycle endurance testing in eleven moderate-severe COPD subjects, alongside other non-invasive cardiopulmonary exercise, bioreactance cardiac output, pulmonary function, biomarkers and daily domiciliary measures. Participants received titrated doses of either bisoprolol (maximim 5 mg) or celiprolol (maximum 400 mg) in randomised crossover fashion, each over 4 weeks.

Results Clinically relevant DH occurred between resting and exercise isotime IC but showed no significant difference with either beta-blocker compared with post-run-in pooled baseline or between treatments. There were no other significant differences observed for remaining exercise ventilatory; non-invasive cardiac output; resting pulmonary function; beta-2 receptor and cardiac biomarkers; domiciliary pulmonary function, oxygen saturation and symptom outcomes, either between treatments or compared with baseline. No significant adverse effects occurred.

Conclusions Significant DH in moderate-severe COPD subjects was no different between bisoprolol or celiprolol or versus baseline. A broad spectrum of other non-invasive cardiopulmonary and domiciliary safety outcomes was equally reassuring. Bronchoprotection with a concomitant long-acting muscarinic antagonist might be an important safety measure in this context.

Trial registration number NCT02380053.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Incident cardiovascular disease is common in patients with chronic obstructive pulmonary disease (COPD), often requiring beta-blocker therapy. We compared the cardioselective beta-blockers bisoprolol and celiprolol, hypothesising the partial beta-2 agonist activity of celiprolol may provide greater protection against dynamic hyperinflation on cardiopulmonary exercise testing.

WHAT THIS STUDY ADDS

⇒ Neither beta-blocker worsened existing exercise dynamic hyperinflation in moderate-severe patients with COPD, with no difference between beta-blockers, nor were they detrimental to other cardiopulmonary and domiciliary safety outcomes at clinically recommended doses.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These highly cardioselective beta-blockers, therefore, appear safe to use and could be studied further in longer term treatment trials of COPD.

INTRODUCTION

The morbidity and mortality of chronic obstructive pulmonary disease (COPD) are frequently compounded by comorbid incident cardiovascular disease.[1] Indeed, COPD is itself a risk factor for cardiovascular disease, due to the shared risks of smoking, increasing COPD severity over time and exacerbations.[2] Ischaemic heart disease, cardiac failure and cardiac arrhythmias are particularly prevalent as comorbid pathologies in COPD but may go unrecognised due to the burden of symptoms attributed to COPD alone.

Cardioselective beta-blockers are one of the pillars of treatment for these cardiovascular diseases in the general population. However, beta-blockers are chronically underutilised for these indications in patients with COPD.[3 4] This is driven by clinical concern over worsening airflow obstruction, resulting in increased breathlessness and reduced exercise capacity. Furthermore, greater dynamic hyperinflation (DH) during exercise on

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blockade of the airway beta-2 adrenoceptors occurs,[5] thus increasing breathlessness further.[6] Pointedly, this risk may be more significant when airway calibre is not protected by a concomitant long-acting muscarinic antagonist (LAMA) that blocks the bronchoconstrictor effect of unopposed acetylcholine transmission across airway neuromuscular junctions, itself precipitated by pre and postjunctional beta-2 adrenoceptor blockade.[7]

Cardioselective beta-blockers do, however, provide a degree of protection in this regard by more selectively blocking beta-1 over beta-2 adrenoceptors. Nevertheless, the various cardioselective beta-blockers in clinical use are pharmacologically diverse, with some more cardioselective than others. For example, bisoprolol is approximately six times more selective towards the beta-1 adrenoceptor (13.5:1) than metoprolol (2.3:1) despite both being similarly classified as cardioselective agents per se.[8] Retrospective observational studies have suggested that cardioselective beta-blockers are not only safe[9] but may also improve survival in COPD even without overt cardiovascular disease.[10 11] However, a more recent prospective study has cast some doubt on their safety, with metoprolol leading to a greater propensity for severe or very severe exacerbations compared with placebo in patients without overt cardiovascular disease, although the overall exacerbation and mortality rates were no different.[12]

Given these mixed signals, it is imperative that we identify the optimal cardioselective beta-blocker for further long-term prospective studies to safely investigate any survival advantage in COPD. Celiprolol is a unique cardioselective beta-blocker. It is even more cardioselective than bisoprolol in not only blocking the beta-1 adrenoceptor but also additionally displaying partial agonist activity (PAA) at the airway beta-2 adrenoceptor.[13] Celiprolol might, therefore, bronchodilate or at least provide greater bronchoprotection than bisoprolol[14]; while also providing sufficient cardiac beta-1 blockade.

In the present study, we prospectively compared chronic dosing of bisoprolol versus celiprolol in moderate to severe patients with COPD on cardiopulmonary exercise and safety outcomes. We primarily explored any difference in the degree of DH on exercise, hypothesising this might not be so marked with celiprolol due to its PAA. Important secondary outcomes included novel non-invasive cardiac output (CO) monitoring during exercise, along with domiciliary pulmonary function and oxygen saturation measurements.

METHODS

Study subjects

We recruited volunteers aged between 40 and 80 years (figure 1) with stable, moderate-severe COPD defined as Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2/3, with a postbronchodilator forced expiratory volume in 1 s (FEV_1) 30%–80% and an FEV_1/FVC ratio <0.7. The main inclusion criteria were a tobacco smoking history ≥10 pack-years; oxygen saturations ≥92% on room air at rest; an ECG demonstrating sinus rhythm and a transthoracic echocardiogram demonstrating a structurally normal heart with no significant ventricular

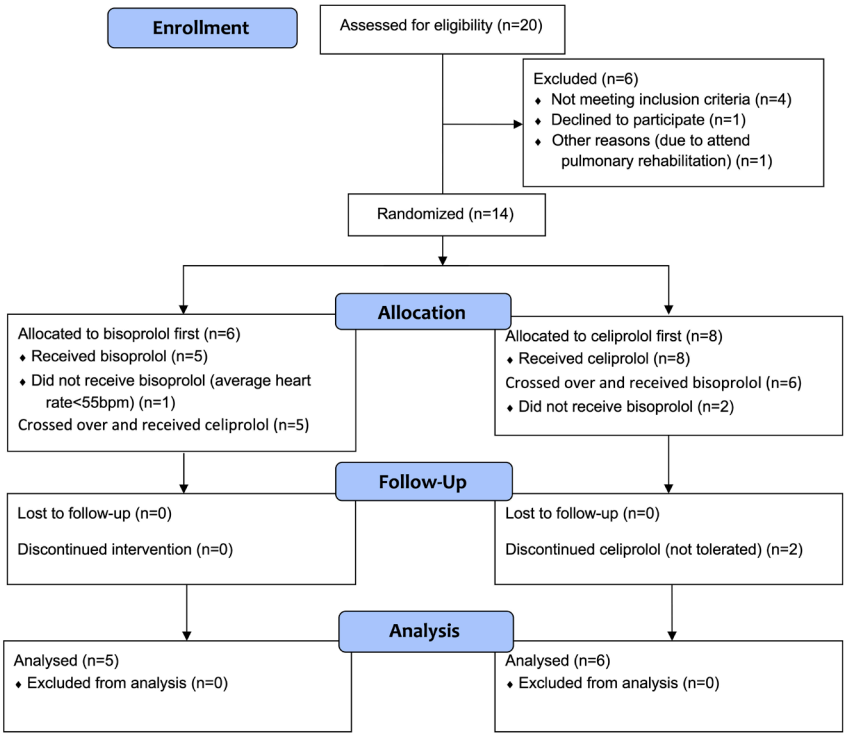

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials.

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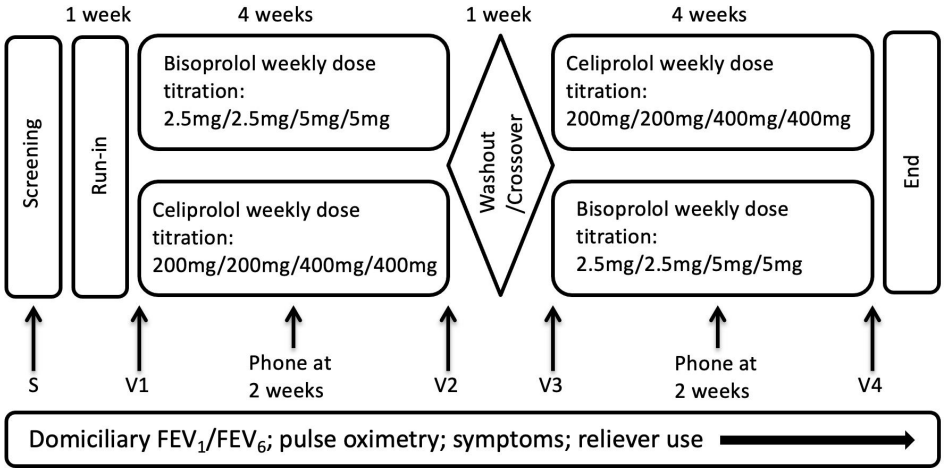

Figure 2 Study flowchart. Screening visit (S) including incremental, symptom limited cardiopulmonary exercise test. Study visits 1–4 (V1–V4) measurements: impulse oscillometry; slow vital capacity; spirometry; plethysmography; lying/standing heart rate and blood pressure; oxygen saturations at rest; venous blood for NT-pro-BNP, Galectin-3, Cholesterol/HDL, creatine kinase, potassium; ECG; SGRQ; constant work rate CPET with non-invasive cardiac output monitoring. CPET, cardiopulmonary exercise test; FEV_1, forced expiratory volume in 1 s; FEV_6, forced expiratory volume in 6 s; HDL, high-density lipoprotein; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; SGRQ, St George's Respiratory Questionnaire.

or valvular impairment. The main exclusion criteria were current use of domiciliary oxygen therapy; any hospitalisation with a COPD exacerbation within 3 months of screening visit; any history of another obstructive lung disease or clinically significant cardiac or peripheral vascular disease.

Study design

We performed a randomised, single-centre (University Hospital), open-label, crossover study (figure 2). Following a 1-week run-in on their usual COPD medications, participants received either bisoprolol (Generic, Accord Healthcare) 2.5 mg/day (2 weeks), then 5 mg/day (2 weeks) or celiprolol (Celectol, Zentiva) 200 mg/day (2 weeks), then 400 mg/day (2 weeks), followed by a 1-week washout before crossover to the alternate beta-blocker. Participants were contacted remotely at 2 weeks into each treatment period to ensure their safety of beta-blocker dose escalation by algorithm (online supplemental file 1). Randomisation was achieved using Randomisation.com by a member of the study team.

The primary outcome was the difference in rest-to-isotime inspiratory capacity (IC) during cycle endurance tests between treatments and compared with baseline, that is, comparison of degree of DH during steady-state exercise between bisoprolol and celiprolol. Secondary and safety outcomes included selected other cardiopulmonary exercise test (CPET) outcomes from cycle endurance tests; non-invasive bioreactance CO measures during exercise; spirometry; impulse oscillometry; total body plethysmography; lying/standing blood pressure; cardiovascular biomarkers (NT-pro BNP, Galectin); beta-2 agonist activity biomarkers (cholesterol/high-density lipoprotein (HDL), creatinine kinase (CK), serum potassium); St George's Respiratory Questionnaire (SGRQ); diarised domiciliary diurnal FEV_1/FEV_6, resting pulse oximetry, symptom scores and reliever use.

METHODS

Those who kindly volunteered to participate in the study were screened having withheld any long and/or short-acting bronchodilators for 48 hours and 6 hours, respectively. The screening measurements included impulse oscillometry (Masterscreen IOS, Carefusion, Hochberg, Germany); spirometry (Superspiro, Micromedical, Chatham, UK) with reversibility to 400 µg salbutamol according to American Thoracic Society (ATS) guidelines[15]; resting ECG; pulse oximetry breathing air after ≥5 min rest; lying/standing heart rate and blood pressure (average of three readings); practise incremental CPET with breath by breath measurements to symptom limit using a cycle ergometer and metabolic cart (VMAX, Carefusion, Hochberg, Germany) confirming cycling ability and to counter 'learning effect' in future visits according to ATS guidelines[16] ; venous full blood count, renal function, liver function, random glucose; transthoracic echocardiogram (if not performed within previous year); SGRQ.[17] Participants were provided with a portable monitor (PiKO-6, nSpire Health) to record domiciliary FEV_1 and FEV_6 two times per day (best of three blows) alongside domiciliary pulse oximetry to be recorded at rest two times per day. They also completed a diurnal diary of reliever use and symptoms from the screening visit to the end of study. Participants then only withheld short-acting bronchodilators for 6 hours prior to remaining visits. The primary outcome measurements for all study visits were obtained during cycle endurance tests. These comprised a constant work rate protocol[16 18] and targeted cadence of approximately 60 rpm; including 2 min rest, 3 min unloaded cycling,

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Table 1 Demographics

Variable	n=11
Age (years)	69 (65, 73)
Gender (n) (male:female)	7:4
BMI (kg/m^2)	27.4 (25.3, 29.5)
Smoking status (n) (current:ex-smoker)	2:9
Smoking history (pack years)	45 (32, 58)
ICS/LAMA/LABA (n)	6
LAMA/LABA only (n)	3
LAMA only (n)	1
LABA only (n)	1
SABA (n)	11
Post-salbutamol FEV_1 (% predicted)	56 (49, 63)
FVC (% predicted)	100 (86, 114)
FEV_1/FVC ratio (%)	46 (36, 53)
RV/TLC ratio (%)	50 (44, 56)
SGRQ score	38 (29, 47)
Oxygen saturations (%)	96 (95, 97)
Heart rate (bpm) (lying; standing)	77 (72, 81); 87 (82, 92)
Systolic BP (mm Hg) (lying; standing)	139 (131, 147); 141 (130, 151)
Diastolic BP (mm Hg) (lying; standing)	77 (72, 81); 79 (74, 84)

Data are presented as means (95% CIs) or absolute values.
BMI, body mass index; BP, blood pressure; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; RV, residual volume; SABA, short-acting beta-2 agonist; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

then symptom-limited cycling (no encouragement) at constant work rate of 75% of the peak work rate obtained during screening incremental CPET. Dyspnoea and leg discomfort as exercise progressed were assessed using the modified Borg scales[19] and IC manoeuvres to examine for DH[20] were performed at rest, throughout exercise at 2 min intervals, and at symptom limitation (peak exercise). Non-invasive thoracic bioreactance-based CO monitoring (Cheetah NICOM, Cheetah Medical (UK)) was performed during all visit CPETs using manufacturer's instructions, with measurements recorded at the same intervals as IC. Venous blood sampling prior to exercise testing at each visit comprised Galectin-3 (R&D systems, USA); NTproBNP (Biomedica, Germany), assay sensitivity 3.0 pmol/L (25.4 pg/mL), interassay variation <10%; cholesterol/HDL, creatine kinase, potassium. The remaining visit measurements are delineated in figure 2.

Analysis

The primary outcome measure was the change in IC from rest to an exercise isotime, that is, the same time point at the same (per individual) work rate between tests; thus, measuring and comparing DH between treatments. An increase of 200 mL in IC is suggested to be approximately equivalent to a 90 s improvement in endurance time[21]—where the minimum clinically important difference is proposed to be 105 s in patients with COPD. Therefore, to detect a difference of 200 mL in IC at isotime between treatments, assuming an SD (of the difference) of 160 mL[5] to achieve 93% power, two-tailed, p<0.05, required 10 patients in a crossover design. The null hypothesis was that there is no difference in the degree of DH between bisoprolol and celiprolol during cycle endurance testing. Analyses were performed using repeated measures analysis of variance, factoring treatment and sequence effects, followed by Bonferroni correction for all pairwise comparisons to avoid confounding the overall alpha error (two tailed). All baselines were pooled as they were statistically no different (paired t-tests, two tailed or non-parametric equivalent). All data were assessed for normality of distribution. Any non-parametric variables were logarithmically transformed to achieve normality prior to analysis. If normality could not be achieved through transformation, then we used the equivalent non-parametric statistical test on the untransformed data (see tables in the Results section). Statistical significance was set at p<0.05. All analyses were performed using IBM SPSS V.25.

RESULTS

Participants

Eleven participants completed per protocol from 2017 to 2019 following full recruitment to the study (table 1, figure 1).

The mean age of participants was 69 years (95% CI 65 to 73). Their mean postbronchodilator FEV_1 was 56% predicted (95% CI 49 to 63) and their mean residual volume/total lung capacity (RV/TLC) ratio was 50% predicted (95% CI 44 to 56) at screening. Two participants did not increase their beta-blocker dose at 2 weeks into their first treatment period following the safety algorithm (online supplemental file 1); one bisoprolol, one celiprolol. However, both participants completed the full treatment period on the initial dose. Both then subsequently completed their second treatment period after successfully incrementing to the higher dose of alternate beta-blocker. No significant adverse events occurred for any participant.

Ventilatory outcomes

The primary outcome, DH between resting IC and an exercise isotime IC at 4 min (the time point that all participants successfully reached), showed no significant difference with either beta-blocker compared with post-run-in pooled baseline, mean DH −470 mL (95% CI −730 to −200) or between celiprolol −490 mL (95% CI −820 to −130) and bisoprolol −420 mL (−610 to −230), p=0.87 overall. This was also true for the absolute 4 min isotime IC: baseline mean IC 1.94 L (95% CI 1.54 to 2.33);

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Table 2 Ventilatory outcomes

Outcome measure	Baseline	Celiprolol	Bisoprolol	P value
CPET				
DH (L), isotime 4 min	−0.47 (−0.73,−0.20)	−0.49 (−0.82,−0.13)	−0.42 (−0.61,−0.23)	0.87
IC (L), isotime 4 min	1.94 (1.54, 2.33)	1.97 (1.48, 2.47)	2.05 (1.72, 2.38)	0.59
IC (L), peak	1.89 (1.43, 2.34)	1.95 (1,71, 2.19)	2.06 (1.71, 2.41)	0.49
Peak VO_2 (L/min)	1.20 (1.00, 1.39)	1.24 (1.02, 1.45)	1.21 (1.00, 1.42)	0.71
Peak VE (L/min)	50.1 (43.0, 57.2)	48.3 (41.0, 55.6)	48.2 (41.0, 55.4)	0.31
Peak RR (breaths/min)	34 (31, 37)	31 (28, 34)	34 (30, 38)	0.053
Peak O_2 sats (%)*	97 (93, 99)	97 (91, 99)	97 (90, 98)	0.60
BR (%), peak	1.8 (−7.8, 11.4)	−3.5 (−14.3, 7.2)	1.1 (−7.8, 10.0)	0.25
Borg SOB, peak*	6.3 (5.0, 7.7)	6.6 (5.2, 8.2)	6.3 (4.8, 8.1)	0.72
Borg Legs, peak*	16.6 (15.4, 17.9)	17.4 (16.1, 18.8)	17.0 (15.8, 18.3)	0.16
Exercise time (min)	6.7 (5.5, 8.4)	7.2 (5.4, 8.9)	6.5 (4.5, 8.5)	0.83
PFT				
FEV_1 (%pred)	54 (47, 61)	52 (45, 59)	52 (45, 59)	0.90
FVC (%pred)	102 (88, 116)	100 (88, 112)	102 (87, 117)	0.59
Relaxed VC (%pred)	109 (95, 122)	109 (96, 121)	108 (93, 124)	0.99
RV/TLC ratio (%)	49.8 (44.4, 55.1)	49.6 (44.8, 54.3)	47.7 (43.3, 52.0)	0.06
R5 (%)*	146 (131, 161)	163 (149, 179)†	144 (124, 167)	0.04
AX (kPa/L)	1.78 (1.16, 2.41)	2.44 (1.74, 3.13)†	1.98 (1.24, 2.73)	0.004

Data presented as mean (95% CIs).
All baselines are pooled between treatments. Peak values represent time of symptom limit per individual on cycle endurance test. Repeated measures analysis of variance with Bonferroni correction. Statistical significance set at p<0.05.
*Geometric mean (95% CIs).
†Significant difference versus baseline.
AX, reactance at 5Hz (impulse oscillometry); Borg Legs, Borg scale for leg discomfort; Borg SOB, Borg scale for breathlessness; BR, breathing reserve; CPET, cardiopulmonary exercise test; DH, dynamic hyperinflation; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; IC, inspiratory capacity; O_2 sats, oxygen saturations; PFT, pulmonary function tests; %pred, percentage of predicted value; R5, resistance at 5Hz (impulse oscillometry); RR, respiratory rate; RV, residual volume; TLC, total lung capacity; VC, vital capacity; VE, minute ventilation; VO_2, oxygen uptake.

celiprolol 1.97 L (95% CI 1.48 to 2.47); bisoprolol 2.05 L (95% CI 1.72 to 2.38), p=0.59 overall (table 2, figure 3A).

There were no other significant differences for remaining ventilatory CPET outcomes (table 2), peak Borg scores (table 2, figure 3B) or total exercise endurance time (table 2). There was no significant exercise desaturation signal at baseline or on either beta-blocker at peak exercise. Participants' exercise was respiratory limited given little or no breathing reserve at peak exercise across the groups. Resting spirometry and RV/TLC ratios were not significantly different between groups (table 2). Both total airway resistance at 5 Hz (R5) and reactance (AX) on impulse oscillometry were significantly higher with celiprolol compared with baseline, but not bisoprolol (table 2).

Cardiac outcomes

Peak exercise heart rate was significantly lower with both beta-blockers compared with pooled baseline (p<0.001 overall), mean HR 133 bpm (95% CI 125 to 141); celiprolol 104 bpm (95% CI 99 to 108), p<0.001 versus baseline; bisoprolol 102 bpm (95% CI 96 to 109), p<0.001 versus baseline; but there was no significant difference between beta-blockers (table 3, figure 4A).

However, pre-exercise resting heart rate was only significantly lower with bisoprolol compared with both baseline and celiprolol (figure 1C). Peak exercise mean arterial blood pressure was significantly lower with both beta-blockers versus baseline, with no difference between treatments, p=0.03 overall. Heart rate recovery over 3 min was significantly reduced with celiprolol compared with baseline and bisoprolol (table 3). Peak exercise non-invasive CO was not significantly different between groups, p=0.7 overall (table 3, figure 3D). Both peak non-invasive stroke volume (SV) and peak oxygen pulse (O2P), the CPET surrogate of SV, were significantly higher with both beta-blockers compared with baseline, but not between treatments (table 3).

Domiciliary, safety and biomarker outcomes

Domiciliary diurnal measurement of oxygen saturations, FEV_1 and FEV_6 revealed no significant differences with

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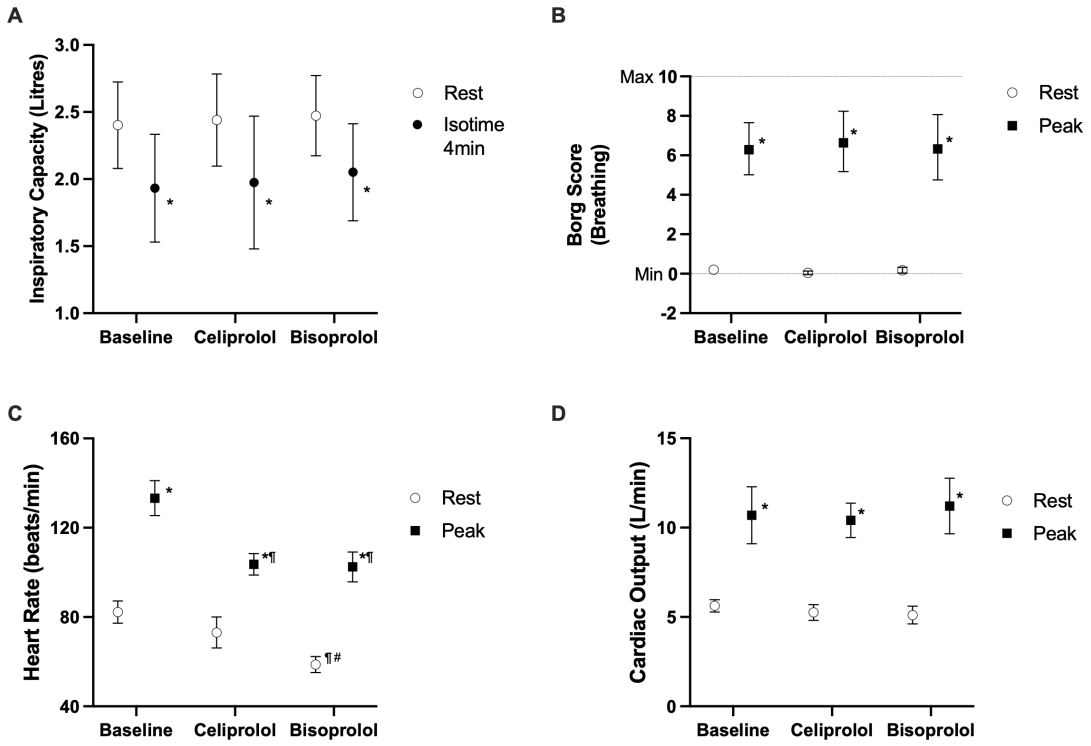

Figure 3 Cardiopulmonary exercise outcomes. (A) Inspiratory capacity at rest and 4 min isotime exercise. (B) Borg score of perception of breathing at rest and peak (symptom limited) exercise (higher score indicates greater breathlessness). (C) Heart rate at rest and peak exercise. (D) Cardiac output (non-invasive) at rest and peak exercise. Data presented as mean values with 95% CI bars (Geometric mean for Borg Score). All baselines are pooled between treatments. Repeated measures analysis of variance with Bonferroni correction for normally distributed data or Friedman's two-way analysis of variance by ranks (Borg score). Statistical significance set at p<0.05. *Significant difference to resting value, ¶Significant difference to baseline value, #Significant difference to celiprolol.

either beta-blocker versus baseline or between treatments (table 4, figure 4A,C).

Furthermore, there were no significant differences in daily symptoms, reliever use or SGRQ scores between groups (table 4). Diurnal HR measurements were significantly lower in a stepwise fashion with both celiprolol and bisoprolol versus baseline, p<0.001 overall both morning and evening, with bisoprolol also causing a further significant HR reduction versus celiprolol (table 4, figure 4B). NT-pro-BNP was significantly higher with bisoprolol versus baseline but not versus celiprolol, p=0.01 overall (table 4) but did not reach a level of clinical relevance.

Table 3 Cardiac outcomes

Outcome measure	Baseline	Celiprolol	Bisoprolol	P value
CPET				
Peak HR (bpm)	133 (125, 141)	104 (99, 108)*	102 (96, 109)*	<0.001
O_2P (ml/beat)	8.9 (7.8, 10.0)	11.7 (9.8, 13.5)*	11.6 (10.0, 13.3)*	<0.001
MAP, peak (mm Hg), n=8	116 (105, 127)	106 (93, 120)*	106 (91, 120)*	0.03
HRR, 3 min (bpm), n=10	7.1 (5.8, 8.5)	4.6 (3.5, 5.7)*	6.7 (5.3, 8.0)†	0.02
NICOM				
Peak cardiac OP (L/min)	10.7 (9.1, 12.3)	10.4 (9.4, 11.4)	11.2 (9.7, 12.8)	0.7
Peak SV (ml/beat), n=10	81 (63, 99)	105 (96, 113)*	122 (102, 142)*	0.003

Data presented as mean (95% CIs).
All baselines are pooled between treatments. Repeated measures analysis of variance with Bonferroni correction. Statistical significance set at p<0.05.
*Significant difference versus baseline.
†Significant difference versus celiprolol.
CPET, cardiopulmonary exercise test; HR, heart rate; HRR, heart rate recovery 3 min postexercise; MAP, mean arterial blood pressure; NICOM, non-invasive cardiac output monitoring; O_2P, oxygen pulse; OP, output; SV, stroke volume.

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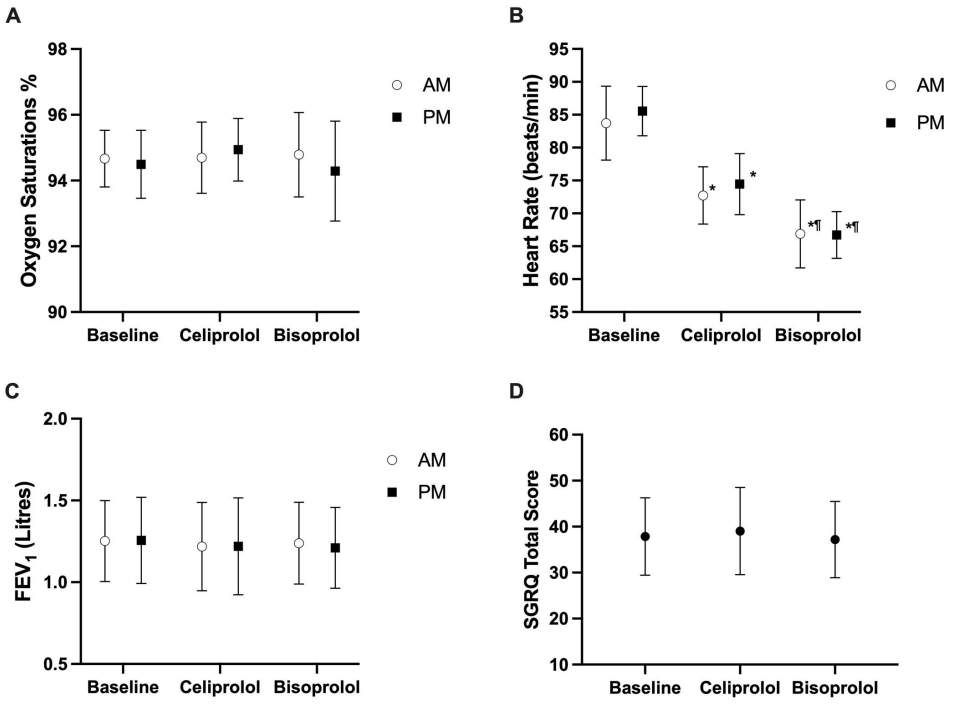

Figure 4 Safety and domiciliary outcomes. (A) Domiciliary morning (AM) and evening (PM) resting oxygen saturations. (B) Domiciliary morning (AM) and evening (PM) resting heart rate. (C) Domiciliary morning (AM) and evening (PM) forced expiratory volume in 1 s (FEV_1). (D) Visit St George's Respiratory Questionnaire (SGRQ) total score. Data presented as mean values with 95% CI bars. All baselines are pooled between treatments. Repeated measures analysis of variance with Bonferroni correction. Statistical significance set at p<0.05. *Significant difference to baseline, ¶Significant difference to celiprolol.

Most measures of beta-2 agonist activity were not significantly different between groups, including potassium, CK and total cholesterol; however, the Chol/HDL ratio was significantly higher with bisoprolol versus celiprolol, but not compared with baseline (table 4).

DISCUSSION

In the present study, we found no significant differences in the degree of DH during constant work rate exercise between the cardioselective beta-blockers celiprolol, bisoprolol or pretreatment baseline in moderate-severe COPD subjects. Clinically significant DH during exercise did still occur both with and without beta-blocker treatment, as would be expected in this cohort of volunteers with moderately severe COPD, given their baseline pulmonary function and symptom scores. Participants were also ventilatory limited (little or no breathing reserve) when they reached peak exercise, again both with and without beta-blocker treatment.

In a similar previous study, DH was worse with 2 weeks treatment with bisoprolol 10 mg versus placebo.[5] Importantly, only 62% of subjects in that trial were receiving a muscarinic antagonist, not described as long acting, whereas all but one of the subjects in the present study were regularly receiving a LAMA. Moreover, as that study did not employ a crossover design, it is not clear how many subjects in the bisoprolol arm were receiving any muscarinic antagonist. It is clinically logical that airway calibre should be protected by a LAMA when considering the use of beta-blockade in COPD. LAMAs prevent the bronchoconstricting effect of unopposed acetylcholine transmission across the airway neuromuscular junction that ensues on blockade of the beta-2 adrenoceptor at the prejunctional parasympathetic neuron.[22] Certainly, dual bronchodilation treatment with LABA/LAMA combinations is now more the norm in the UK, to maximise symptom benefit in COPD via optimal bronchodilation.[23] We also elected to use a lower dose of bisoprolol (5 mg) as this would be a more commonly used dose in clinical practice in patients with COPD.

We hypothesised that celiprolol, a highly cardioselective beta-blocker with PAA at the beta-2 adrenoceptor, might be even more protective in terms of airway calibre and, therefore, might either prevent or at least mitigate against the development of DH during exercise. However, there was no difference in this regard between celiprolol versus bisoprolol on any ventilatory CPET outcome, or indeed domiciliary pulmonary function measures. It could simply be that a near maximal bronchodilator effect had already been achieved with the subjects' usual inhaled therapies, thus negating any further room for improvement with celiprolol. Another explanation might be that prior evidence of the PAA of celiprolol was seen in asthma,[14] an obstructive airways disease that is more likely to respond to bronchodilation, compared with the more 'fixed' airways obstruction observed in COPD.

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Table 4 Domiciliary, quality of life and biomarker outcomes

Outcome measure	Baseline	Celiprolol	Bisoprolol	P value
Domiciliary				
O_2 sats (%)				
AM	95 (94, 96)	95 (94, 96)	95 (94, 96)	0.97
PM	94 (93, 96)	95 (94, 96)	94 (93, 96)	0.35
HR (bpm)				
AM	84 (78, 89)	73 (68, 77)*	67 (62, 72)*†	<0.001
PM	86 (82, 89)	74 (70, 79)*	67 (63, 70)*†	<0.001
FEV_1 (L)				
AM	1.25 (1.00, 1.50)	1.22 (0.95, 1.49)	1.24 (0.99, 1.49)	0.46
PM	1.26 (0.99, 1.52)	1.22 (0.92, 1.52)	1.21 (0.96, 1.46)	0.33
FEV_6 (L)				
AM	2.42 (2.02, 2.83)	2.41 (1.96, 2.86)	2.41 (2.01, 2.81)	0.91
PM	2.41 (1.97, 2.86)	2.38 (1.91, 2.85)	2.35 (1.89, 2.80)	0.40
Symptoms‡				
AM	0.5 (0, 1)	0 (0, 1)	0 (0, 1)	0.55§
PM	0.5 (0, 1)	1 (0, 1)	1 (0, 1)	0.94§
Reliever‡				
AM	0 (0, 1)	0 (0, 1)	0 (0, 0)	0.65§
PM	0.5 (0, 1)	0 (0, 2)	0 (0, 2)	0.54§
SGRQ				
Symptoms	43 (34, 52)	45 (30, 60)	45 (24, 47)	0.19
Activity	59 (47, 71)	60 (47, 73)	60 (47, 72)	0.96
Impacts	24 (16, 33)	25 (17, 33)	25 (16, 33)	0.86
Total score	38 (29, 46)	39 (30, 49)	37 (29, 45)	0.60
Biomarkers				
Cardiovascular				
NT-pro-BNP (pmol/L)‡	3.25 (1.14, 7.6)	3.97 (1.55, 8.69)	6.3 (3.2, 11.6)*	0.01
Galectin-3 (ng/ml)	7.9 (6.2, 9.5)	8.5 (7.0, 10.0)	8.0 (6.3, 9.7)	0.37
B2 activity				
CK (U/L), n=10	116 (89, 143)	131 (91, 171)	112 (78, 147)	0.27
Total cholesterol	4.9 (4.4, 5.4)	4.7 (4.2, 5.2)	4.8 (4.2, 5.4)	0.35
Chol/HDL ratio	3.1 (2.7, 3.4)	3.0 (2.6, 3.3)	3.2 (2.8, 3.6)†	0.015
Potassium (mmol/L)	4.3 (4.2, 4.4)	4.4 (4.2, 4.6)	4.5 (4.3, 4.6)	0.09

Data presented as mean (95% CIs).
Presented domiciliary data are averages of 3 days prior to visit one for baseline, final 3 days of treatment periods for celiprolol and bisoprolol.
All baselines are pooled between treatments. Repeated measures analysis of variance with Bonferroni correction.
*Significant difference vs baseline.
†Significant difference vs celiprolol.
‡Median (IQR).
§Friedman's two-way analysis of variance by ranks. Statistical significance set at p<0.05.
AM, morning; B2, beta-2 receptor; Chol/HDL, total cholesterol to high density lipoprotein ratio; CK, creatinine kinase; FEV_1, forced expiratory volume in 1s; FEV_6, forced expiratory volume in 6s; HR, heart rate; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; O_2 sats, oxygen saturations; PM, evening; Reliever, recorded diurnal short-acting bronchodilator use (AM, number of puffs in the morning; PM, number of puffs for the remainder of the day; SGRQ, St George's Respiratory Questionnaire with itemised domains; Symptoms, recorded diurnal diary symptoms (0, none; 1, mild; 2, moderate; 3, severe).

It is reassuring that the doses of both bisoprolol and celiprolol used in the present study were not deleterious in any marker across cardiopulmonary exercise, resting visit or domiciliary outcomes, albeit in a small number of moderate-severe COPD subjects. The safety of beta-blocker use in obstructive airways disease has been of major concern for some time now. This is despite growing evidence of safety in retrospective studies[9–11] and indeed the potential for longer term benefit,[10] mainly regarding the treatment of underlying overt or covert cardiovascular disease. The cardioselectivity of a beta-blocker as pertains to beta-1 over beta-2 adrenoceptor blockade is

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paramount when considering the safest long-term treatment in this context. Bisoprolol and celiprolol are both highly cardioselective in this regard. Pointedly, metoprolol is much less cardioselective than bisoprolol (2.3:1 vs 13.5:1, β1:β2).[8] It is also short acting, given two times per day. However, metoprolol was used in the BLOCK COPD trial to assess for any protective effect on future exacerbation rate.[12] There were safety concerns raised due to a higher rate of severe exacerbations in the treatment group but notably with no difference in overall hospitalisation or mortality. That study included a more severe group of patients with COPD than in the present one. They demonstrated a mean FEV_1 of 41%, with 40% of patients receiving supplemental oxygen and they were predominantly GOLD 3/4 status. Interestingly, 28% of those patients were not receiving LAMA treatment. There was no difference in their FEV_1 or 6 min walk distance over the course of the study, but the metoprolol group did display an increase in overall symptomatology versus the placebo group over time. Increasing COPD symptoms (GOLD status) are one of the key predictors of a future exacerbation,[24] in addition to prior history of exacerbation. We did not find a change in domiciliary symptoms in the present study with either beta-blocker, which could allude to the development of this underlying safety concern in the longer term.

Our novel use of non-invasive bioreactance CO monitoring during exercise was also reassuring, with no differences observed in CO between groups despite documented DH, and in keeping with the surrogate CPET outcome for CO, the O2P. Furthermore, we found a predictable significant fall in HR and BP measurements with bisoprolol more than celiprolol versus baseline. However, this did not impede overall CPET endurance exercise time, nor cause any adverse cardiovascular events. SV was found to be higher during exercise for both beta-blockers versus baseline, but this is not surprising in the context of lower HR and given that CO was stable, where CO=SV × HR. Indeed, the ability to increase SV and maintain CO in the context of exercise DH in the present study is an important finding, and particularly with the addition of two different cardioselective beta-blockers. A previous study identified a reduced O2P with exercise in GOLD 3/4 patients with COPD who had prior resting hyperinflation versus those who did not.[25] This effect is predominantly due to the mechanical external pressure of hyperinflated lungs on the heart's ability to increase muscular contractility, an effect also demonstrated to improve following lung volume reduction surgery.[26] We elected to study patients who demonstrated resting and DH because they, as a specific phenotypic group of COPD, would be most likely to fare worse with beta-blockade over those who do not, thus making the findings of this study more broadly relevant to the general COPD population.

The strengths of the present study included detailed cardiopulmonary physiological testing at rest and during exercise in moderate-severe COPD patients who demonstrated DH, which gave us an optimal phenotypical group in which we might uncover early detrimental cardiopulmonary effects of beta-blockade in addition to studying our hypothesised primary outcome. Furthermore, our inclusion of daily domiciliary safety measurements also proved reassuring. This study was adequately powered for the primary outcome using a crossover design to achieve this, which serendipitously helped to minimise participant exposure to beta-blocker treatment while safety concerns remain. Moreover, careful dose titration using highly cardioselective beta-blockers additionally improved our risk/benefit ratio. The limitations of the study included the short study duration, thus precluding information on exacerbations, a limited number of participants reducing the likelihood of picking up idiosyncratic beta-blocker adverse effects as well as the inability to study more severe COPD patients due to their very limited exercise capacity already, and potential for needing supplemental oxygen therapy. However, the optimal timing of potentially beneficial long-term beta-blocker treatment (early vs late) as COPD progresses is not yet known.

In conclusion, the observed clinically significant DH in moderate-severe COPD subjects was no different between chronic dosing of bisoprolol or celiprolol or versus baseline during cycle endurance testing. The broad spectrum of other cardiopulmonary and domiciliary safety outcomes was equally reassuring both between treatments and versus baseline. Further long-term studies using highly cardioselective beta-blockers for either preventing comorbid cardiovascular disease in COPD, or indeed treating COPD itself, are urgently needed.

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Contributors WA contributed to the conception and design of the study; the acquisition, analysis and interpretation of the data; drafted, revised and finalised the manuscript and is accountable for all aspects of the submitted work. WA is the guarantor for the study. PS contributed to the conception and design of the study; critically revised the manuscript for important intellectual content; gave final approval of the version to be published and is accountable for all aspects of the submitted work. RR contributed to the acquisition of the data; critically revised the manuscript for important intellectual content; gave final approval of the version to be published and is accountable for all aspects of the submitted work. BJL contributed to the conception and design of the study; the analysis and interpretation of the data; critically revised the manuscript for important intellectual content and is accountable for all aspects of the submitted work.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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BISOPROLOL VERSUS CELIPROLOL ON DYNAMIC HYPERINFLATION, CARDIOPULMONARY EXERCISE AND DOMICILIARY SAFETY IN COPD: A SINGLE CENTRE, RANDOMISED, CROSSOVER STUDY

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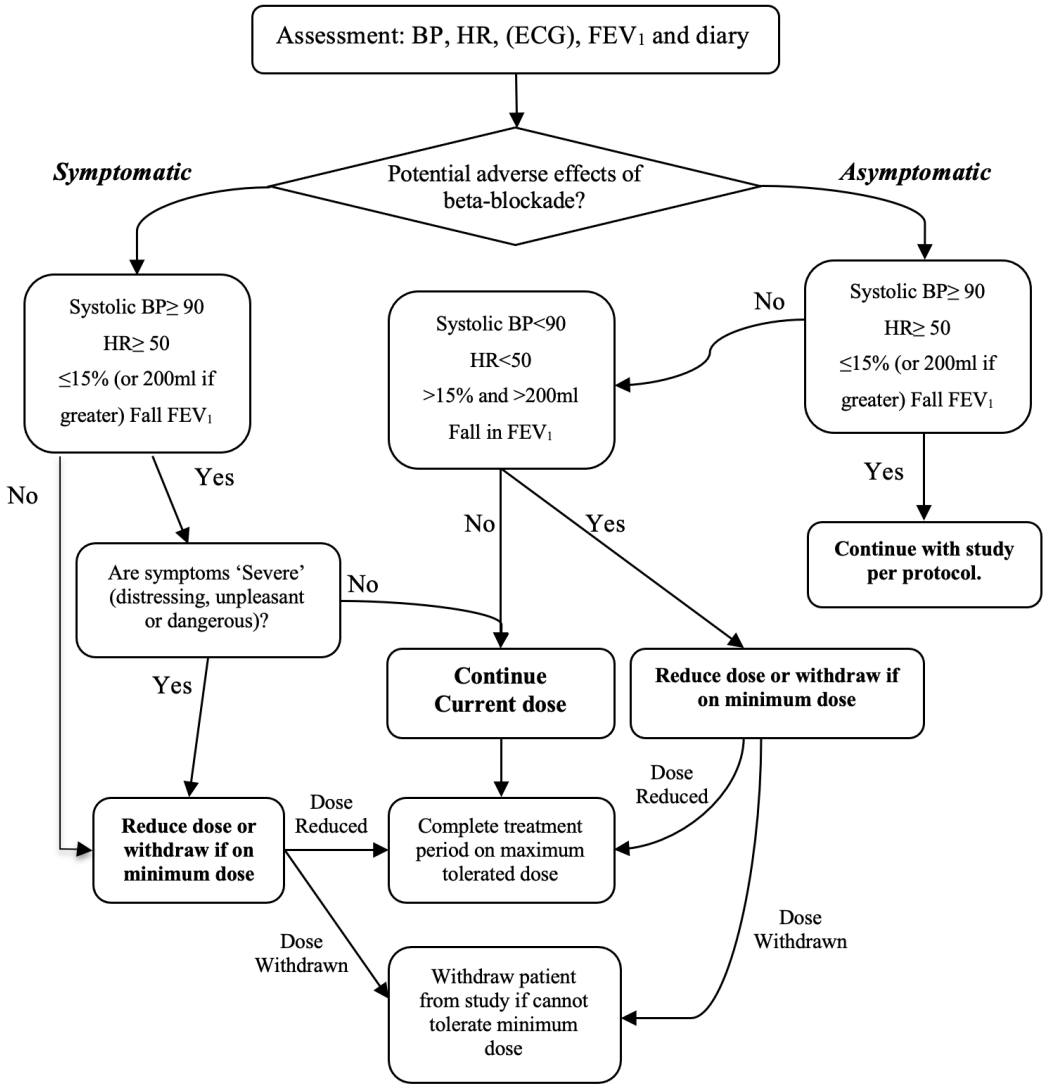
Supplemental Figure

Safety Algorithm for Beta-blocker Dose Titration.



Abbreviations: BP, blood pressure. HR, heart rate. ECG, electrocardiogram. FEV_1, forced expiratory volume in 1 second. Diary, daily diurnal diary of symptom scores and reliever use. Dose, dose of study beta-blocker.