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Extended Research Article

# Bisoprolol for patients with chronic obstructive pulmonary disease at high risk of exacerbation: the BICS RCT

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## Scientific summary

### Bisoprolol for patients with chronic obstructive pulmonary disease at high risk of exacerbation: the BICS RCT

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# Scientific summary

## Background

In the UK, there are 1.2 million people living with chronic obstructive pulmonary disease (COPD) and it is the third leading cause of death. People with COPD usually have a significant tobacco smoking history and typically present with progressively worsening breathlessness on exertion and a productive cough. The progressive airflow limitation impacts the quality of life and is associated with increasing disability and morbidity, and premature mortality. Exacerbations are a feature of COPD characterised by an acute deterioration in symptoms (usually precipitated by viral or bacterial infection and/or air pollution). Exacerbations are typified by increasing breathlessness, cough, sputum expectoration and malaise, and may result in hospitalisation. COPD is the second leading cause of emergency admission to hospitals in the UK and is one of the costliest inpatient conditions treated by the NHS.

Despite advances in management, there is still an unmet need for improved pharmacological treatment of COPD, particularly the prevention of exacerbations.

Beta-blockers reduce morbidity and mortality in people with ischaemic heart disease and heart failure. Reports from secondary analyses of observational and interventional studies of beta-blockers used for cardiovascular indications show that beta1-selective beta-blockers are safe in COPD and their use is associated with reductions in exacerbations and mortality, but there is a lack of evidence from randomised controlled trials (RCTs).

In the bisoprolol in COPD study, we tested the hypothesis that adding the beta1-selective beta-blocker bisoprolol to the treatment of people with COPD at high risk of exacerbation reduces the rate of moderate/severe exacerbations.

## Objectives

The primary objective was to determine the clinical effectiveness (in terms of number of exacerbations requiring change in management defined as treatment with antibiotics and/or oral corticosteroids) and cost-effectiveness of adding bisoprolol (maximal dose 5 mg once a day, or maximum tolerated dose) to usual COPD therapies in patients with COPD at high risk of exacerbation because of a history of at least two COPD exacerbations in the previous year.

The secondary objectives were to compare the following outcomes between participants treated with bisoprolol and those treated with placebo:

- Hospital admissions with a primary diagnosis of COPD exacerbation.
- Total number of emergency hospital admissions.
- Total number of major adverse cardiovascular events.
- Lung function (NB, *during the COVID-19 pandemic, lung function could not be assessed in participants*).
- Changes in breathlessness during treatment.
- All-cause and respiratory mortality.
- Drug reactions and serious adverse events (SAEs).
- Health-related quality of life.
- Disease-specific health status.
- Healthcare utilisation.
- Incremental cost per exacerbation avoided and quality-adjusted life-years (QALYs).
- Costs to the NHS and patients and lifetime cost-effectiveness based on extrapolation modelling (NB, *because of COVID-19 pandemic, this was not undertaken*).
- Modelled lifetime incremental cost per QALY (NB, *because of COVID-19 pandemic, this was not undertaken*).

## Methods

Bisoprolol in COPD study was a pragmatic, double-blind, placebo-controlled, multicentre RCT comparing adding bisoprolol or placebo to current therapy in people with COPD at high risk of exacerbation.

Eligible patients included those aged ≥ 40 years with diagnosed COPD [forced expiratory volume in 1 second ($FEV_1$)/forced vital capacity < 0.7] and at least moderate airflow obstruction ($FEV_1$ < 80% predicted), > 10 years pack year smoking history and two or more exacerbations treated with antibiotics and/or oral corticosteroids in the previous year. Exclusion criteria included an asthma diagnosis before the age of 40, predominant respiratory disease other than COPD, resting heart rate < 60 b.p.m. and/or resting systolic blood pressure < 100 mmHg. Participants were recruited from primary and secondary care settings across the UK.

Following informed consent, baseline data were collected and participants were randomised 1 : 1 to bisoprolol or placebo using a computerised web-based randomisation service created and administered by the Centre for Healthcare Randomised Trials, University of Aberdeen. Randomisation was stratified by trial centre (or for primary care site, area) and recruitment setting (primary or secondary care), and used permuted blocks of size 2 or 4. Participants were allocated a drug pack which was dispensed from a central clinical trials pharmacy and directly couriered to the participant's home.

Bisoprolol was prepared as 1.25 mg tablets and packaged in bottles of 168 tablets, and identical placebo tablets were similarly packaged. Participants started on one tablet per day and were titrated over a period of approximately 4–7 weeks to a maximum of four tablets per day (equivalent to 5 mg bisoprolol or placebo) based on tolerance to study medication, heart rate, systolic blood pressure, lung function and participant wishes. Prior to the COVID-19 pandemic, titration was conducted face to face with a member of the local research team and lung function was assessed using spirometry. When recruitment restarted in August 2021 after the first two waves of the COVID-19 pandemic, titration was conducted remotely – participants were provided with a digital sphygmomanometer to measure heart rate and blood pressure, and self-reported changes in breathlessness.

Once the dose was fixed, a 24-week supply of study medication was directly couriered to the participant's home. A further 24-week supply was couriered halfway through the study.

Participants were followed up in the study for 52 weeks, and outcome data were collected at 26 and 52 weeks – prior to the COVID-19 pandemic, these were conducted in a face-to-face setting; while, during and after the COVID-19 pandemic, these were primarily conducted by telephone. The primary outcome was a participant-reported number of COPD exacerbations requiring antibiotics and/or oral corticosteroids during the 52-week treatment period. Secondary outcomes included time to first exacerbation, unscheduled hospital admissions (COPD related, unrelated), COPD-related health status [assessed using the COPD assessment test (CAT)], breathlessness [assessed using the Transition Dyspnoea Index (TDI)], health-related quality of life [assessed using the EuroQoL-5 Dimensions, five-level version (EQ-5D-5L)], mortality (all cause, COPD/respiratory) and adverse reactions. Participants who ceased taking study medication remained in follow-up unless they requested otherwise.

The original intent of the study was to recruit and randomise 1574 participants, with at least 50% being recruited in primary care. This was based on detecting a clinically important reduction of 15% in COPD exacerbations (from an average of 2.22 exacerbations to 1.89 in the year of follow-up) and allowing for an estimated 15% withdrawal from study treatment. All analyses were pre-specified in a statistical analysis plan.

## Results

In total, 519 participants were recruited to the study from 76 primary and secondary care research sites across the UK (429 between October 2018 and March 2020, when recruitment to the study was paused because of the COVID-19 pandemic; and 90 between August 2021 when the study re-opened to recruitment and May 2022 when it closed to recruitment). Recruitment was closed because the funder could not support the study extension needed to enrol

additional participants. One hundred and seventy-eight participants were identified and recruited in primary care, 133 were identified in primary care and signposted to a secondary care site for recruitment, and 208 were identified and recruited in secondary care. There were four post-randomisation exclusions.

Baseline characteristics were well-balanced across the bisoprolol and placebo groups. The mean [standard deviation (SD)] age of participants was 67.7 (7.9) years, and just over half (53.2%) were male. About one-third (31.1%) were current smokers. The mean (SD) pack years smoked was 45.2 (25.2) pack years. Mean (SD) body mass index (BMI) was 26.8 (6.2) kg/m$^2$, with 58.0% being overweight or obese (BMI ≥ 25.0 kg/m$^2$). The mean (SD) number of participant-reported exacerbations in the 12 months prior to recruitment was 3.5 (1.9). Measurement of lung function at baseline revealed that the mean (SD) $FEV_1$ was 50.1 (19.1) per cent predicted. The majority of participants (73.8%) were prescribed the 'triple therapy' combination of inhaled corticosteroids, long-acting beta2 agonist (LABA) and long-acting muscarinic antagonist. Comorbidities were common, with 29.5% having a diagnosis of hypertension, 28.7% having anxiety and/or depression treated in the previous 5 years, 13.8% having diagnosed osteoporosis and 10.7% a diagnosis of diabetes mellitus. Based on the CAT scores, COPD was having a high or very high impact on the health and well-being of 61.7% of participants. The mean (SD) EQ-5D-5L utility score was 0.59 (0.25).

Almost one-fifth of participants were unable to tolerate the study medication, and the final titrated dose was zero tablets/day; however, this was balanced between the two treatment groups (bisoprolol 17.8%, placebo 16.4%). More participants allocated to placebo were able to tolerate four tablets/day than those allocated to bisoprolol (5 mg/day) (bisoprolol 27.4%, placebo 43.0%).

Primary outcome data were available for 99.8% of participants (bisoprolol 259, placebo 255).

In the intention-to-treat (ITT) analysis, the mean (SD) number of exacerbations per participant per year was 2.03 (1.91) in those allocated to bisoprolol and 2.01 (1.75) in those allocated to placebo. The adjusted incidence rate ratio (bisoprolol vs. placebo) and 95% confidence interval (CI) for exacerbation was 0.97 (0.84 to 1.13), indicating no significant difference in the exacerbation rate during the 12-month follow-up period for those on bisoprolol compared with placebo.

The results of this trial need to be interpreted with caution because it did not recruit the required number of participants to achieve intended statistical power; however, the estimates of the effect size of bisoprolol were close to unity and consideration of the CIs suggests that the ITT analysis narrowly failed to exclude a predefined clinically important ≥ 15% reduction in COPD exacerbations.

There was no difference in time to first COPD exacerbation, COPD exacerbations requiring hospital admission or in non-COPD-related hospital admissions. The number of participants with SAEs was similar between groups (bisoprolol 37, placebo 36), and bisoprolol was not associated with an excess of respiratory SAEs. Overall, the number of adverse reactions was also similar between groups; there was an excess of adverse reactions coded 'vascular disorders' in the bisoprolol group. There were 24 deaths during follow-up, 11 (2 COPD) in the bisoprolol group and 13 (9 COPD) in the placebo group.

The TDI showed deterioration in both groups from baseline. The deterioration was borderline statistically significantly greater in the participants allocated to bisoprolol, mean difference −0.73 (95% CI −1.44 to −0.01), $p = 0.047$. At 12 months, there were no significant differences between groups with respect to EQ-5D-5L utility, EQ-5D-5L visual analogue scale or CAT scores.

Treatment adherence/compliance was defined as participants having taken ≥ 70% of expected doses of study tablets. In total, there were 357 participants defined as adherent and are included in the protocol analysis (174 bisoprolol, 183 placebo). The results of per-protocol analysis were not substantially different from the results from the ITT analysis.

Analysis of healthcare utilisation found that there was no significant difference between arms in resource use costs; results show a trend for higher total costs (£636, 95% CI −£118 to £1391) in the bisoprolol arm compared to placebo arm; however, this result is uncertain. QALYs, a measure of quality and length of life, were higher in the placebo arm

compared to the bisoprolol arm, with a difference of 0.035 (95% CI 0.059 to 0.010). These findings indicate that including bisoprolol alongside usual care for people with COPD is marginally more costly and less effective than placebo; bisoprolol intervention would be termed as 'dominated'. The incremental cost per exacerbation is £31,800; however, this result cannot be compared to the National Institute for Health and Care Excellence willingness-to-pay threshold to assess cost-effectiveness and would also be considered dominated. Due to the reduced sample size from the original target sample, care should be taken in interpreting these results.

## Conclusions

In this trial that did not recruit to target, bisoprolol did not reduce the likelihood of exacerbation in people with COPD and cannot be recommended for the treatment of COPD.

The trial also indicates that bisoprolol is safe to use in people with COPD, and we anticipate that guideline recommendations for beta-blocker use in people with cardiovascular disease will now be able to make definitive statements about the safety of bisoprolol for cardiovascular indications in people with COPD.

## Trial registration

This trial is registered as ISRCTN10497306.

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## This article

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